β-PHENYLETHYLAMINES AND β-AMINO ALCOHOLS OF POTENTIAL PHARMACOLOGICAL INTEREST.

BY

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A Thesis presented for the degree of

DOCTOR OF PHILOSOPHY

in the

University of Aston in Birmingham

July, 1971

Pharmacy Department

University of Aston in Birmingham

SUMMARY

The biological properties of some tetrahydroisoquinolines, piperazines, and piperidines are described with particular reference to derivatives with analgesic or C.N.S. activity. A brief account is given of the development of narcotic analgesic antagonists.

The mechanism of action of sympathomimetic amines is described together with the biological properties of some β-phenylethanolamine derivatives.

The difficulties involved in the direct 1-alkylation of pyrrole are discussed and a summary is given of the methods most usually employed. The biological properties of some pyrroles are described.

The practical work described in this thesis is divided into three sections. The first concerns the preparation of alkyl and acyl derivatives of 1,2,3,4-tetrahydroisoquinoline, 1-phenylpiperazine, and 4-diphenylmethylpiperidine.

In the second part the synthesis of β-amino alcohols, by the fission of epoxides with amines, is discussed. Cyclisation of the β-amino alcohols gave examples of the oxazolidine, 2-oxazolidinone, 2-oxathiazolidinone, 2-morpholinone, and morpholine-2,3-dione ring systems. A previously claimed synthesis of 3,5-diphenyloxazolidin-2-one, from phosgene and styrene oxide, is shown to yield the 3,4-diphenyl isomer. The possible conformation of 4-cyclohexyl-6-phenylmorpholine-2,3-dione is discussed on the basis of n.m.r. data. Preparation of the N-amino derivative of 2-cyclohexylamino-1-phenylethanol is described together with the cyclisation to yield the first reported example of the 2H-1,3,4-oxadiazine-2-thione ring system.

The preparation of some novel 1-substituted pyrroles, from the reaction of methyl pyrrole-2-carboxylate and epoxides, is described in the third part. Examples of the 1H-pyrrolo [2,1-c] [1,4] oxazine and the novel 4H-pyrrolo [2,1-c] [1,4] benzoxazine ring systems are described. A mechanism is suggested for the reaction of pyrrole salts with epoxides. Various unsuccessful attempts to cyclise 1-substituted vinylpyrrole-2-carboxylic acids to pyrrolo [2,1-c] [1,4] oxazines are described. The photochemical isomerisation of trans-1-styrylpyrrole-2-carboxylic acid is discussed. Mass spectral data of some 1-substituted pyrroles is presented.

In conclusion the pharmacological results of a selected number of compounds are reported and discussed. 1-Cyclopropylmethyl-4-phenylpiperazine has interesting C.N.S. activity and produces effects similar to chlorpromazine.

ACKNOWLEDGEMENTS

I would like to thank Dr. N. J. Harper for his assistance at the start of this work, and Organon Laboratories for the award of a research grant. My special thanks are given to Dr. W. J. Irwin for his help and encouragement during the completion of this work. I would also like to mention Dr. A. Z. Britten and Dr. J. Raines for many fruitful discussions.

I would like to thank the Cambridge University Press for permission to use Figure 1 (reference 23).

TO

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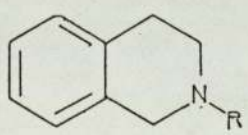
INTRODUCTION

A. STRUCTURE-ACTIVITY RELATIONSHIPS IN SOME TETRAHYDROISOQUINOLINES, PIPERAZINES, AND PIPERIDINES.

The compounds described in Part A of the discussion are derivatives of 1,2,3,4-tetrahydroisoquinoline (1), 1-phenylpiperazine (2), and 4-diphenylmethylpiperidine (3). These ring systems show an increasing separation of the aromatic ring(s) from the R-substituted nitrogen by two, three, and four atoms respectively. There appeared a possibility that some useful structure-activity relationships could be drawn between derivatives of these compounds.



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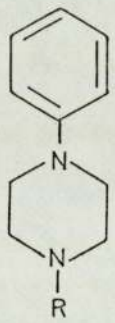

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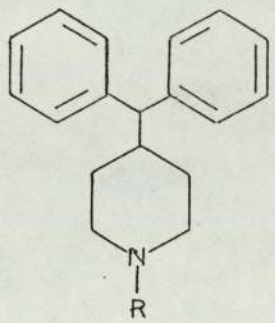


(3)

1. Biological properties.

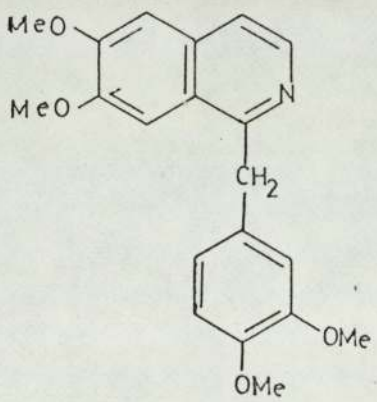
(a) Tetrahydroisoquinoline.

The isoquinoline nucleus, either in its aromatic or partially hydrogenated form, is found in many naturally occurring drugs (see Table 1.).

Isoquinoline Drug		Action
Emetine	(6)	Emetic, amoebicidal
Papaverine	(4)	Vasodilator
Morphine	(7)	Analgesic, euphoric
Tubocurarine	(8)	Neuromuscular blocking agent

Table 1

Papaverine (4) has a direct action on organs containing smooth muscle causing a reduction in tone and motility.[1] The action is more prominent when the smooth muscle tone is high due to drugs or nervous activity. It also has a general dilatatory effect on arterial blood vessels, and as such is useful in the treatment of angina pectoris.



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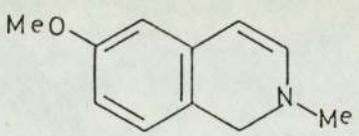

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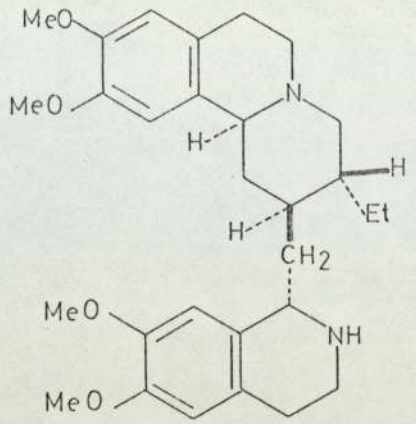
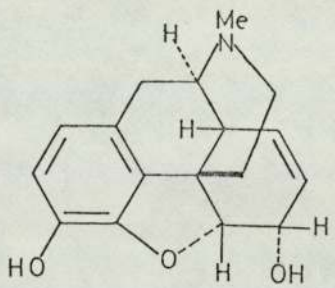
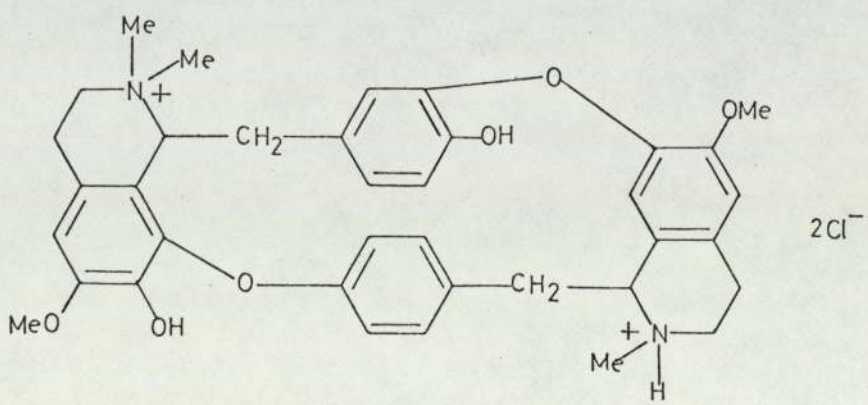
The simple 1,2-dihydro compound (5) is reported to cause a marked and sustained fall in blood pressure in hypertensive dogs.[2] Many 1,2,3,4-tetrahydroisoquinolines, however, possess a pressor activity greater than


MeO
MeO
N
H
H
H
Et
CH2
MeO
MeO
NH

(6)

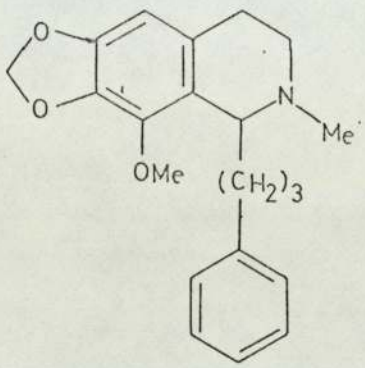

H
Me
N
H
H
HO
O
H
OH

(7)


Me
Me
N+
CH2
OH
O
OMe
2Cl−
O
CH2
MeO
OH
+N
Me
H

(8)

that of the corresponding phenethylamines. The increased toxicity that is produced outweighs any useful increase in pharmacological activity.



(9)

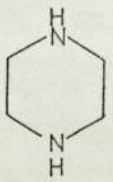
Analgesic activity comparable to codeine, has been observed in some 1-substituted tetrahydroisoquinolines.[3] The 1-phenylpropyl derivative of cotarnine (9) has codeine-like activity with the advantage of low physical dependence. In general, however, the tetrahydro isoquinoline series has yielded few analgesics of clinical interest.

(b) Piperazine.

The piperazine ring system is found in a wide variety of pharmacologically active compounds. The simplest piperazine derivatives are useful as anthelmintics whilst the more complex derivatives have C.N.S. activity.

Piperazine (10) is a very good vermifuge in the treatment of oxyuriasis (enterobiasis) and ascariasis (roundworm) infestations.[4,5] It is employed as the adipate, citrate or tartrate salt, the worms being narcotized, paralysed and expelled alive.

Diethylcarbamazine (11) is a most effective antifilarial drug used in the treatment of infestations caused by W.bancrofti, B.malayi and L.loa.[6,7] The drug appears to sensitize the microfilariae to the actions of phagocytes in the blood.



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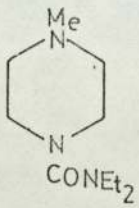
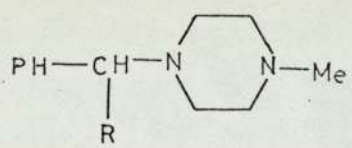


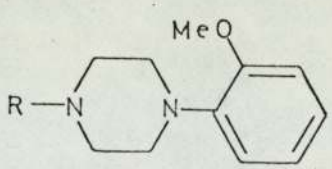
(11)

Cyclizine (12) and chlorcyclizine (13) were developed as antihistamines and have an activity approximately equal to diphenhydramine.[8] They have a slow onset and a prolonged duration of action, and are now widely used as motion sickness preventatives.

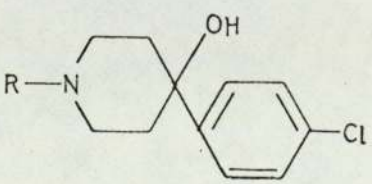


(12) R = Ph

(13) R = 4-ClC_6H_4



(14) R = $(CH_2)_3CO$-4-FC_6H_4



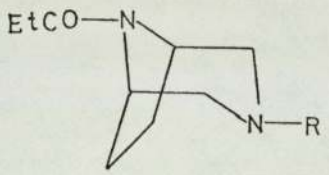
(15) R = $(CH_2)_3CO$-4-FC_6H_4

Fluanisone (14) is the piperazine analogue of a large group of chemically related butyrophenones[9] of which Haloperidol (15) is the

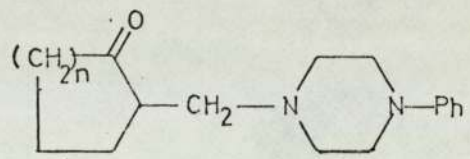
prototype. These compounds have potent anti-psychotic or neuroleptic properties and act in a similar manner to chlorpromazine. They are used in the treatment of schizophrenia characterised by paranoid and catatonic symptoms.

Analgetic activity in the piperazine series is not very common. The 3-cinnamyl-8-propionyl-3,8-diazobicyclo[3,2,1]octane (16) possesses significant analgesic activity (10 x morphine).[10] It may be regarded as a piperazine derivative with the 1,5-position linked by a bimethylene bridge.

Activities of the order of one-third to one-fifth that of morphine are claimed for the Mannich bases (17) obtained from 1-phenylpiperazine and a cycloalkanone.[11]



(16) R = $CH_2CH{=}CHPh$



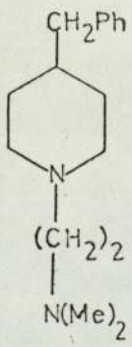
(17) n = 1 or 2

(c) Piperidines.

The piperidine ring is found in many compounds of widely differing pharmacological activity. Although piperidine itself has little or no activity, it provides a cyclic structure containing one basic centre from which structural analogues of high activity can be prepared.

Some structurally similar compounds have quite different pharmacological actions. 4-Benzyl-1-(2-dimethylaminoethyl)piperidine dihydrochloride (pimetine hydrochloride, 18) slows down the development

of atherosclerotic lesions in the rabbit.[12] This action is not due to a hypocholesterolemic effect but to a direct mobilisation of deposited cholesterol or the inhibition of its deposition. The β-anilinoethyl derivative (19), however, which is related to piminodine (20) has considerable analgesic activity (1300 x pethidine).[13]



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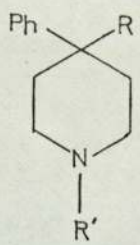
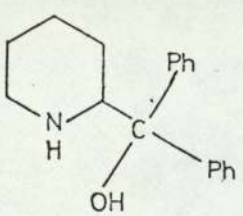


(19) R = OCOEt; R' = CH_2CH_2NPh

(20) R = COOEt; R' = $CH_2CH_2CH_2NPh$

The benzhydrol piperidines show a similar diversity of action. α-(2-Piperidyl)benzhydrol(pipradrol, 21) is a ganglion stimulating agent of similar activity to amphetamine and is used in the treatment of depressive states.[14] It rouses animals from a barbiturate hypnosis but it differs from amphetamine in that the animals do not become irritable and their appetite is not affected. α-(4-Piperidyl)benzhydrol(azacyclonal, 22) is a behavioural depressant and is used in the treatment of mild conditions characterised by agitation, anxiety, and stress.[15]



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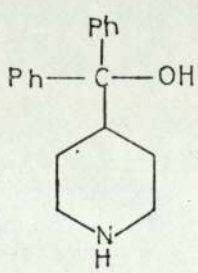
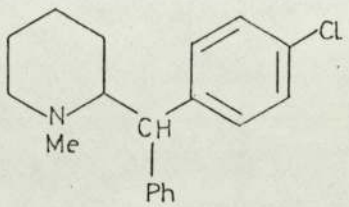


(22)

The activities of the diphenylmethylpiperidines closely resemble their benzhydrol analogues. The 2-diphenylmethylpiperidine (23) has C.N.S. stimulant activity[16] whereas the 4-diphenylmethylpiperidine (24) has depressant activity.[17]



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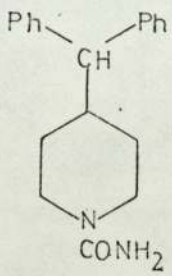
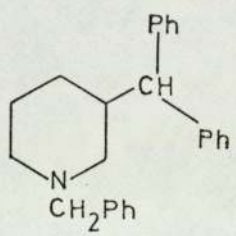


(24)

Resolution of 1-benzyl-3-diphenylmethylpiperidine (25) has shown that the two optical isomers possess quite different pharmacological actions.[18] The (+)-isomer causes a marked decrease in gastric secretion and protects animals against tremorine induced tremors. The (-)-isomer however, has C.N.S. stimulant activity.



(25)

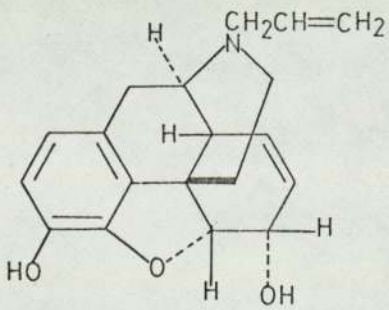
2. Narcotic analgesic antagonists.

The rationale behind the preparation of many of the N-substituted analogues in Part A of the discussion is found in the development of

clinically useful narcotic analgesic antagonists.[19,20]

For many years the effective treatment of severe pain has relied upon the use of morphine. The strong analgesic properties of morphine are, however, accompanied by several side effects which limit its usefulness. The two main disadvantages are respiratory depression and the tendency to cause addiction. Since the early 1930's a multitude of chemical compounds has been prepared in an attempt to separate analgesic activity from addiction liability.

In 1943 it was discovered that N-allylnormorphine (nalorphine, 26) would antagonise some of the actions of morphine, especially that associated with respiratory depression. Nalorphine has an analgesic potency similar to that of morphine but its hallucinogenic side effects preclude its clinical use. These findings led Archer and his associates[21] to synthesise many N-substituted derivatives of α-(±)-2'-hydroxy-5,9-dimethyl-6,7-benzomorphan of which pentazocine (27) and cyclazocine (28) are in current use.



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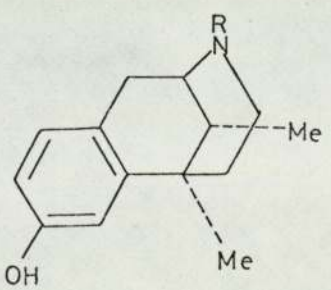
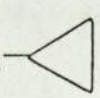


(27) R = $CH_2CH{=}CMe_2$

(28) R = CH_2- 

Both compounds antagonise the effects of pethidine in the rat tail flick test but fail to give positive analgesic responses when used alone in this or similar tests. This failure to give positive responses in the

usual analgesic screening tests (tail flick and hotplate) has led to the phenylquinone writhing test being used to detect potential narcotic analgesic antagonists.

All of the active narcotic analgesic antagonists possess an N-substituted allyl or N-cyclopropylmethyl group. It is known that the cyclopropylmethyl group possesses significant allylic character.[22] It is not, however, suggested that the mere possession of an N-cyclopropylmethyl group will confer narcotic analgesic activity on a molecule, although such a compound might be expected to possess some interesting pharmacological activity.

B. BIOLOGICAL PROPERTIES OF SOME β-PHENYLETHANOLAMINE DERIVATIVES.

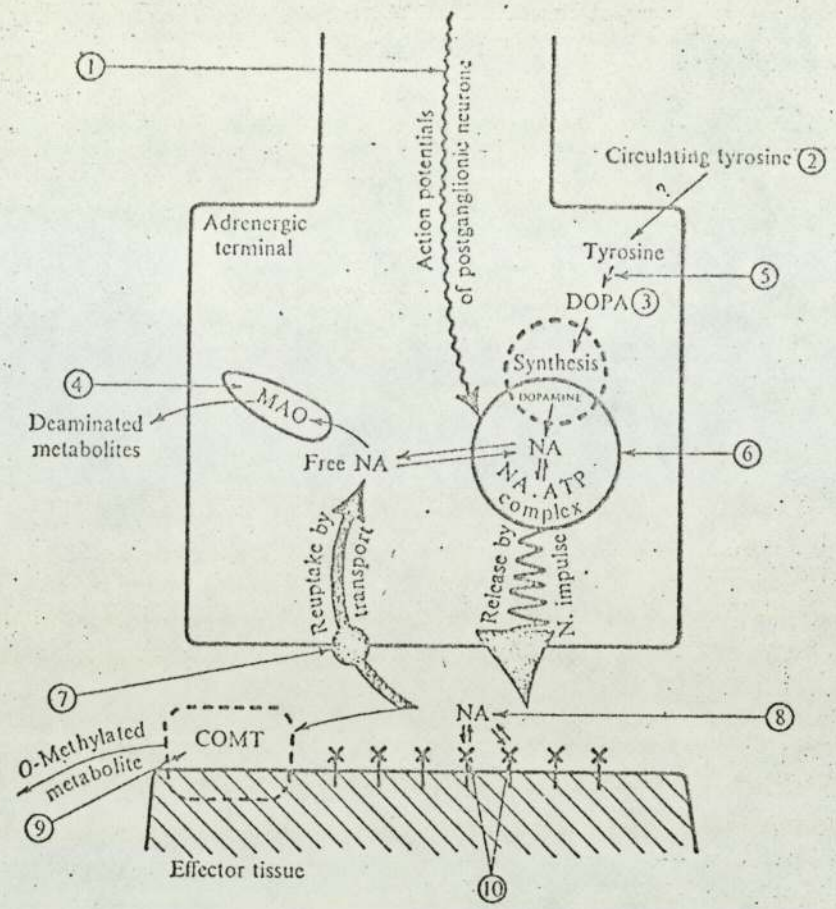
1. Mechanism of action of sympathomimetic amines.

The majority of compounds described in Part B of the discussion are derivatives of either β-phenylethanolamine or phenethylamine. For an understanding of the pharmacological actions of these amines it is necessary to consider the mechanism of action of adrenergic drugs in general.[23,24].

Stimulation of a postganglionic adrenergic nerve fibre causes noradrenaline to be released from the nerve ending. The interaction of noradrenaline with the adrenergic receptor can lead to either an excitatory or inhibitory response, depending on which organ is innervated. Stimulation of the coronary blood vessels causes them to dilate whilst blood vessels in the skin are constricted.

Ahlquist[25] suggested that different effector cells contain different receptors which he designated α- and β-receptors. The α-receptor is associated with an excitatory response whilst the β-receptor is generally associated with an inhibitory response. It has been shown that not only do some tissues contain both α- and β-receptors but that the same receptor has different properties in different tissues. The nature of the structural differences between the different receptors has yet to be resolved.[26]

The sequence of events that follow stimulation of the adrenergic nerve is shown in Figure 1.[23] Noradrenaline, released from the bound pool (NA-ATP complex), diffuses from the nerve ending and can then interact with the adrenergic receptor. The released noradrenaline is then taken up by an active transport mechanism into the nerve ending against a concentration gradient of about 10,000:1. The re-uptake of noradrenaline into the sympathetic nerve is the major process by which its actions,



Possible sites of action of drugs interfering with adrenergic mechanisms.

(1) Action potentials propagate to the terminals of sympathetic postganglionic neurones. Propagation in terminal regions may be blocked by adrenergic neurone-blocking drugs such as bretylium and guanethidine. Propagation may also be blocked at the synapse between pre- and postganglionic neurones by ganglion blocking drugs such as pempidine and chlorisondamine.

(2) Circulating tyrosine is the probable precursor used by adrenergic terminals for the biosynthesis of noradrenaline, circulating tyrosine enters the adrenergic terminal possibly by a carrier-mediated transport process (?). Structurally related drugs such as α-methyl-*m*-tyrosine can take the place of tyrosine and be converted by the biosynthetic process into false adrenergic neurotransmitters.

(3) False neurotransmitters can also be synthesized from drugs which are related to other intermediates in noradrenaline biosynthesis, for instance α-methyl DOPA can take the place of DOPA.

(4) Free noradrenaline in the axoplasm is destroyed by monoamine oxidase, situated in intraneuronal mitochondria. This enzyme can be inhibited by a wide range of MAO inhibitors such as pheniprazine, nialamide or iproniazid.

(5) The rate-limiting step in noradrenaline biosynthesis, tyrosine hydroxylase, can be inhibited by drugs such as α-methyl-*p*-tyrosine or 3-iodotyrosine.

(6) The storage of noradrenaline in intraneuronal storage particles is prevented by drugs such as reserpine.

(7) The re-uptake of noradrenaline released by nerve impulses is effected by a membrane transport process which can be inhibited by many drugs, including cocaine, desipramine and many sympathomimetic amines.

(8) Many drugs can also be taken up into the adrenergic neurone by acting as substrates for this transport process. Once inside the neurone, drugs may displace noradrenaline from intraneuronal stores (indirect acting sympathomimetics), and may further take the place of noradrenaline by acting as false neurotransmitters (metaraminol, octopamine, α-methyl noradrenaline).

(9) The extraneuronal metabolism of noradrenaline by catechol-*O*-methyl transferase can be inhibited by pyrogallol and tropolones.

(10) The interaction of noradrenaline with α- and β-adrenergic receptors can be blocked by receptor blocking drugs such as phenoxybenzamine, phentolamine, DCI and pronethalol. The actions of noradrenaline on adrenergic receptors can be mimicked by direct-acting sympathomimetic amines such as adrenaline or synephrine.

Figure 1

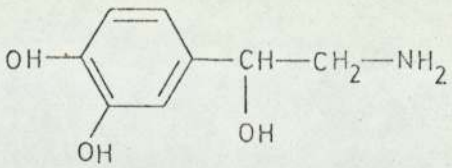
following adrenergic stimulation, are terminated. The metabolism of noradrenaline by catechol-o-methyl transferase and monoamine oxidase may be considered minor processes in this context. The taken up noradrenaline, which is in a free form, will be changed into bound-noradrenaline or metabolised by monoamine oxidase in the intraneuronal mitochondria.

There is evidence that the uptake of catecholamines from the circulation into tissues constitutes an important route for the rapid removal of catecholamines from the circulation after injection. This might be an important route for terminating the actions of catecholamines released from the adrenal medulla. However, the presence of high concentrations of catechol-o-methyl transferase and monoamine oxidase in the liver in most species will inactivate, though more slowly, circulating catecholamines if tissue uptake is blocked.

β-Phenylethanolamine and phenethylamine are sympathomimetic amines and have similar pharmacological actions to adrenaline and noradrenaline. Fleckenstein[27] has divided sympathomimetic amines into three classes according to their action on the chronically denervated cat nictitating membrane:

1. Direct acting: Those that are potentiated by denervation and cocaine.
2. Mixed acting: Those that are essentially unaffected by these procedures.
3. Indirect acting: Those that are ineffective or significantly less effective afterwards.

Noradrenaline (29), β-phenylethanolamine (30), and phenethylamine (31), are respectively, representatives of these three classes.



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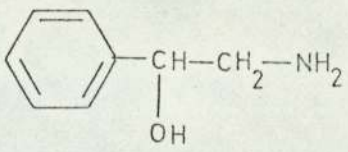

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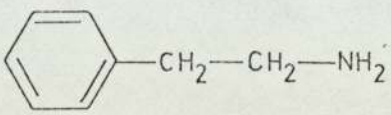


(31)

The basic structural requirements for direct acting compounds among the phenethylamines appears to be the presence of a catechol group or a 3'-phenolic and β-hydroxy group. It should be noted, however, that a rigid classification into direct, mixed, and indirect acting amines is not possible, and that each amine probably possesses both direct and indirect actions. The overall action of any amine will depend, therefore, on the relative potency of its two types of action. An amine may be direct acting on one tissue but have indirect or mixed actions on another tissue in the same animal.

The mechanism of action of indirectly acting amines remains controversial. Current opinion[23] holds that phenethylamine and other indirectly acting amines enter the nerve terminal through the catecholamine uptake mechanism and displace noradrenaline from intraneuronal storage granules. Some indirectly acting amines which are taken up into the nerve may be β-hydroxylated to give compounds (false transmitters) which are themselves released by noradrenaline but which lack the pharmacological activity of noradrenaline. Displacement of noradrenaline also occurs from tissue storage sites simultaneously with inhibition of the re-uptake mechanism of the catechol amine. This explains why the very small amount of noradrenaline released by indirectly acting amines can have such potent effects.

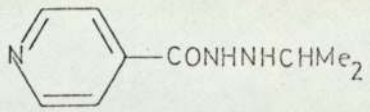
2. Biological properties of some related derivatives.

The mechanism of action of sympathomimetic amines has been discussed. It is appropriate to discuss some derivatives of phenethylamine and β-phenylethanolamine in which the sympathomimetic activity is either enhanced or diminished. Reference is also made to derivatives that possess quite different pharmacological activity.

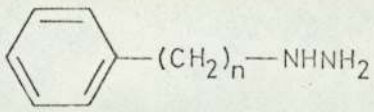
(a) Hydrazines and hydrazides.

Many hydrazines and hydrazides have been tested for monoamine oxidase (MAO)-inhibitory action and several comprehensive reviews on structure-activity relationships are available.[28,29] Although hydrazine lacks any significant MAO-inhibitory action,[30] alkyl substitution may confer strong activity. 1,1-Dialkyl substituted hydrazines, ($R^1R^2NNH_2$), however, have insignificant MAO-inhibitory activity. A hydrogen atom on the alkyl substituted hydrazine nitrogen seems to be essential for MAO-inhibitory activity.

Phenylhydrazine (32) is a relatively weak MAO-inhibitor *in vitro* and is devoid of significant *in vivo* activity (reversal of reserpine induced sedation in mice).[30] Benzylhydrazine (33) however, has considerable *in vitro* and *in vivo* inhibitory activity (40 x iproniazid).[30] Potencies are expressed relative to iproniazid (35) which was the prototype of these antidepressant drugs. Further lengthening of the alkyl chain gives phenelzine (34) which has decreased inhibitory activity (4 x iproniazid).[30]



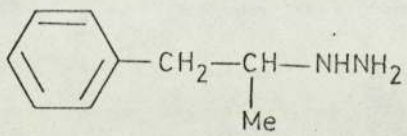
(35)



(32) n = 0

(33) n = 1

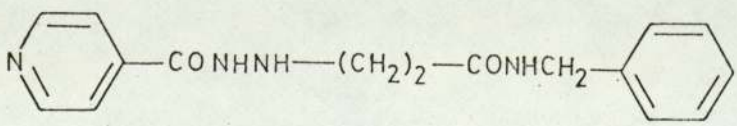
(34) n = 2



(36)

Branching of the side chain to give pheniprazine (36) produces enhanced activity (40 x iproniazid).[30] Due to the occurrence of side effects, the use of iproniazid has been discontinued, in favour of less toxic compounds.

Although unsubstituted hydrazides, ($R \cdot CONHNH_2$) do not possess significant MAO-inhibitory activity, monosubstitution of the free amino group of the hydrazide, $R \cdot CONHNH \cdot R^1$, may, however, introduce powerful inhibitory activity.[30] The main function of the acyl group appears to be as a "carrier", it being hydrolysed metabolically to release a MAO-inhibitory substituted hydrazine. Nialamide (37) has considerable MAO-inhibitory activity (3-12 x iproniazid) without producing liver damage.[30]

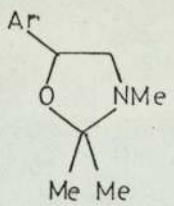


(37)

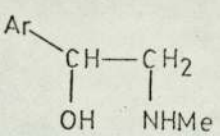
(b) Oxazolidines.

The clinical use of oxazolidines is limited but they have been used in the treatment of epilepsy in children[31] and as appetite suppressants (anorexigenic agents).[32]

5-(3-Aminophenyl)-2,2,3-trimethyloxazolidine (38) possesses greater sympathomimetic activity than the β-amino alcohol (39) from which it is derived and is also less toxic.[33]



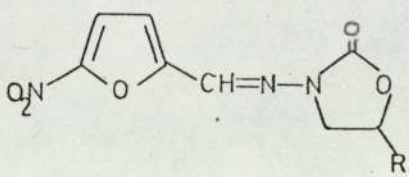
(38) Ar = 3—$NH_2C_6H_4$



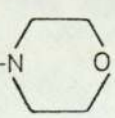
(39)

(c) Oxazolidinones.

Furazolidone (40) has a very broad antimicrobial spectrum and is especially useful in the treatment of Trichomonas infections.[34] It is also used in the treatment of coccidiosis in fowl, and giardiasis.[35]



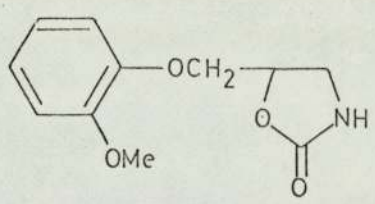
(40) R = H

(41) R = CH_2— 

(-)-Furaltadone (41) has found some use in the treatment of South American trypanosomiasis (Chagas' disease), a disease that is still

difficult to treat.[36,37] It is also reported to have good antibacterial properties, especially against Staphylococcus infections.[34]

In addition to these antibacterial oxazolidinones are also those with C.N.S. and muscle relaxant properties. Mephenoxalone (42) is an anti-anxiety agent[38] of similar action to meprobamate (44). These compounds are interneuronal blocking agents and act by depressing nerve impulse transmission in polysynaptic reflex pathways.[39] Metaxalone (43), is used clinically as a muscle relaxant.



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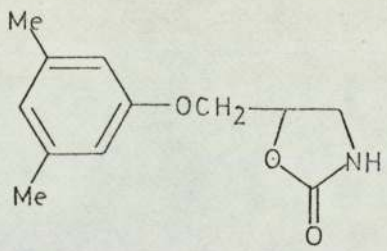

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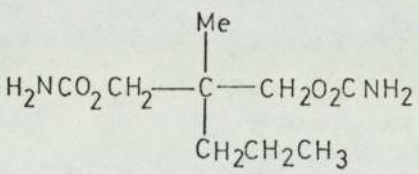

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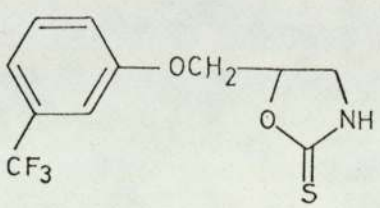


(45)

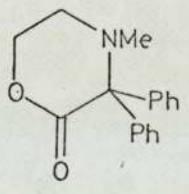
The 2-oxazolidinethione (45) was synthesised as a potential muscle relaxant but was found to have antifertility activity in the rat.[40]

(d) Morpholinones and morpholinediones.

The pharmacological activity of 2-morpholinones and morpholine-2,3-diones has been little studied. 3,3-Diphenyl-4-methyl-2-morpholinone (46) showed no activity in tests for analgetics, anhistamines, anticonvulsants and sympathomimetics.[41]

Similarly, 4,5-dibenzylmorpholine-2,3-dione (47) showed no antihypertensive, anti-inflammatory or analgetic activity.[42]

Whereas 3-methyl-2-phenylmorpholine (phenmetrazine, 48) has sympathomimetic activity similar to amphetamine and is used clinically as an appetite suppressant,[43] the N-substituted oxazine (49) is inactive.[44]



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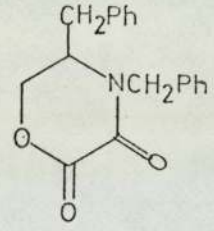
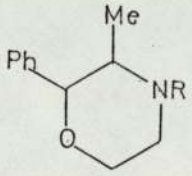


(47)



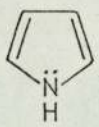
(48) R = H

(49) R = Alkyl

C. CHEMICAL AND BIOLOGICAL PROPERTIES OF SOME 1-SUBSTITUTED PYRROLES.

1. Preparation of 1-alkyl derivatives of pyrrole.

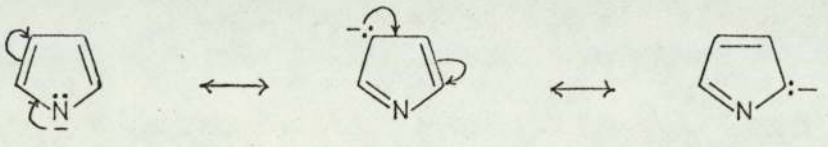
Pyrrole (50) is a five membered π-excessive heterocyclic compound possessing considerable aromatic character arising from the delocalisation of four carbon π electrons and two paired electrons donated by the nitrogen atom. This combination forms a sextet of delocalised electrons which has a high degree of aromatic character.[45;46].



(50)

The structure of pyrrole can be described as a hybrid of several resonance forms (eg. 50a to 50c). Dipole moment studies[47] indicate that the dipolar resonance forms (eg. 50b and 50c) contribute significantly to the hybrid.

(50a) (50b) (50c)



(51a) (51b) (51c)

Pyrrole, with a pka[48] of greater than 15, is weakly acidic and can form alkali metal salts and Grignard reagents. There are two reasons

for the acidic nature of pyrrole. The π electron system of the resultant anion (eg. 51a to 51c) is stabilised by delocalisation and, in contrast to pyrrole, involves no charge separation. A second factor is the greater s-character of the N-H bond in pyrrole compared to ammonia and amines. The bonding electrons are held more tightly by the nitrogen, allowing the hydrogen to leave more easily as a proton.

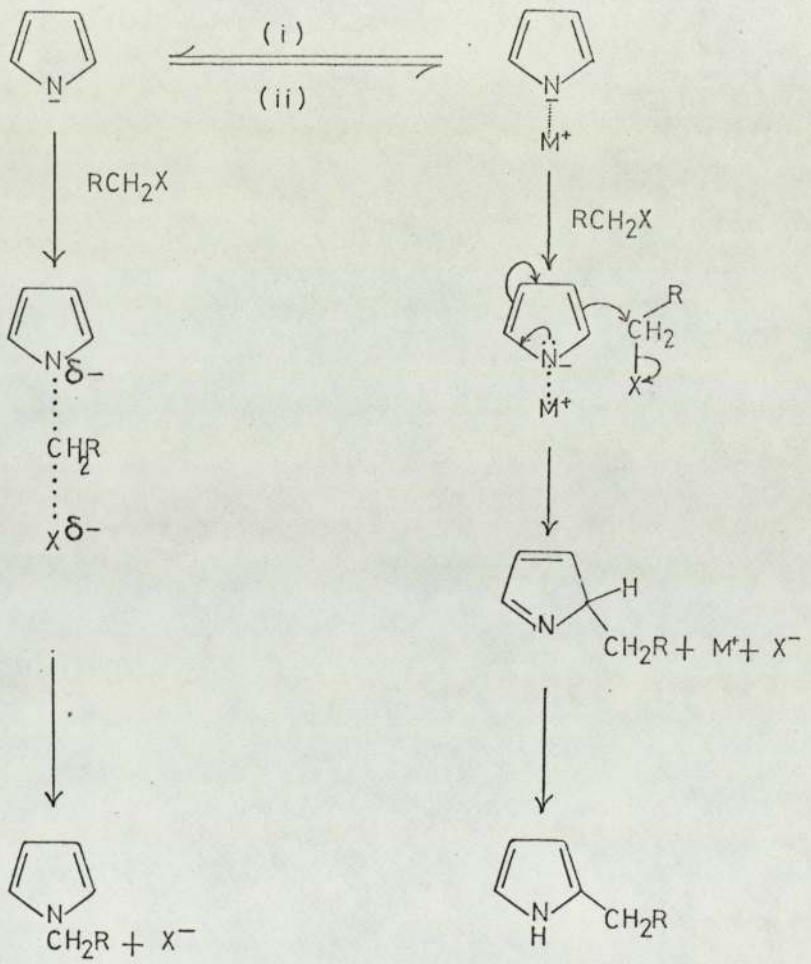
(a) Alkali metal salts.

The reaction of alkali metal salts of pyrrole with alkyl halides usually gives 1-alkylpyrroles. Although 1-alkylation does occur with potassium salts and methyl iodide[49] or dimethyl sulphate,[50] with higher alkyl halides the situation is confused. With ethyl iodide and potassium salts, 1-ethylpyrrole is obtained together with some 2- and 1,2-diethylpyrrole[51]

The situation has been clarified to some extent by work on the alkenylation of pyrrole.[52] In these experiments lithium, sodium and potassium pyrrole were treated with allyl, crotyl and benzyl halides in the presence of different solvents. Mixtures of 1- and 2-substituted pyrroles were obtained with traces of 3-substituted pyrrole. It was found that the nature of the solvent and cation employed had a considerable influence on the products obtained. The following conclusions were drawn:

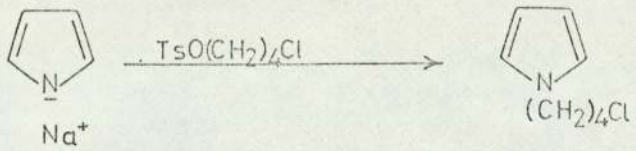
1. For a particular cation, the most polar solvent gave the greatest proportion of N-substituted product.
2. For a given solvent the proportion of N-substitution depended on the cation in the order $Li^+ < Na^+ < K^+ < Me_3\overset{+}{N}Ph$
3. For potassium pyrrole, the proportion of N-substitution increased with increasing solubility of the salt in the solvent employed.

It was suggested that dissociation (i) of the pyrrole salt in the solvent would favour N-substitution whilst ionic association (ii) favoured C-substitution. It can be seen from Figure 2 that dialkylated products could arise from the 2-substituted product (53) but not from the 1-substituted product (52).



(52) Figure 2 (53)

Tosylate salts are useful in the preparation of 1-alkyl derivatives of pyrrole. The original procedure[53] has recently been improved by Collington and Jones.[54] Sodium pyrrolide was reacted with 4-tolylsulphonyloxybutyl chloride to give the N-chlorobutylpyrrole (54) in good yield.



(54)

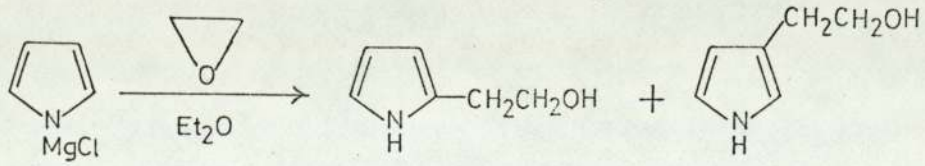
A comparison of the ability of allyl tosylate and allyl bromide to alkylate the alkali metal salts of pyrrole has been carried out.[55] When allyl tosylate was reacted with potassium pyrrole in dimethylsulphoxide the relative proportion of the 1-allylpyrrole produced increased from 89% to 99%, compared to allyl bromide. This experiment demonstrates that good leaving groups, like tosylate, favour N-substitution.

Ethylene oxide has been reacted with potassium pyrrole to give 1-(2-hydroxyethyl)pyrrole in moderate yield.[56]

(b) Pyrryl magnesium halides.

The alkylation of pyrryl magnesium halides leads almost exclusively to C-substituted products.[57] Both 2- and 3-alkylpyrroles are produced by the reaction of pyrryl magnesium bromide with alkyl halides.

The reaction of pyrryl magnesium chloride with ethylene oxide has been reported recently[58] to give the 2- and 3-(2-hydroxyethyl)pyrrole, (55) and (56) respectively. When the reaction was performed in ether the product ratio of (55):(56) was 1:3. With tetrahydrofuran as solvent the sole product was the pyrrole (56).



(55) (56)

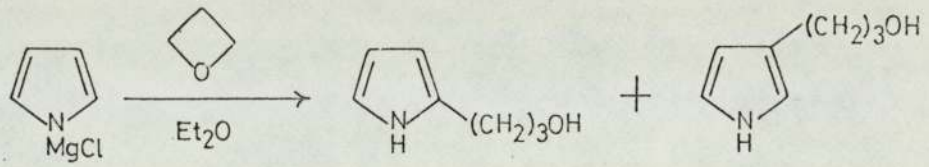
An explanation was given in terms of the relative solvating powers of the ethers :

$$4\text{-} > 5\text{-} > 6\text{-} > \text{3-membered ring} > Et_2O$$ [59]

Ether molecules will complex with the magnesium and sterically hinder the 2-position. Ethylene oxide, having a stronger solvating power, will displace the ether molecules from the magnesium and then react at the 2-position to give the pyrrole (55). The formation of the pyrrole (56) proceeds without any steric hindrance.

The stronger solvent tetrahydrofuran will not be displaced from its magnesium complex and so pyrrole (56) will be formed exclusively.

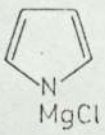
The reaction of pyrryl magnesium chloride with trimethylene oxide leads to the formation of 2-(3-propan-1-ol)pyrrole (57) and 3-(3-propan-1-ol)pyrrole (58) in the ratio 4:1. [60]



(57) (58)

Trimethylene oxide, being the strongest solvent among the ethers, will complex preferentially to the magnesium leading to a greater proportion of the 2-substituted pyrrole (57).

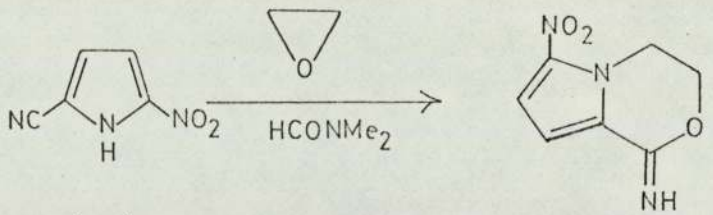
N.m.r. studies [61] on pyrryl magnesium chloride, in ether, have shown that it has the structure (59). An ionic structure, though not highly dissociated, can also be postulated. In this case the mainly C-substitution reactions can be explained in similar terms as the alkenylation reactions of the alkali metal salts of pyrrole.



(59)

(c) Direct alkylation.

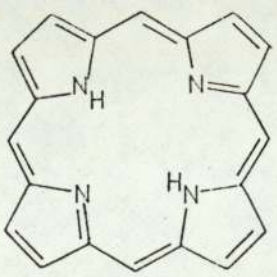
A suitably substituted pyrrole (60) has been reacted with ethylene oxide to give the pyrrolooxazine (61) directly.[62]



(60) (61)

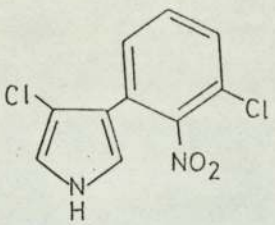
2. Biological properties of some related pyrroles.

The porphyrin ring system (62) consists of a fully conjugated cyclic structure of four pyrrole rings linked together through their 2- and 5-positions by four methine bridges. It is found in several important natural products, notably, haemoglobin, chlorophyll, and vitamin B_{12}. The chemistry of porphyrins has recently been reviewed.[63]



(62)

A few monopyrrole compounds which possess antibiotic activity have been isolated from natural sources. Pyrrolonitrin (63) is used clinically in Japan as an antifungal agent and was isolated from Pseudomonas cultures.[64] Pyoluteorin (64) is produced by a certain strain of Pseudomonas aeruginosa.[65] The antibacterial, bromine rich pyrrole (65) has been isolated from a marine bacterium.[66,67]



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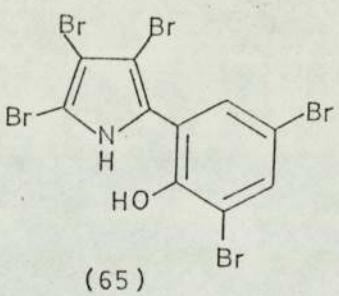

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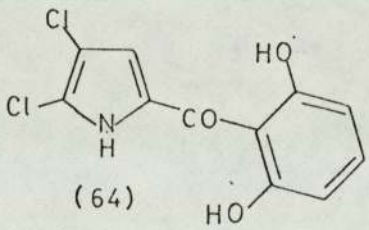
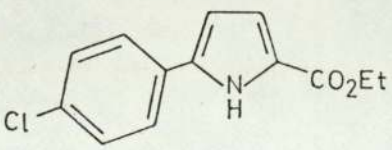


(64)

Recent Japanese[68] and German[69] patents have listed the synthetic pyrroles (66 and 67) respectively, as useful antibacterial and antiprotozoal compounds.



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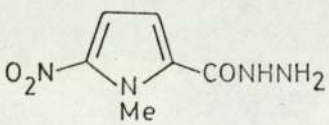
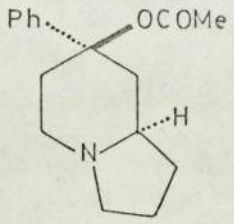


(67)

The potential analgesic activity of some bridgehead nitrogen compounds has been investigated but 7-acetoxy-7-phenylindolizidine (68) was found to be inactive.[70]



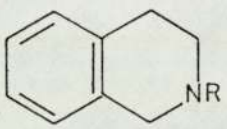
(68)

DISCUSSION

A. SYNTHESIS OF SOME TETRAHYDROISOQUINOLINE, PHENYLPIPERAZINE, AND DIPHENYLMETHYLPIPERIDINE DERIVATIVES.

1. Tetrahydroisoquinoline.

2-Cyclopropylmethyl-1,2,3,4-tetrahydroisoquinoline (69) was obtained in good yield by the reaction of 1,2,3,4-tetrahydroisoquinoline with cyclopropanecarboxylic acid chloride in benzene. The infrared spectrum of the intermediate amide showed the characteristic carbonyl absorption at 1640 cm.$^{-1}$ The known conjugating ability of the cyclopropane ring with suitably constituted carbonyl groups[22] is partly responsible for the absorption figure being towards the lower limit of the normally quoted range (1680 - 1630 cm.$^{-1}$).[71] The amide was reduced with lithium aluminium hydride in ether to give 2-cyclopropylmethyl-1,2,3,4-tetrahydroisoquinoline (69) which was characterised as the hydrochloride. Although cyclopropanes may undergo hydrogenolysis under certain conditions, the ring is normally stable to metal hydride reductions[72,73] and was observed as a strong absorption at 1020 cm.$^{-1}$ in the infrared spectrum[74] of the amine hydrochloride (69).



(69) R = CH_2-c-C_3H_5

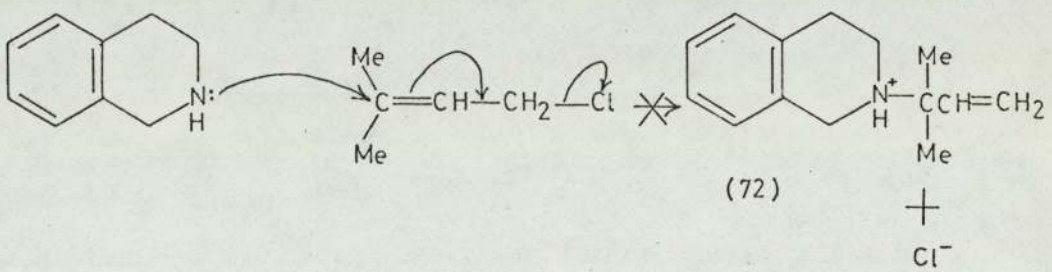
(70) R = CH_2-c-C_4H_7

(71) R = $CH_2CH{=}CMe_2$

2-Cyclobutylmethyl-1,2,3,4-tetrahydroisoquinoline (70) was prepared from 1,2,3,4-tetrahydroisoquinoline and cyclobutanecarboxylic acid chloride. The intermediate amide showed the carbonyl absorption at 1650 cm.$^{-1}$ indicating the lack of any conjugation with the cyclobutane ring. Reduction of the amide with lithium aluminium hydride gave 2-cyclobutylmethyl-1,2,3,4-tetrahydroisoquinoline (70) which was

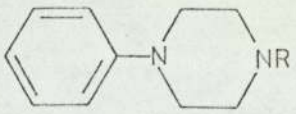
characterised as the hydrochloride. The infrared spectrum of the amine hydrochloride (70) showed an absorption at 930 cm.$^{-1}$ which was probably due to the presence of the cyclobutane ring.[75]

2-(3,3-Dimethylallyl)-1,2,3,4-tetrahydroisoquinoline (71) was prepared in good yield by the reaction of 1,2,3,4-tetrahydroisoquinoline and 1-chloro-3-methyl-2-butene in dimethylformamide using sodium bicarbonate as base.[21,76] The reaction performed in dimethylformamide gave better yields than were obtained when either benzene or toluene was used. The infrared spectrum of the amine hydrochloride (71) showed the typical allyl (C:C) absorption at 1680 cm.$^{-1}$ The nm.r. spectrum of the amine (71) was consistent with the assigned structure and the possibility of nucleophilic substitution having occurred <u>via</u> an S_N2' producing the isomeric amine (72) was ruled out. The steric hindrance afforded by the geminal methyl groups must effectively block the approach of the amine.



2. <u>Phenylpiperazine</u>.

1-Cyclopropylcarbonyl-4-phenylpiperazine (73) was prepared in good yield from the reaction of 1-phenylpiperazine and cyclopropanecarboxylic acid chloride in benzene. The infrared spectrum of the amide hydrochloride (73) showed a typical carbonyl absorption at 1625 cm.$^{-1}$ and the cyclopropane skeletal stretch at 1020 cm.$^{-1}$



(73) R = CO-c-C_3H_5

(74) R = CH_2-c-C_3H_5

(75) R = CO-c-C_4H_7

(76) R = CH_2-c-C_4H_7

Reduction of the amide (73) with lithium aluminium hydride in ether gave 1-cyclopropylmethyl-4-phenylpiperazine (74) which showed the cyclopropane skeletal stretch at 1030 $cm.^{-1}$ in the infrared spectrum of the dihydrochloride salt.

1-Cyclobutylcarbonyl-4-phenylpiperazine (75) was obtained from the reaction of 1-phenylpiperazine and cyclobutanecarboxylic acid chloride. The infrared spectrum of the amide (75) showed the characteristic carbonyl absorption at 1620 $cm.^{-1}$ and the cyclobutane skeletal stretch at 910 $cm.^{-1}$

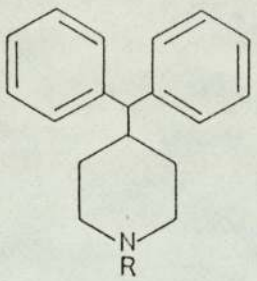
The amide (75) was reduced with lithium aluminium hydride to give 1-cyclobutylmethyl-4-phenylpiperazine (76) which was characterised as the hydrochloride and showed the cyclobutane skeletal stretch at 930 $cm.^{-1}$ in the infrared spectrum.

The reaction of 1-(o-chlorophenyl)piperazine and cyclopropanecarboxylic acid chloride yielded 1-(o-chlorophenyl)-4-cyclopropylcarbonylpiperazine (77) which showed in the infrared spectrum the carbonyl absorption at 1630 $cm.^{-1}$ and the cyclopropane skeletal stretch at 1020 $cm.^{-1}$

3. Diphenylmethylpiperidine.

1-Cyclobutylcarbonyl-4-diphenylmethylpiperidine (79) was obtained in good yield from the reaction of 4-diphenylmethylpiperidine and cyclobutanecarboxylic acid chloride in benzene. The infrared spectrum of the product showed a typical carbonyl absorption at 1630 $cm.^{-1}$

The amide (79) was reduced with lithium aluminium hydride in ether to give 1-cyclobutylmethyl-4-diphenylmethylpiperidine (80) in good yield, which was characterised as the hydrochloride. The infrared spectrum of the product showed an absorption at 930 $cm.^{-1}$ which indicated the presence of the cyclobutane ring.



(78) R = H

(79) R = CO-c-C_4H_7

(80) R = CH_2-c-C_4H_7

(81) R = CH_2-c-C_3H_5

(82) R = CO·C·Me_3

(83) R = CH_2·C·Me_3

(84) R = $(CH_2)_3$CO-4-FC_6H_4

1-Cyclopropylmethyl-4-diphenylmethylpiperidine (81) was obtained from the reaction of 4-diphenylmethylpiperidine and cyclopropanecarboxylic acid chloride. The intermediate amide, which showed the carbonyl absorption at 1630 $cm.^{-1}$ in the infrared spectrum, was reduced with lithium aluminium hydride to give 1-cyclopropylmethyl-4-diphenylmethylpiperidine (81). The cyclopropane skeletal stretch was seen at 1030 $cm.^{-1}$ in the infrared spectrum of the amine hydrochloride.

4-Diphenylmethyl-1-trimethylacetylpiperidine (82) was prepared by the reaction of 4-diphenylmethylpiperidine and trimethylacetyl chloride. The amide (82), which showed the carbonyl absorption at 1620 $cm.^{-1}$ in the infrared spectrum, was reduced with lithium aluminium hydride to give 4-diphenylmethyl-1-neopentylpiperidine (83) which was characterised as the hydrochloride.

The alkylation of 4-diphenylmethylpiperidine with 4-chloro-4'-

fluorobutyrophenone was accomplished by means of the three stage reaction indicated in Figure 3.

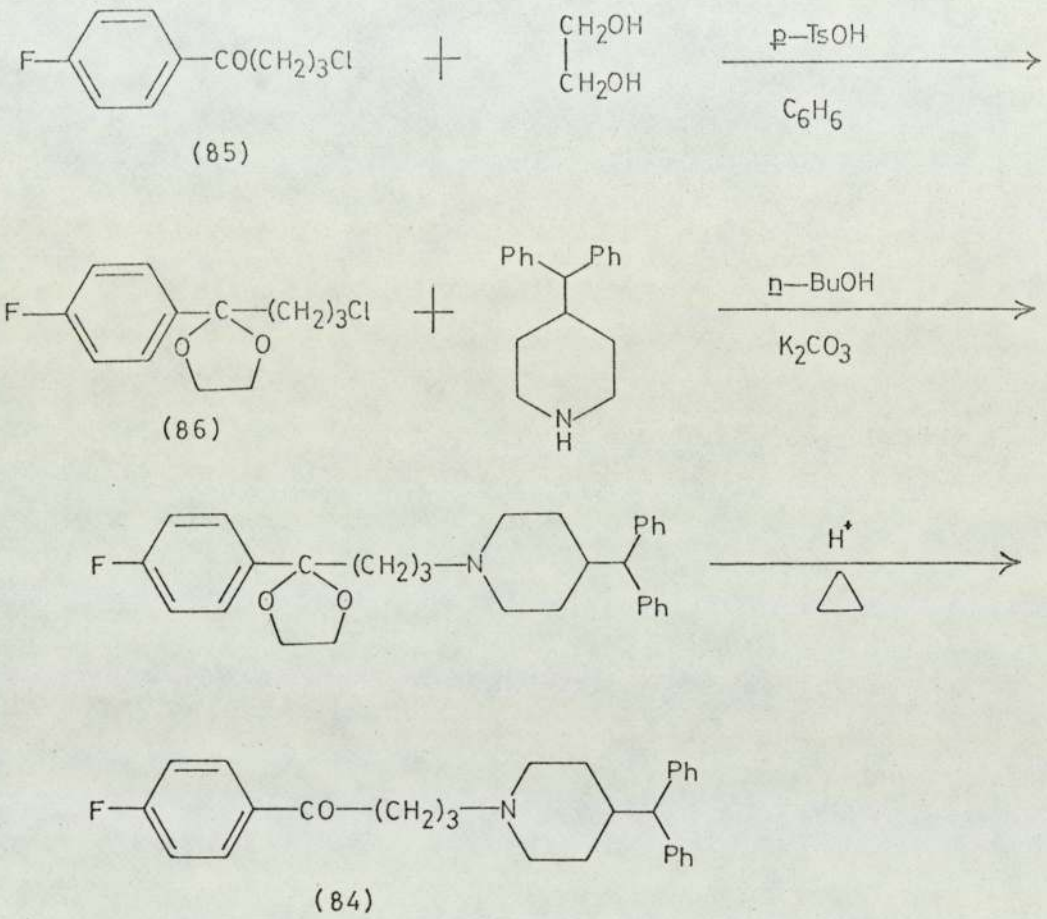


Figure 3

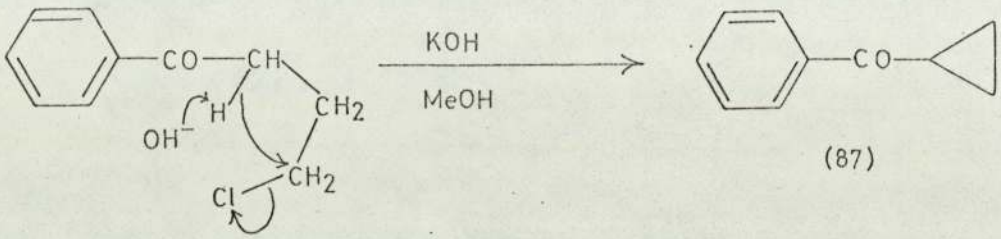
The ethylene ketal [2-(3-chloropropyl)-2-(4-fluorophenyl)-1,3-dioxolane, 86][77] was obtained from the reaction of 4-chloro-4'-fluorobutyrophenone (85) and ethane-1,2-diol in the presence of p-toluenesulphonic acid.[78]

Reaction of the ethylene ketal (86) with 4-diphenylmethylpiperidine followed by acid hydrolysis gave 4-(4-diphenylmethylpiperid-1-yl)-4'-fluorobutyrophenone (84) which showed the typical carbonyl absorption at 1680 cm.$^{-1}$ in the infrared spectrum.

Welstead et al[79] found that deactivation of the butyrophenone (85) by ketal formation considerably reduces the occurrence of two side

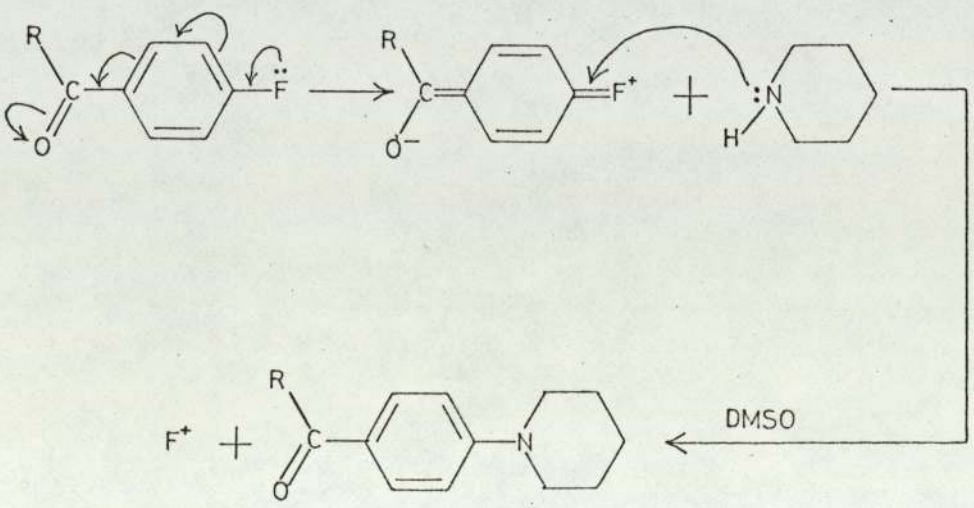
reactions, namely, cyclopropane formation and nucleophilic displacement of the fluoride ion from the aromatic ring by an amine.

Close[80] found that 4-chlorobutyrophenone was susceptible to γ-elimination under basic conditions forming cyclopropylphenyl ketone (87).



(87)

Nucleophilic displacement of a fluoride ion from an activated aromatic ring by an amine has been found to occur quite readily in polar aprotic solvents such as dimethylsulphoxide (DMSO) and dimethylformamide.[81] The piperidylacetophenone (88, R=Me) has been obtained in good yield from this reaction.[81] The accepted mechanism for aromatic bimolecular substitution is as follows:[82]



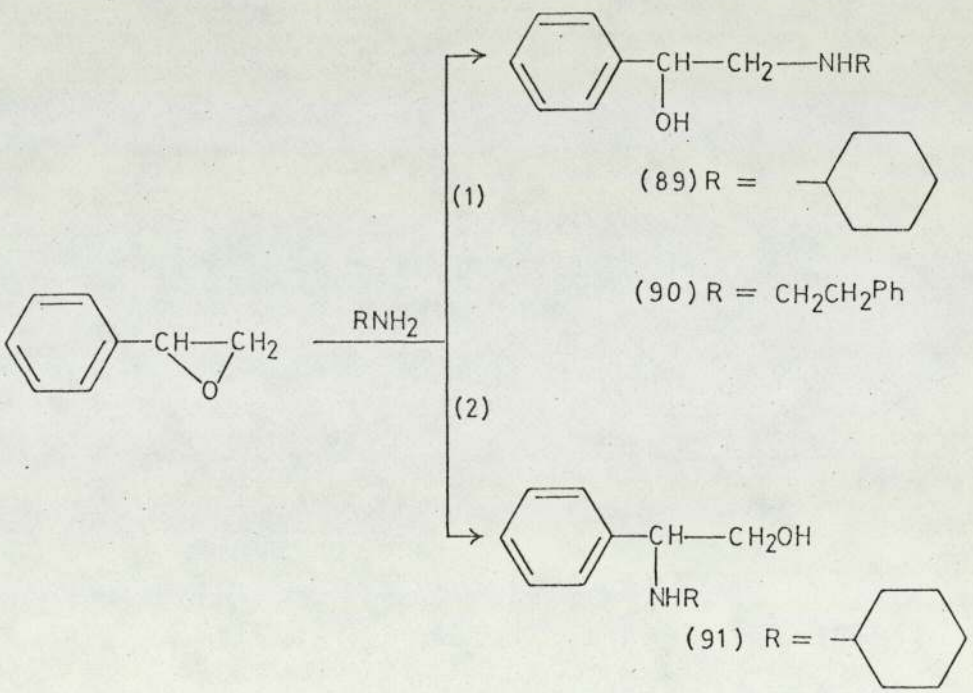
(88) R = Me, Et

B. SYNTHESIS OF SOME β-PHENYLETHANOLAMINE DERIVATIVES.

1. β-Amino alcohols and acylated derivatives.

(a) Synthesis of β-amino alcohols.

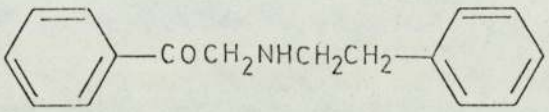
A convenient one-step synthesis of β-amino alcohols is via the cleavage of an epoxide ring by an amine. Krassusky's[83,84] original notation, later restated by Chapman and coworkers,[85,86] is adopted whereby attack of the amine at the terminal, β-carbon atom of a monosubstituted epoxide is referred to as "normal" (route 1), whilst attack at the α-carbon atom is termed "abnormal" (route 2). The β-amino alcohols (89 and 90), obtained from the reaction of styrene oxide with cyclohexylamine and phenethylamine respectively, were used as the basis for the preparation of various cyclic and non-cyclic derivatives.



2-Cyclohexylamino-1-phenylethanol (89) has been prepared by various workers[87,88] from styrene oxide and cyclohexylamine using vigorous conditions. It was found however, that styrene oxide and

cyclohexylamine would react at room temperature giving the amino alcohol (89) in good yield. The product was identical with that obtained commercially, showing in the infrared spectrum the characteristic secondary alcohol (C·OH) stretch at 1120 cm.$^{-1}$ No evidence was found for the production, via abnormal attack, of the isomeric amino alcohol (91) although benzylamine and styrene oxide under similar conditions have been found to produce small quantities of abnormal product.[89]

The reaction of phenethylamine and styrene oxide gave 2-phenethylamino-1-phenylethanol (90), via normal attack, which had identical physical characteristics to that obtained by reduction[90] of the amino ketone (92). The n.m.r. spectra of the amino alcohols (89 and 90) were consistent with their assigned structures (see page125).



(92)

No products were isolated which resulted from abnormal fission of the epoxide. Conjugating groups attached directly to the epoxide ring can increase the proportion of abnormal product obtained, but the interplay of these and steric effects resulted in normal products being isolated.[85]

The ease with which an amine can react with an epoxide may be a function of its basic strength (see Table 2). Strong bases such as cyclohexylamine and phenethylamine gave crystalline reaction products with styrene oxide under mild conditions. Cyclopropylamine and aniline, which are weaker bases, failed to produce any crystalline product under similar conditions although workers employing more vigorous conditions

have obtained products.[91,92]

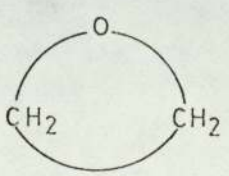
Amine	pKa
Cyclohexylamine[93]	10.66
Phenethylamine[94]	9.83
Cyclopropylamine[95]	8.66
Aniline[93]	4.63

Table 2

(b) Mechanism of epoxide reactions with nucleophilic reagents.

Epoxides, in contrast to noncyclic ethers, are very susceptible to nucleophilic attack, the main reason being the release of a considerable amount (13 kcal./mole) of strain energy on cleavage of the three-membered ring.[96]

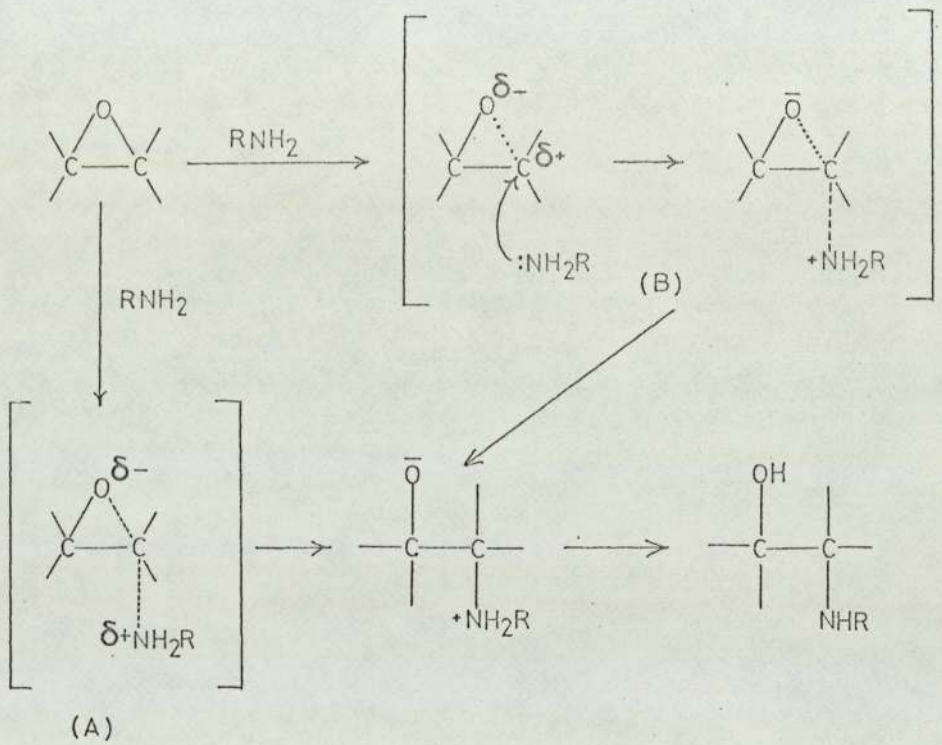
An important theoretical model[97] of ethylene oxide proposes that the C-C hybridisation has an intermediate value between sp^2 and sp^3. The calculated value for the hybridisation state is $sp^{2.22}$ which implies that the atomic orbitals of carbon are not directed along the internuclear axis. The bonds in ethylene oxide can be termed, therefore, "bent bonds", and are represented in formula (93).



(93)

The mechanism of epoxide cleavage by nucleophiles has been the

subject of much discussion. Parker and Isaacs[85] have formulated a mechanism which probably accounts for the majority of epoxide reactions. According to their theory, epoxides may react by two processes, which are of the true S_N2 (A) and of the "borderline S_N2" (B) type respectively.

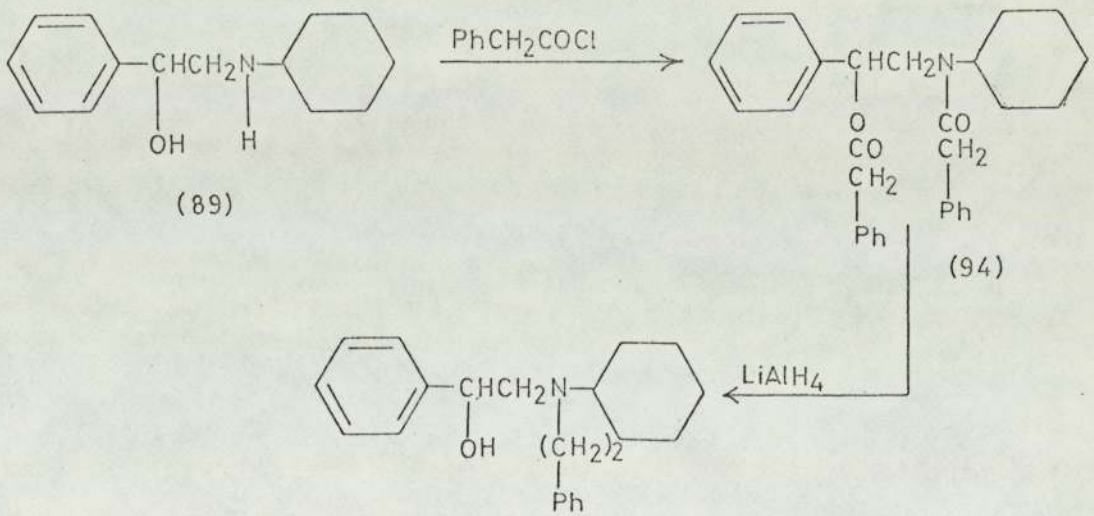


In common with the classical S_N2 mechanism of nucleophilic substitution these processes involve inversion at the point of attack, but they differ however in the relative proportion of bond-forming and bond-breaking in the transition states involved. Thus the transition state (B) involves less bond-forming than does state (A), and therefore more closely resembles a conventional S_N1 transition state. Numerous stereochemical studies demonstrating inversion indicate that a normal carbonium ion is not formed. This information, together with thermodynamic studies, provides a basis for transition state (B) being designated as a "borderline S_N2" transition state. The transition state (A) closely resembles a true S_N2 transition state.

Although inversion of configuration is the main feature of nucleophilic attack on epoxides, in some instances retention of configuration is observed.[98]

(c) Acylated products.

2-Cyclohexylamine-O,N-diphenylacetyl-1-phenylethanol (94) was prepared by the reaction of the amino alcohol (89) and excess phenylacetyl chloride in benzene. Molar quantitites of the acylating reagent resulted in mixtures of O-acylated and N-acylated products. The infrared spectrum of the amide-ester (94) showed the ester (C:O) at 1730 $cm.^{-1}$, and the amide (C:O) at 1620 $cm.^{-1}$



Reduction of the amide-ester (94) with lithium aluminium hydride in ether gave 1-cyclohexyl-1-(2-hydroxy-2-phenylethyl)phenethylamine (95) which was characterised as the hydrochloride.

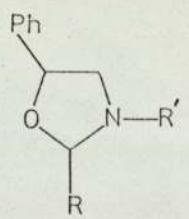
2. Oxazolidines.

(a) Synthesis.

3-Cyclohexyl-5-phenyloxazolidine (96) was obtained in good yield by the reaction of 2-cyclohexylamino-1-phenylethanol (89) and formalin

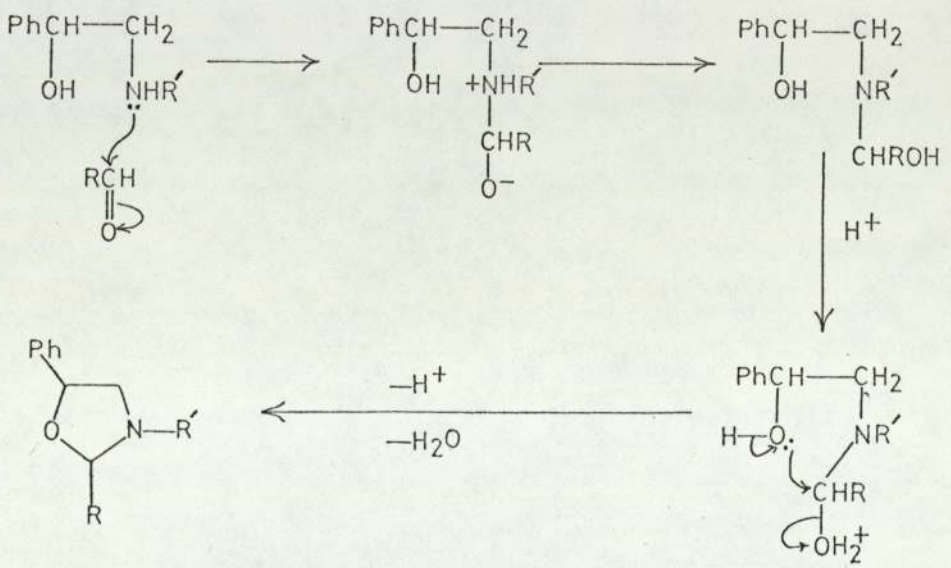
solution.[99] Although oxazolidines are liable to hydrolysis,[100] a stable hydrochloride salt was obtained which showed an absorption at 1120 cm.$^{-1}$ in the infrared spectrum, which was due to the presence of the O·C·N structure. Bergman states that the O·C·N system in the oxazolidine ring is characterised by a triplet of bands in the 1200-1080 cm.$^{-1}$ region.[100]

2-Phenethylamino-1-phenylethanol (90) and formalin solution reacted to give 3-phenethyl-5-phenyloxazolidine (97) which was characterised as the hydrochloride and showed an absorption at 1104 cm.$^{-1}$ in the infrared spectrum due to the O·C·N structure.



(96) R = H; R' = -c-C_6H_{11}
(97) R = H; R' = CH_2CH_2Ph
(98) R = 4-$NO_2C_6H_4$; R' = -c-C_6H_{11}
(99) R = Me; R' = -c-C_6H_{11}
(100) R = Me; R' = CH_2CH_2Ph
(101) R = 4-FC_6H_4; R' = -c-C_6H_{11}

The initial step in the reaction is the attack of the lone pair of electrons of the nitrogen atom onto the electron deficient carbon atom of the aldehyde, as shown below :



The formation of oxazolidines (96 and 97) was achieved without an added catalyst but one was needed when substituted benzaldehydes were used. Although benzaldehyde itself failed to give an oxazolidine, benzaldehydes substituted with electron-withdrawing groups (R = 4-FC_6H_4, 4-$NO_2C_6H_4$) were successfully cyclised in the presence of an acid catalyst. p-Toluenesulphonic acid proved to be effective in the preparation of 3-cyclohexyl-2-(4-nitrophenyl)-5-phenyloxazolidine (98) by the azeotropic distillation of 2-cyclohexylamino-1-phenylethanol and 4-nitrobenzaldehyde in benzene. The oxazolidine (98) was unstable to heat and although it hydrolysed during the attempted preparation of the hydrochloride salt, a stable picrate was obtained.

3-Cyclohexyl-2-(4-fluorophenyl)-5-phenyloxazolidine (101) was prepared by the azeotropic distillation of 4-fluorobenzaldehyde and 2-cyclohexylamino-1-phenylethanol (89) in benzene, in the presence of p-toluenesulphonic acid, and showed an absorption at 1140 $cm.^{-1}$ in the infrared spectrum due to oxazolidine (O·C·N) ring.

Acetaldehyde reacted with the amino alcohols (89 and 90) in ether at room temperature[101] to give 3-cyclohexyl-2-methyl-5-phenyloxazolidine (99) and 2-methyl-3-phenethyl-5-phenyloxazolidine (100) respectively. The infrared spectra of these oxazolidines showed an absorption at 1140 $cm.^{-1}$ due to the oxazolidine (O·C·N) ring. The attempted preparation of hydrochloride salts of 2-substituted oxazolidines resulted in hydrolytic ring opening.[102]

(b) N.m.r. data of the oxazolidines.

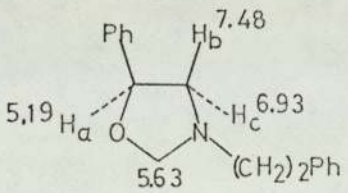
The n.m.r. spectra of the oxazolidines were complicated and in only one case was a full spectral analysis possible. The following conclusions were drawn, however, concerning the chemical shift of the 2-H proton (Table 3).

Oxazolidine	Solvent	Chemical Shift 2-H τ
97	Neat	5.63
98	CCl_4	4.48
99	Neat	5.28
100	Neat	5.78
101	CCl_4	4.63

Table 3.

It can be seen that the presence of electron-withdrawing groups in oxazolidines (98 and 101) resulted in the deshielding of the 2-H proton, the effect being more pronounced with the $4\text{-}NO_2C_6H_4$ group in (98).[103]

A full spectral analysis of 3-phenethyl-5-phenyloxazolidine (97) was possible and is shown in Figure 4.



$J_{b,c} = -10.5Hz$

$J_{a,b} = 7.0$ Hz

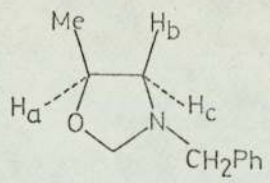
$J_{a,c} = 7.0$ Hz.

Figure 4

The 2-H_2 protons were seen as a singlet at τ 5.63 indicating that the protons were in electrically equivalent environments. The geminal coupling constant (J gem) in X-CH_2 groups is known to be affected by the electronegativity of X(X=N,O),[104,105] and also by the ability of the heteroatom lone pair to overlap with the adjacent CH_2 orbital. The latter effect is at a maximum when the H, H internuclear axis is perpendicular to the C-O-C plane, as exists in the nearly planar oxazolidine ring. Both of these effects produce an algebraic increase in J gem (i.e. becomes more

positive). Cookson and Crabb[104] obtained values for J gem of between -0.8 to -6.0 Hz for the 2-H_2 protons in similar oxazolidines. The wide variation in J gem was due to the changing dihedral angle between the CH_2 group and the lone pairs on adjacent heteroatoms.

The value of $J_{b,c}$ in oxazolidine (97) was -10.5 Hz which compares with a value of -10.6 Hz for the same coupling in 3-benzyl-5-methyloxazolidine (102). In both of these compounds, the 2-H_2 protons appeared as singlets. Nonequivalence of the 2-H_2 protons was only seen in oxazolidines where $J_{b,c}$ was between -8 and -9 Hz.



(102)

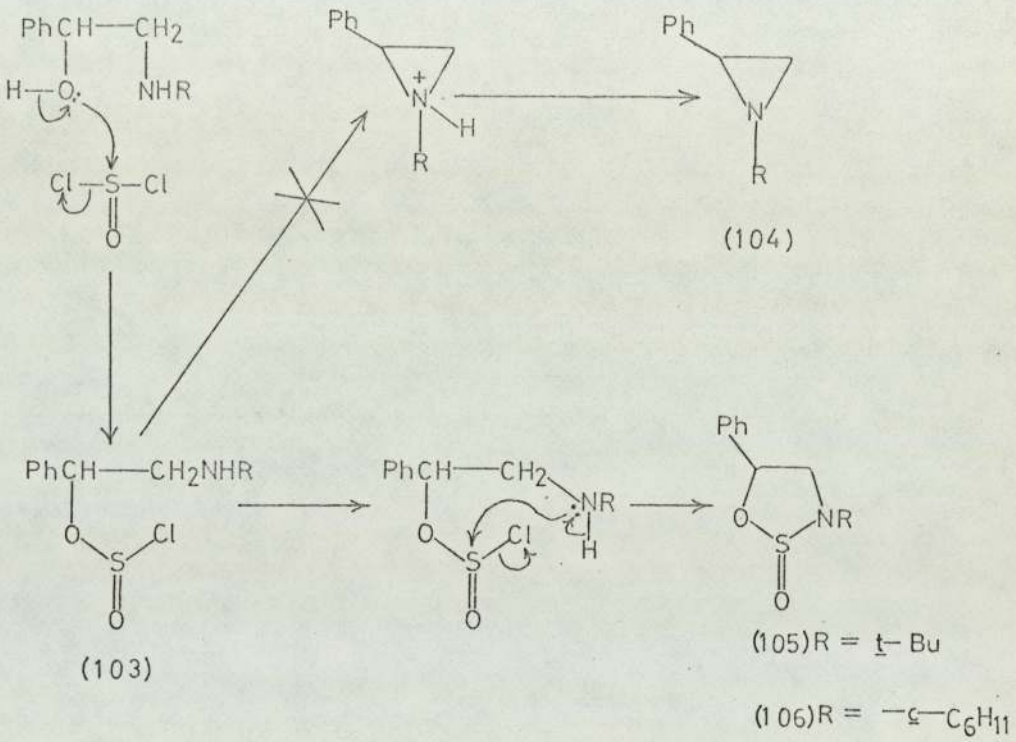
The vicinal coupling constants, $J_{a,b}$ and $J_{a,c}$, in the oxazolidine (97) were idential (7 Hz) which made the assignment of the 4-H2 protons difficult. Calculations have shown, however, that proton H_b, cis-to the phenyl group, will be shielded with respect to proton H_c.[106] Thus proton H_b was assigned at τ 7.48 and proton H_c at τ 6.93.

3. Oxathiazolidinone and Oxazolidinones.

(a) Oxathiazolidinone

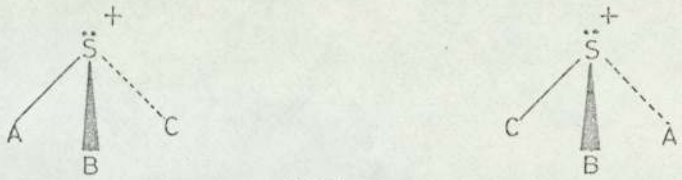
The Gabriel synthesis[107] of aziridines involves the conversion of β-amino alcohols to β-haloamines which then undergo base catalysed cyclisation. Deyrup and Moyer[108] attempted to prepare substituted aziridines by the reaction of β-amino alcohols with thionyl chloride in the presence of base, in the hope that the chlorosulphite ester (103) formed initially, would undergo intramolecular decomposition to give the

aziridine (104). It was found however, that the lone pair of electrons of the nitrogen atom attacked the chlorosulphite ester to give the oxathiazolidinone (105) with the elimination of hydrogen chloride. This novel ring system has recently been reported by other workers.[109,110]

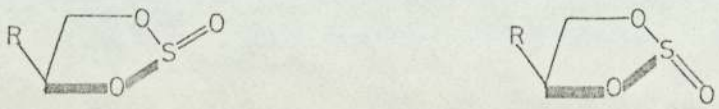


The reaction of 2-cyclohexylamino-1-phenylethanol (89) with thionyl chloride in the presence of triethylamine as base gave 3-cyclohexyl-2-oxo-5-phenyl-1,2,3-oxathiazolidine (106) in low yield. The infrared spectrum of the product showed absorptions at 1140 and 1135 cm.$^{-1}$ due to sulphoxide (S:O)[108] stretching vibrations.

It has been shown that the 2-oxo-1,2,3-oxathiazolidines can exist as geometrical isomers[108] due to the sulphur atom exhibiting configurational stability. This gives rise to enantiomeric forms in the sulphonium ion (107)[111] and geometrical isomers in the cyclic sulphites (108)[108]



(107)



(108)

The 2-oxo-1,2,3-oxathiazolidine (106) was shown by tlc to consist of one major and one minor component and it was possible to assign the substituent geometry by n.m.r. spectroscopy. The sulphoxide bond possesses diamagnetic anisotropy[112,113] which results in the deshielding of ring substituents that are cis- to the bond. The n.m.r. spectrum of the product showed the presence of both isomers in the ratio of five to one. The 5-H proton in the trans-isomer (110) was seen as a small multiplet at τ 4.15 whilst in the predominant cis-isomer (109) the same proton resonated at τ 4.83. The 4-H_2 and 5-H protons had an ABX pattern which was not further resolved.

(109) (110)

3-Cyclohexyl-2-oxo-5-phenyl-1,2,3-oxathiazolidine (106) was unstable to electron impact and the mass spectrum (Figure 5) did not show a molecular ion peak. The largest fragment, m/e 201 (265-SO_2) was accompanied by other fragments at m/e 159 (265-PhCHO) and at m/e 120 (265-$C_6H_{11}NSO$) corresponding to alternative fissions of the molecule.

Four fragmentation pathways from the ion at m/e 201 were seen. The main fragmentation was to the ion at m/e 110 (201-$PhCH_2$) which then gave the cyclohexyl ion at m/e 83 (110-HCN). Further breakdown of this ion gave the base peak of the spectrum at m/e 55 (83-C_2H_4). Loss of a hydrogen atom gave rise to the ion at m/e 200 (201-H).

Other fragments were seen at m/e 158 (201-CH_3-C_2H_4) and m/e 118 (201-C_6H_{11}) due to the partial or total loss of the cyclohexyl group. Further breakdown of the ion at m/e 118 gave rise to the tropylium ion at m/e 91 (118-HCN).

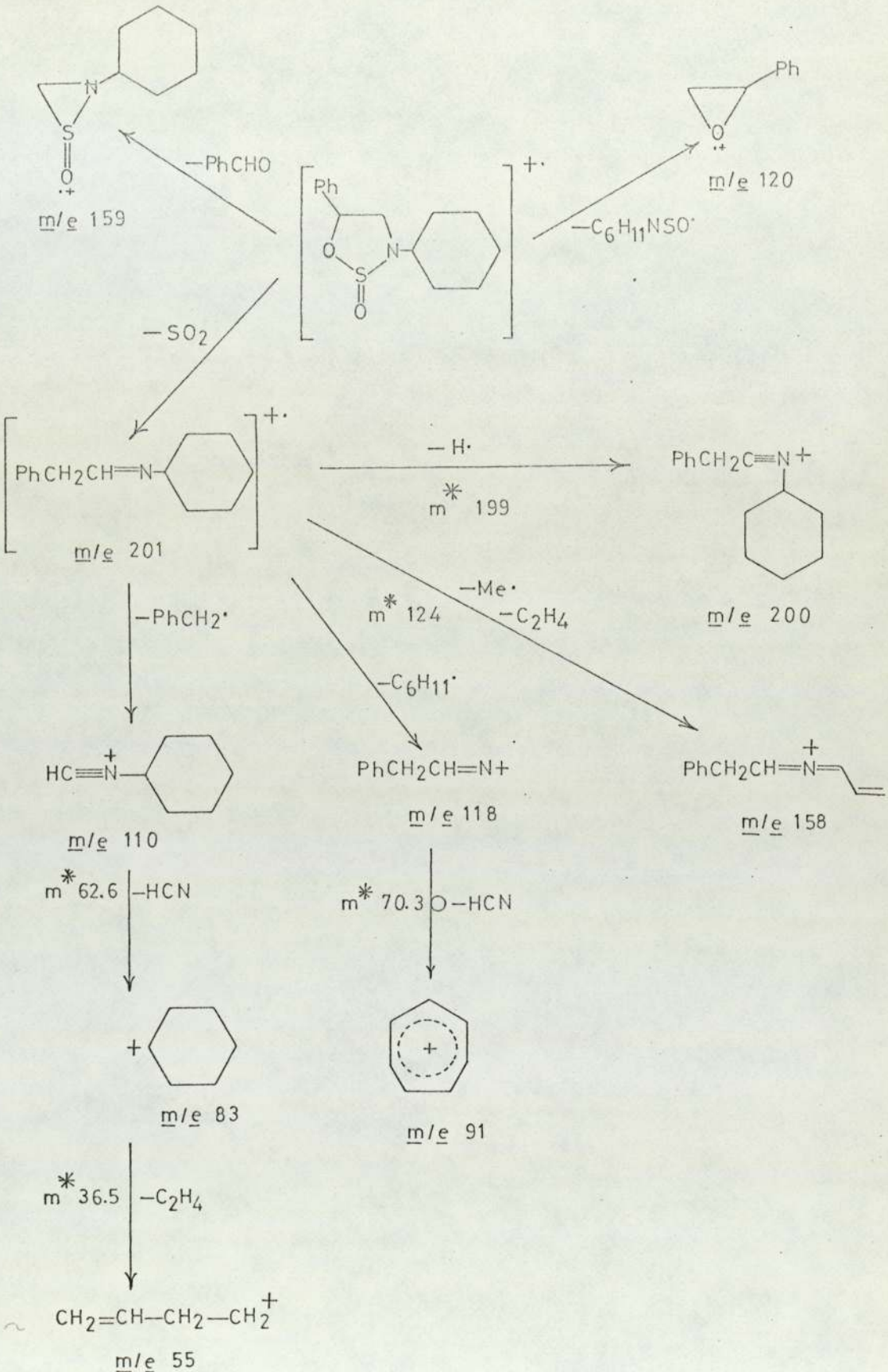
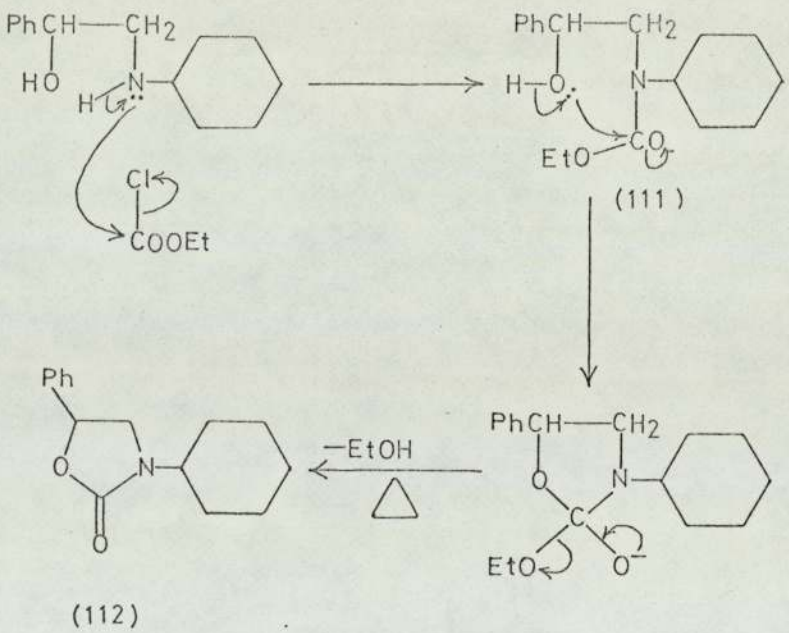

m/e 159
−PhCHO
Ph
+·
m/e 120
−C6H11NSO·
−SO2
PhCH2CH=N
+·
m/e 201
−H·
m* 199
PhCH2C≡N+
m/e 200
−PhCH2·
m* 124
−Me·
−C2H4
−C6H11·
HC≡N+
m/e 110
PhCH2CH=N+
m/e 118
PhCH2CH=N+
m/e 158
m* 62.6
−HCN
m* 70.3
−HCN
m/e 83
m/e 91
m* 36.5
−C2H4
CH2=CH−CH2−CH2+
m/e 55

Figure 5

(b) Oxazolidinones.

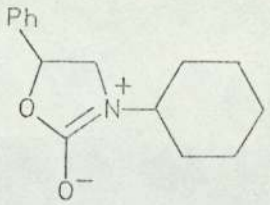
(i) Synthesis.

3-Cyclohexyl-5-phenyloxazolidin-2-one (112) was prepared by the reaction of 2-cyclohexylamino-1-phenylethanol (89) and ethyl chloroformate. The intermediate urethane (111) cyclised on distillation or prolonged heating on an oil bath. The probable mechanism is shown below :



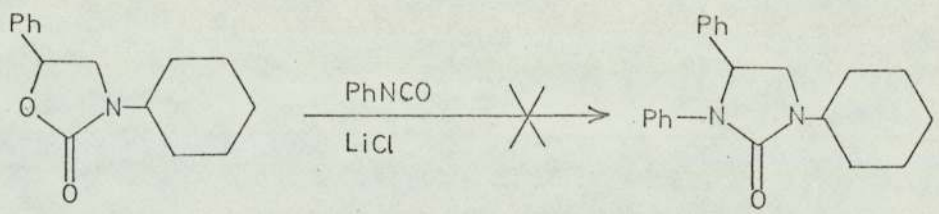
The infrared spectrum of the urethane (111) showed the carbonyl (C:O) absorption at 1680 $cm.^{-1}$ but on cyclisation to the 2-oxazolidinone (112), the absorption moved to a higher frequency at 1740 $cm.^{-1}$ It was possible, therefore, to monitor the thermal cyclisation of the urethane by infrared spectroscopy. The carbonyl absorption of the 2-oxazolidinone (112) was considerably lower than in the corresponding γ-lactone (113),[71] 1780 - 1760 $cm.^{-1}$, probably due to the contribution of the ionic form (114).

(113)



(114)

The reaction of the 2-oxazolidinone (112) with phenyl isocyanate failed to yield any of the expected 2-imidazolidinone (115).[114]



(112) (115)

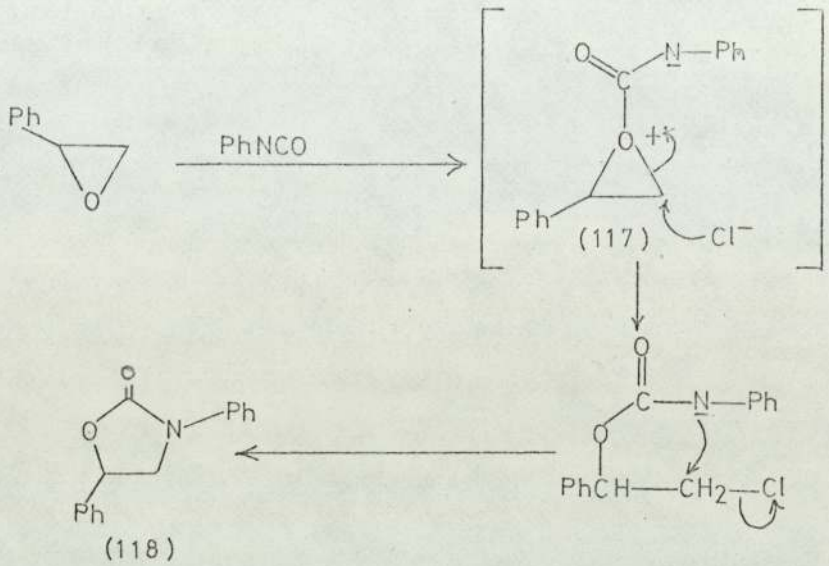
It has been reported that the reaction of monosubstituted epoxides with organic isocyanates yields both the 3,4- and 3,5-isomers although the 3,5-isomer normally predominates.[34] The reaction of phenyl isocyanate and styrene oxide in refluxing dimethylformamide (DMF) gave a mixture of the oxazolidinones (118 and 121). Weiner[115] has shown that aryl isocyanates react with DMF at elevated temperatures to give formamidines (116) but this reaction was suppressed by adding the isocyanate to the epoxide in refluxing DMF.[116]

$$R\text{-}N{=}C{=}O \;+\; Me_2NCH{=}O \longrightarrow R\cdot N{=}CH(NMe)_2 \;+\; CO_2$$

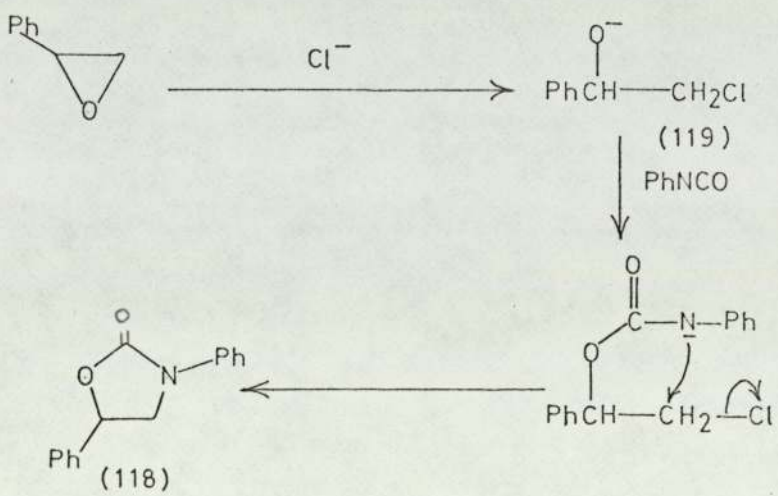
(116)

Two mechanisms have been proposed for the reaction of epoxides with isocyanates. An oxonium ion intermediate (117) may be involved, in a

similar manner to the reaction of carbon dioxide with epoxides:[117]



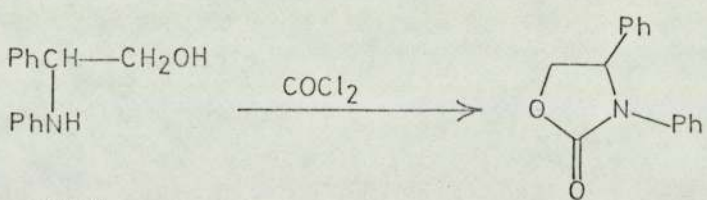
Speranza and Peppel[118] have suggested that the halide ion first opens the epoxide ring and that the resultant β-chloroalkoxide ion (119) attacks the carbon atom of the isocyanate function as shown below :



The production of both the 3,4- and 3,5-isomers can be explained by either mechanism, the product depending only on the direction of ring opening of the epoxide.

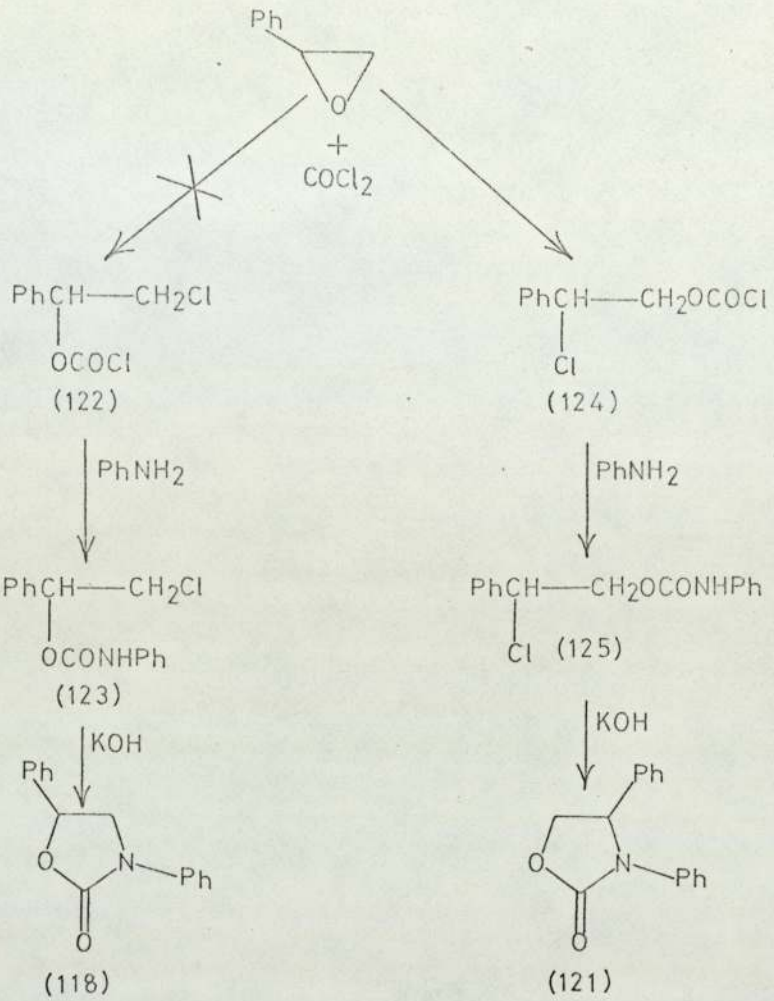
Glc analysis of the product, m.p. 68-70°, from the reaction of phenyl isocyanate and styrene oxide, indicated the presence of two components in the ratio of 3.6 : 1, the major component having the longer retention time. Repeated crystallisation and mechanical separation of the two crystalline forms yielded both the major (m.p. 78-79°) and minor (m.p. 128-129°) components in a pure form.

3,4-Diphenyloxazolidin-2-one (121) (m.p. 129°), has been prepared by an unequivocal synthesis[119] from 2-anilino-2-phenylethanol (120) and phosgene. The minor component was thus identified as the 3,4-isomer (121).

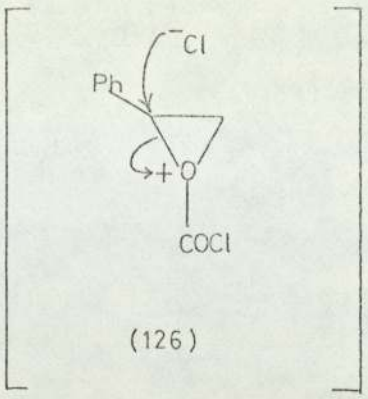


(120) (121)

A claim[120] has also been made for the preparation of 3,5-diphenyloxazolidin-2-one (m.p. 129°). This synthesis, however, is ambiguous and relies upon the ring opening of styrene oxide with phosgene to yield the chloroformate (122). Reaction with aniline and cyclisation of the resulting carbamate (123) was reported to yield the 2-oxazolidinone (118).



This series of reactions has been repeated and compounds with the reported properties were isolated. The n.m.r. spectrum of the chloroformate, however, showed aliphatic absorptions at τ 5.38 (two proton doublet) and τ 4.89 (one proton triplet) and is consistent with the product being 2-chloro-2-phenylethyl chloroformate (124). The two proton quartet in ethyl chloroformate, $CH_3 \cdot \underline{CH_2} \cdot OCOCl$, absorbs at τ 5.61 whereas in ethyl chloride, $CH_3 \cdot \underline{CH_2} \cdot Cl$, the absorption appears at τ 6.43, thus confirming the above assignment. The reaction of the chloroformate (124) and aniline yielded the carbamate (125) which was cyclised to the oxazolidinone with potassium hydroxide. The derived oxazolidinone was shown to be identical to the minor component, known to be the 3,4-isomer (121). The production of the chloroformate (124) from the reaction of styrene oxide and phosgene would suggest that the reaction proceeds <u>via</u> the oxonium intermediate (126).

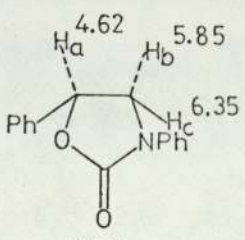


(126)

(ii) N.m.r. data.

The n.m.r. details of the 2-oxazolidinones are shown in Figure 6. The 3,5-isomer (118) and the 3,4-isomer (121) were distinguished by the position of the H_a proton. In the 3,5-isomer, proton H_a was attached to the carbon atom bearing the more electronegative oxygen atom and was thus deshielded with respect to the corresponding proton in the 3,4-isomer. Conversely, protons H_b and H_c in the 3,5-isomer were shielded with respect to the corresponding protons in the 3,4-isomer. Thus the chemical shift difference between the H_a and H_b H_c protons is greater in the 3,5-isomer than in the 3,4-isomer.

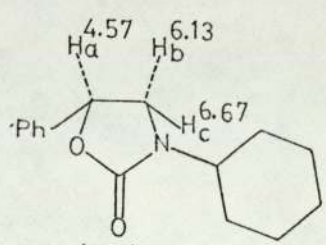
Protons H_b and H_c of 3-cyclohexyl-5-phenyloxazolidin-2-one (112) were shielded with respect to the corresponding protons in 3,5-diphenyloxazolidin-2-one (118) illustrating the deshielding effect of the N-phenyl group.



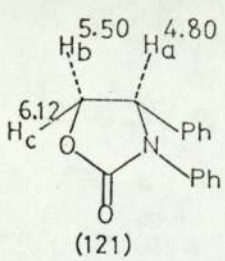
(118)

$J_{a,b} = J_{b,c} = 8.5\,Hz$

$J_{a,c} = 7.5\,Hz$



(112)



(121)

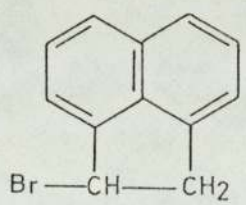
$J_{a,b} = J_{b,c} = 8.5\,Hz$

$J_{a,c} = 6.0\,Hz$

Figure 6

The values of J *cis* and J *gem* (8.5 Hz) were identical in all the 2-oxazolidinones prepared and were in close agreement with reported values.[116] J *trans* was 7.5 Hz in the 3,5-substituted oxazolidin-2-ones and 6.0Hz in 3,4-diphenyloxazolidin-2-one.

Vicinal coupling constants are usually interpreted by referring to the dihedral angle between the C-H bonds, and also the electronegativity of the substituents.[121] Such effects would predict that in a five-membered planar ring the values of J *cis* and J *trans* would be in the ratio of *ca.* 4:1, because the dihedral angles would be 0° (*cis*) and 120° (*trans*). J *cis* and J *trans* in the $CH_2 \cdot CH$. fragment of 1-bromoacenaphthene (127) are, as predicted, 7.4 and 1.9 Hz respectively.[122] In the planar 2-oxazolidinone ring, however, the p-orbitals of the lone pairs of electrons on the heteroatoms can obtain maximum overlap with CH_2 protons and thus contribute towards the CH·CH coupling.



(127)

(iii) *Mass spectra.*

3-Cyclohexyl-5-phenyloxazolidin-2-one

The mass spectrum of 3-cyclohexyl-5-phenyloxazolidin-2-one (112) (Figure 7) showed a strong molecular ion peak at *m/e* 245 (67%) and a base peak at *m/e* 104 (104.062250, C_8H_8). This was in contrast to 3-cyclohexyl-2-oxo-5-phenyl-1,2,3-oxathiazolidine (106) which had a base peak at *m/e* 55.

Three fragmentation pathways from the molecular ion were identified. The main pathway was the fragmentation of the cyclohexyl group to give the

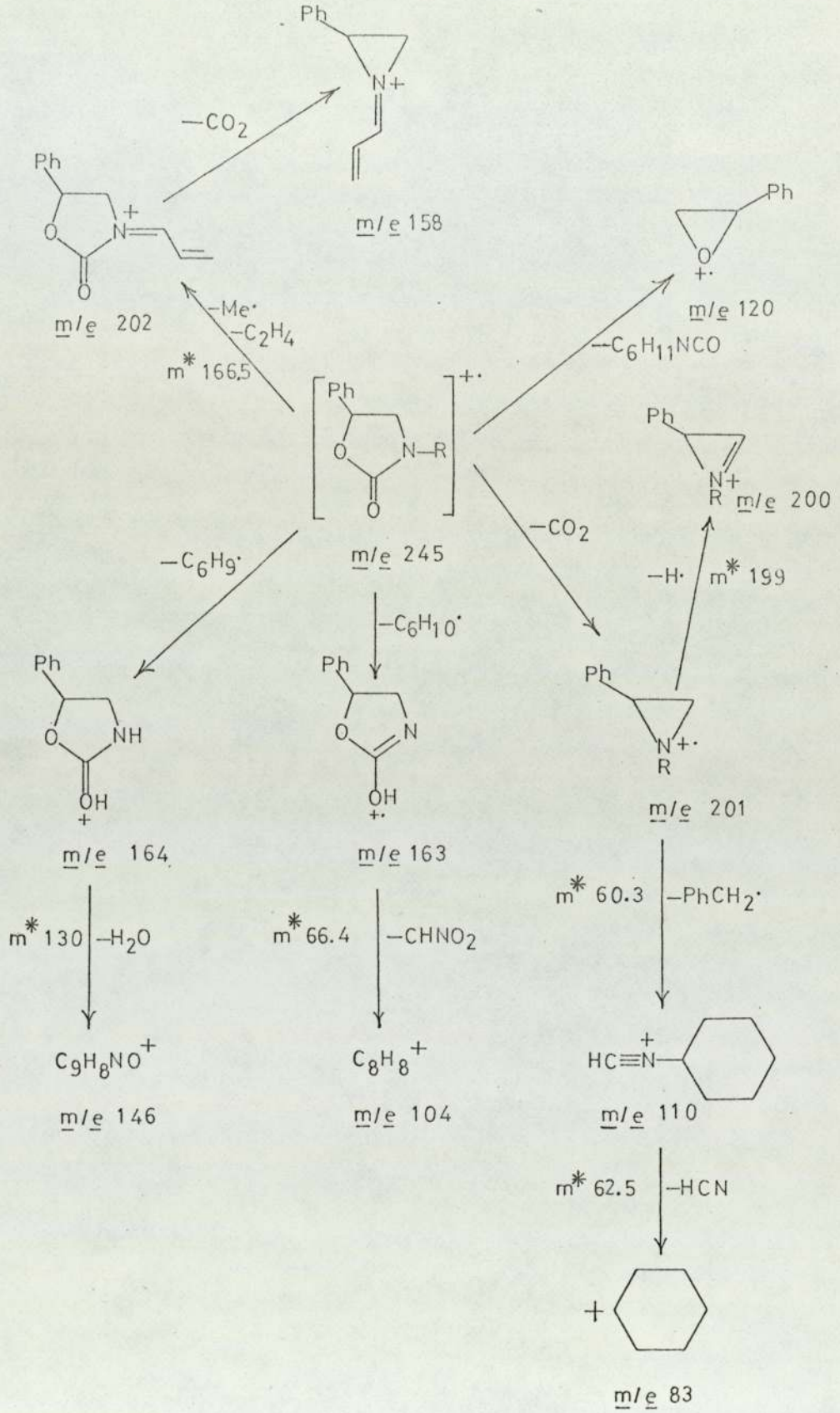
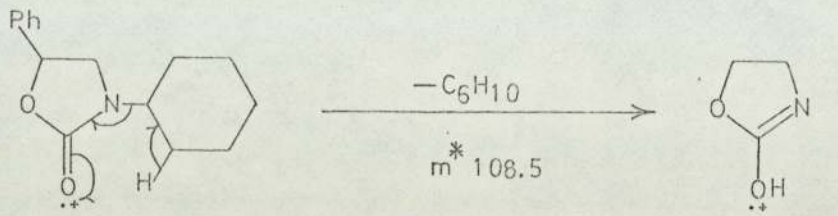


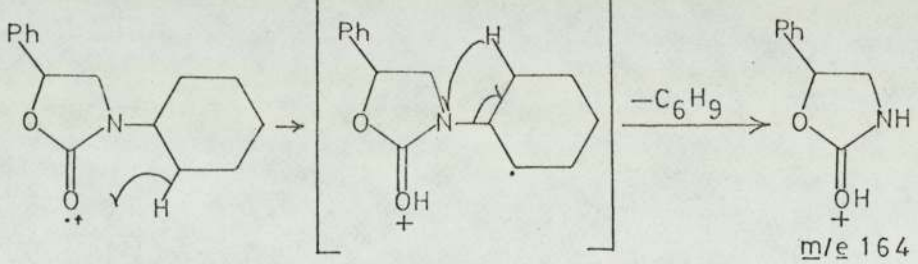
Figure 7 (R = C_6H_{11})

ion at m/e 202 ($M-CH_3-C_2H_4$) which then yielded the ion at m/e 158 ($202-CO_2$). The rearrangement of a hydrogen atom of the cyclohexyl group to the carbonyl function gave the ion at m/e 163 ($M-C_6H_{10}$), which then yielded the base peak at m/e 104 ($163-HCN-O_2$).[123]



m/e 163

A similar rearrangement involving two hydrogen atoms gave rise to the ion at m/e 164 ($M-C_6H_9$) which then yielded the ion at m/e 146 ($164-H_2O$).



m/e 164

Another pathway from the molecular ion gave the aziridine ion at m/e 201 ($M-CO_2$) which gave ions at m/e 200 (201-H) and m/e 110 ($201-PhCH_2$). The latter ion then fragmented to give the cyclohexyl ion at m/e 83 (110-HCN).

A minor route from the molecular ion gave the ion at m/e 120 ($M-C_6H_{11}NCO$).

3,4- and 3,5-Diphenyloxazolidin-2-one

The mass spectral fragmentations of the 3,4- and 3,5-diphenyloxazolidin-2-ones were found to exhibit close similarities (Figure 8) and the base peak in each case was found at m/e 104 (104.049850, C_7H_6N). The routes to this fragment differed, however, and enabled structural assignments to be made.

3,4-Diphenyloxazolidin-2-one (m/e 239) showed three primary decomposition modes initiated by fission β to the ring nitrogen atom. The main fragmentation pathway yielded the ion at m/e 181 (M-HCHO-CO) which gave ions at m/e 180 (181-H) (180.081390, $C_{13}H_{10}N$) and m/e 104 (181-Ph) indicating the 3,4-disposition of substituents. Minor fragments were observed at m/e 238 (M-H), m/e 195 ($M-CO_2$) and m/e 162 (M-Ph).

The 3,5-diphenyl isomer was less stable towards electron impact and the loss of carbon dioxide and hydrogen appeared as a major breakdown pathway m/e 194 (62%). The structure of the 3,5-isomer was confirmed in that no fragments were observed at m/e 162 or m/e 180. The breakdown corresponding to the latter fragmentation gave rise to the base peak at m/e 104 (M-PhCHO-CO-H). Mass measurement of this ion showed it to consist principally of the fragment C_7H_6N (104.049751) together with a minor residue (less than 10%) corresponding to C_8H_8 (104.062250).

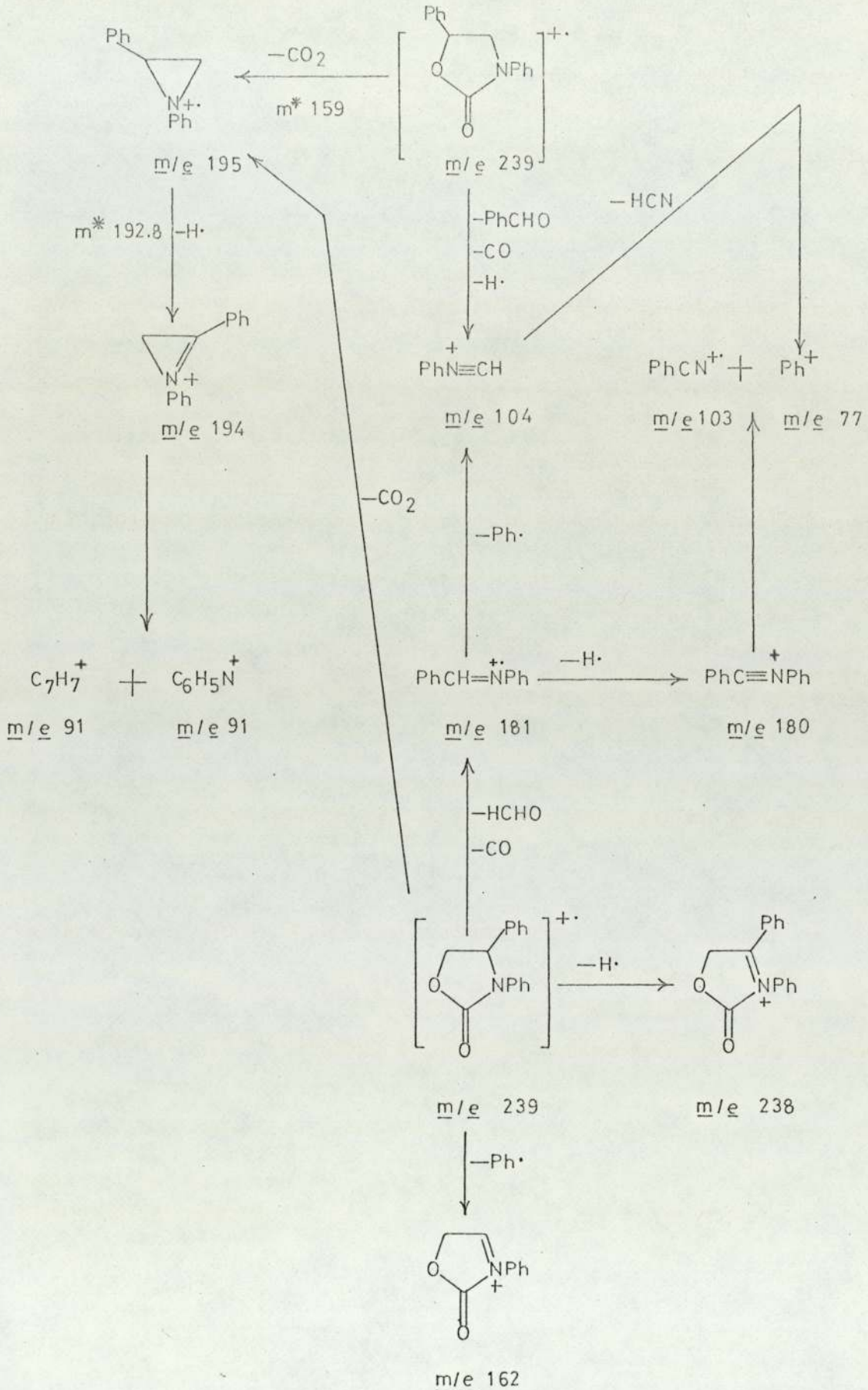
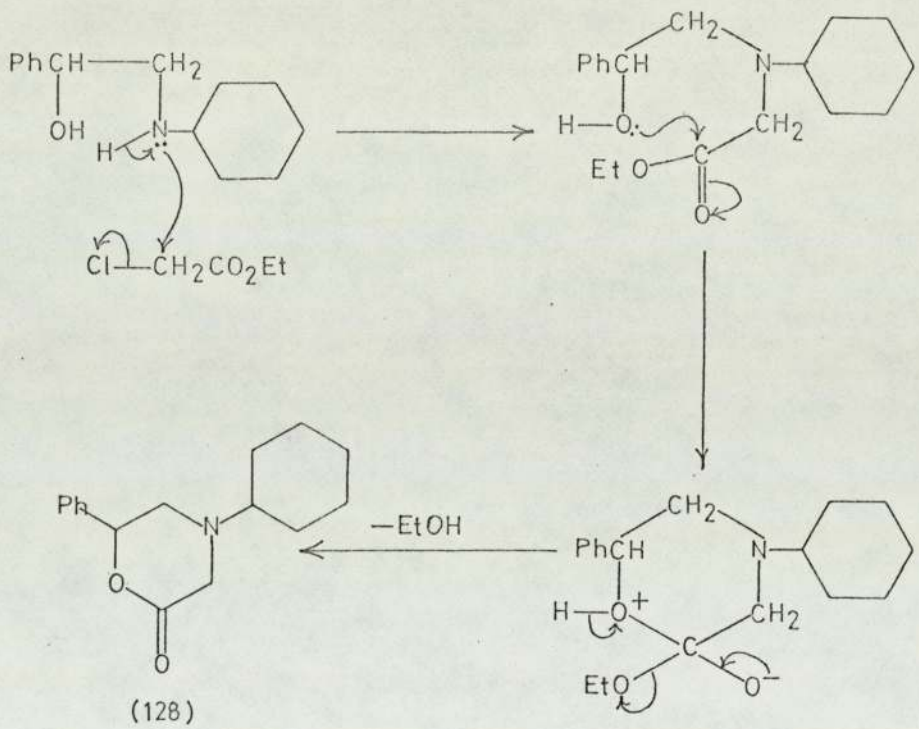

Ph
N+·
Ph
m/e 195
−CO2
m* 159
Ph
O
NPh
O
+·
m/e 239
m* 192.8
−H·
Ph
N+
Ph
m/e 194
−PhCHO
−CO
−H·
−HCN
+
PhN≡CH
m/e 104
PhCN+· + Ph+
m/e 103
m/e 77
−CO2
−Ph·
C7H7+ + C6H5N+
m/e 91
m/e 91
PhCH=NPh+·
m/e 181
−H·
PhC≡NPh+
m/e 180
−HCHO
−CO
−H·
m/e 239
m/e 238
−Ph·
m/e 162

Figure 8

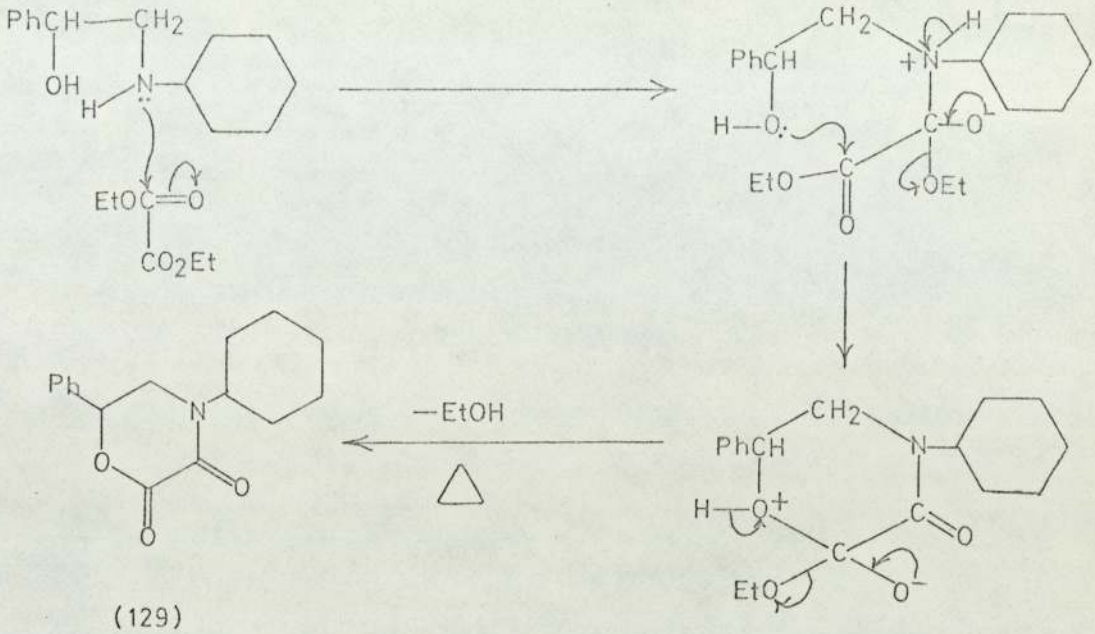
4. Morpholinone and Morpholinedione

(a) Synthesis.

The reaction of 2-cyclohexylamino-1-phenylethanol (89) and ethyl bromoacetate in 1,2-dimethoxyethane gave 4-cyclohexyl-6-phenylmorpholin-2-one (128) which was characterised as the picrate. The infrared spectrum of the picrate showed an absorption at 1740 $cm.^{-1}$ due to the δ-lactone (C:O). The probable mechanism of the reaction is shown below:



The reaction of 2-cyclohexylamino-1-phenylethanol (89) and diethyl oxalate in toluene gave 4-cyclohexyl-6-phenylmorpholine-2,3-dione (129) in good yield.[42] The infrared spectrum of the product showed absorptions at 1745 and 1665 $cm.^{-1}$ due to the lactone and lactam carbonyls respectively. A possible mechanism for the reaction is shown as follows :



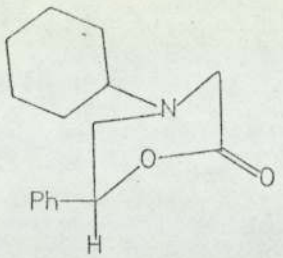
(129)

(b) N.m.r. data

(i) Morpholinone

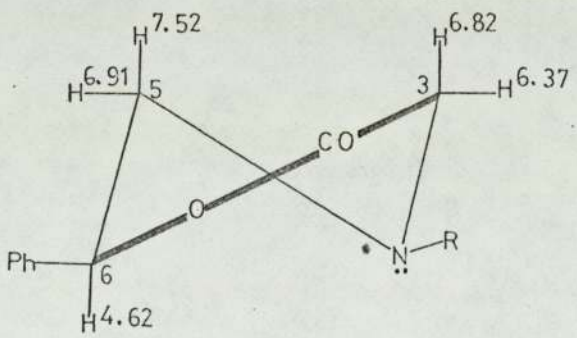
The conformation of δ-lactones has been the subject of much recent work.[124] Workers agree that the C-CO-O-C group has a planar conformation but differ on whether the ring has a boat or a chair conformation. Cahill and Crabb[124] have prepared some morpholin-2-ones and propose that a half-chair conformation explains most adequately the observed n.m.r. values. δ-Lactone carbonyl absorptions in the 1750-1730 $cm.^{-1}$ range have also been reported as indicating half-chair conformations.[125]

The n.m.r. data obtained with 4-cyclohexyl-6-phenylmorpholin-2-one (128) also indicated a half-chair conformation. Although molecular models of the 2-morpholinone (128) adopted the strainless chair conformation (130), electronic effects must stabilise the more strained half-chair conformation (Figure 9).



(130)

The chemical shifts and coupling constants of the 2-morpholinone (128) are shown in Figure 9. The geminal coupling constant (assumed to be negative) for the 3-H_2 protons was -17.0 Hz which showed a decreased coupling relative to values obtained for the methylene protons adjacent to nitrogen in piperidine derivatives (-11 to -14 Hz).[126] A value of -17.0 Hz could only occur if the plane containing the lactone group adopted a conformation that was perpendicular to the H, H axis of the 3-H_2 methylene group.[127] To achieve this stereochemistry whilst maintaining the planarity of the lactone group necessitates the half-chair conformation.



$J_{3ax\ 3eq}$ = -17.0 Hz

$J_{5ax\ 5eq}$ = -12.5 Hz

$J_{5ax\ 6ax}$ = 9.0 Hz

$J_{5eq\ 6ax}$ = 3.5 Hz

$J_{3eq\ 5eq}$ = 1.0 Hz

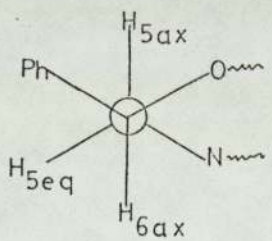
Figure 9. (R = -c-C_6H_{11})

The value of J_{gem} for the 5-H_2 methylene protons was -12.5 Hz which was consistent with a half-chair conformation in which the nitrogen lone pair was axially orientated. An equatorially orientated nitrogen lone pair would have resulted in a decreased value for J_{gem}[128] (see page 64)

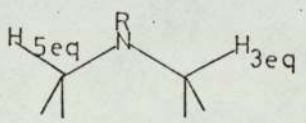
The vicinal coupling constants of 9.0 and 3.5 Hz indicated the projection formula (131), consistent with the proposed half-chair conformation.

The planar W-configuration (132) present in the half-chair conformation was responsible for the long range ^4J coupling of 1.0 Hz between the 3_{eq} and 5_{eq} protons.[129]

The values of J_{vic}, J_{gem}, and $^4J_{3eq\,5eq}$ were consistent with a fixed half-chair conformation in which the phenyl and cyclohexyl groups were equatorially orientated, rather than a system in rapid equilibrium.



(131)



(132)

(ii) Morpholinedione

The n.m.r. spectra of morpholinediones have not previously been reported and the spectrum of 4-cyclohexyl-6-phenylmorpholine-2,3-dione (129) enabled a conformation of this ring system to be proposed.

The spectrum of the 2,3-morpholinedione (129) in deuterochloroform showed a one proton triplet (τ 4.35) and a two proton doublet (τ 6.33) for the 6-H and 5-H_2 protons respectively.

The spectrum obtained in benzene, however, demonstrated the non-equivalence of the 5-H_2 protons and a portion of the spectrum is shown diagramatically in Figure 10a. The spectrum had a complex ABX pattern in which the original triplet was resolved into six lines (X-region) and the doublet into five lines (AB-region). A first order analysis of the spectrum gave the following values;

X-region:

$$\left| J_{AX} + J_{BX} \right| = \text{Line Sep.}^{n}\ 9\text{-}12 = 13.0\ \text{Hz}$$

$$2\ (D_+ - D_-) = \text{Line Sep.}^{n}\ 10\text{-}11 = 3.0\ \text{Hz}$$

$$2\ (D_+ + D_-) = \text{Line Sep.}^{n}\ 14\text{-}15 = 33.0\ \text{Hz}$$

From which $D_- = 7.5$ Hz; $D_+ = 9.0$ Hz

AB-region: Lines 2,4,6 and 8 were identified as an AB quartet in which $J_{AB} = 15.0$ Hz. Lines 3 and 5 of the other quartet were superimposed but lines 1 and 7 were too small to be seen.

Substitution in suitable equations [130,131] gave the following values; $J_{AX} = 11.5$ Hz, $J_{BX} = 1.5$ Hz, $\nu_A = \tau\ 6.32$, $\nu_B = \tau\ 6.4$, and $\nu_X = \tau\ 4.6$ (obtained from spectrum).

Using these values it was possible to calculate the chemical shifts and line intensities of the 5-H_2 and 6-H protons and the spectrum is shown in Figure 10b. The close agreement between the observed and calculated spectra indicates not only that the original line assignments were correct, but also that the calculated coupling constants were accurate. The negative value of J_{AB} did not affect the calculation, and J_{AX} and J_{BX} can be assumed to be positive.[132]

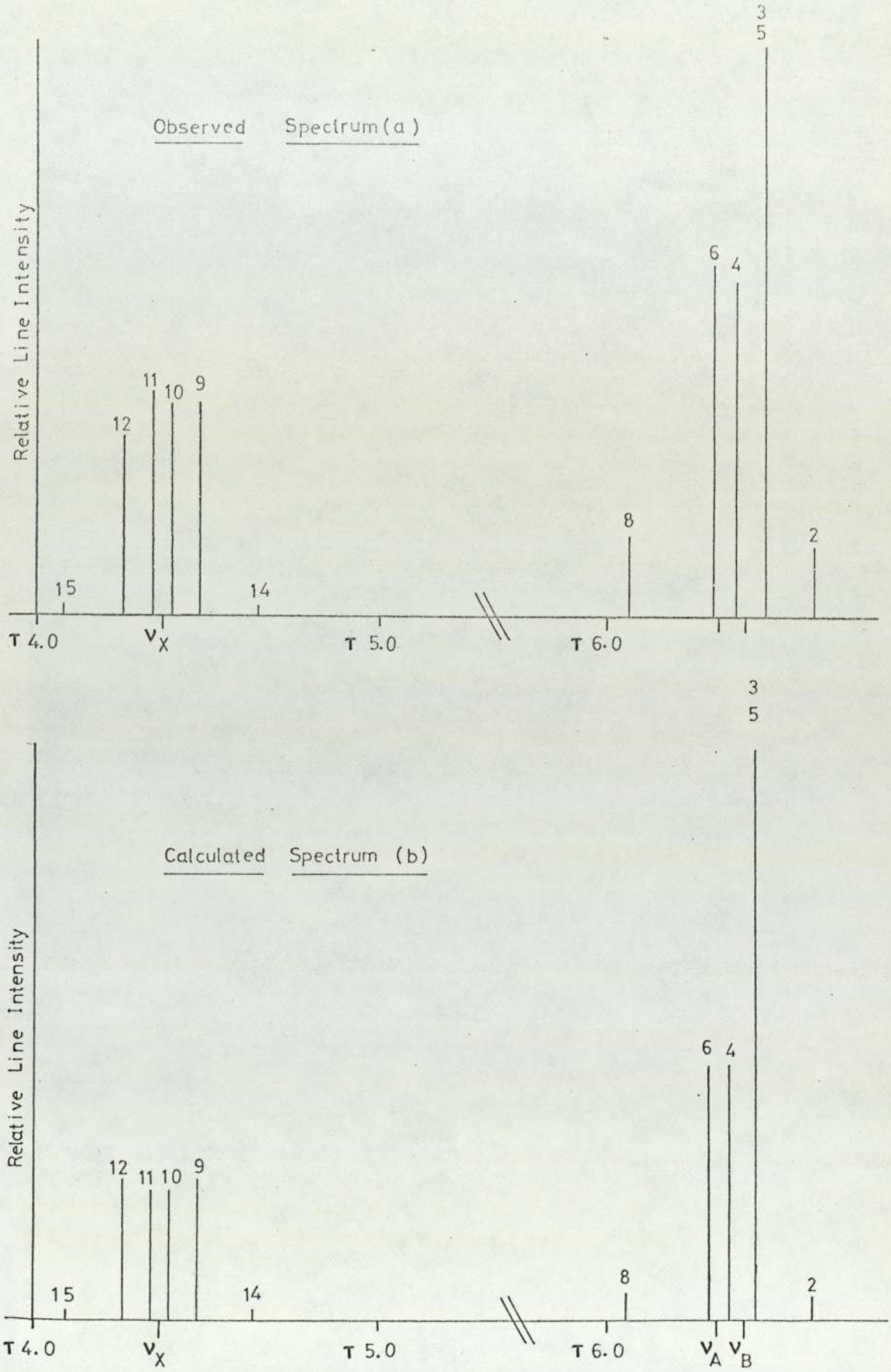
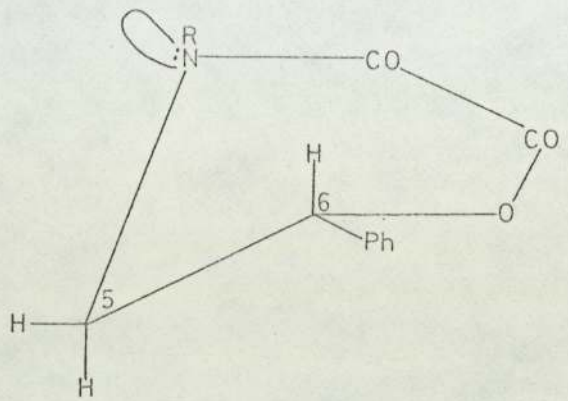

Observed Spectrum (a)
Relative Line Intensity
3
5
6
4
11
10
9
12
8
2
15
14
T 4.0
ν_X
T 5.0
T 6.0
Calculated Spectrum (b)
Relative Line Intensity
3
5
6
4
12
11
10
9
8
2
15
14
T 4.0
ν_X
T 5.0
T 6.0
ν_A
ν_B

Figure 10

The necessity for a planar C-O-CO-C group[124] indicates that the 2,3-morpholinedione (129) would adopt an envelope conformation as shown in Figure 11.



$J_{5ax\,5eq}$ = -15.0 Hz

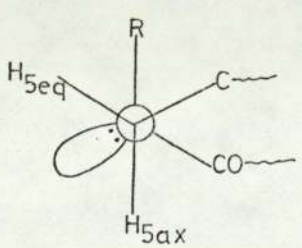
$J_{5ax\,6ax}$ = 11.5 Hz

$J_{5eq\,6ax}$ = 1.5 Hz

Figure 11 (R = -c-C_6H_{11})

The envelope conformation contains an equatorially orientated nitrogen lone pair which has maximum interaction with the 5-H_2 protons, as shown in the projection formula (133). This interaction leads to a decreased value for J_{gem} of -15.0 Hz, compared to the 2-morpholinone (128) where J_{gem} for the 5-H_2 protons was -12.5 Hz.[128]

The vicinal coupling constants of 11.5 and 1.5 Hz were consistent with the proposed envelope conformation.



(133) R = C_6H_{11}

(c) Mass spectrum

The mass spectrum (Figure 12) of 4-cyclohexyl-6-phenylmorpholine-2,3-dione (129) showed a small molecular ion peak at m/e 273 (5%) and a base peak at m/e 104 (104·062250, C_8H_8). Two fragmentation pathways were observed, one involving fission of the morpholinedione ring and the other, fission of the cyclohexyl ring.

The only major fragment (greater than 10%) between the molecular ion and the base peak was at m/e 192 (25%) ($M-C_6H_9$), and resulted from the rearrangement of two hydrogen atoms from the cyclohexyl group to the carbonyl function and nitrogen atom. Fragmentation of this ion gave rise to the ion at m/e 174 ($192-H_2O$) which then gave ions at m/e 146 (174-CO) and m/e 103 ($174-HCN-CO_2$)

Loss of carbon dioxide from the molecular ion resulted in the ion at m/e 229 which yielded the base peak at m/e 104 ($229-C_6H_{11}NCO$).

Minor fragmentations of the molecular ion yielded ions at m/e 230 ($M-CH_3-C_2H_4$) and m/e 201 ($M-CO_2-CO$).

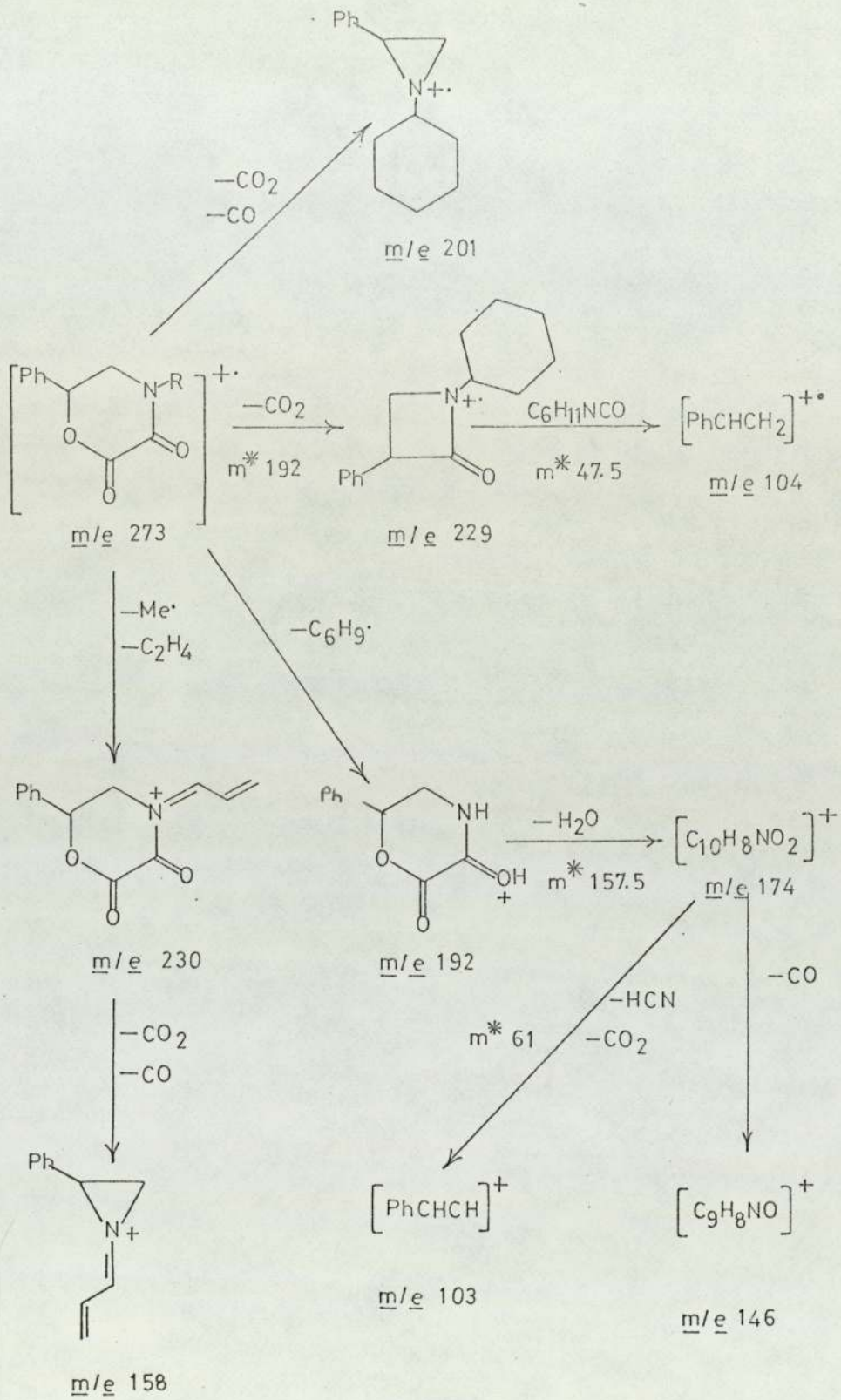
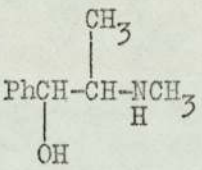

Ph
N+·
−CO2
−CO
m/e 201
Ph
N
R
O
O
O
+·
m/e 273
−CO2
m* 192
N+·
Ph
O
m/e 229
C6H11NCO
m* 47.5
[PhCHCH2]+·
m/e 104
−Me·
−C2H4
−C6H9·
Ph
N+
O
O
O
m/e 230
Ph
NH
O
OH
+
−H2O
m* 157.5
[C10H8NO2]+
m/e 174
−CO2
−CO
−HCN
m* 61
−CO2
−CO
Ph
N+
m/e 158
[PhCHCH]+
m/e 103
[C9H8NO]+
m/e 146

Figure 12

5. Hydrazines.

(a) Synthesis

The reaction of 2-cyclohexylamino-1-phenylethanol (89) with acidified sodium nitrite, under previously reported conditions[133] for the nitrosation of ephedrine (134), failed to yield any N-nitrosamine. The cyclohexyl group affords more shielding of the nitrogen atom than does the methyl group. The N-nitrosamine (136) was obtained in good yield, however, when the reaction temperature was raised (ca. 50°).[134]

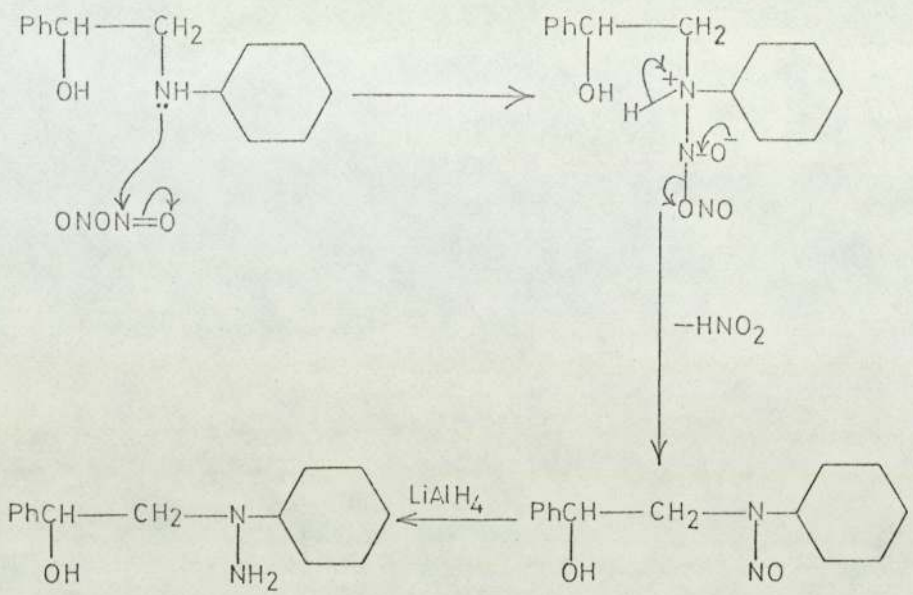


(134)

It is thought that one of the nitrosating agents in nitrous acid is the anhydride, N_2O_3 which is formed relatively slowly in the reaction mixture.[135] The dinitrogen trioxide (135) reacts with the amino alcohol in a manner analogous to an acyl chloride. Reduction of the N-nitrosamine (136) with lithium aluminium hydride gave 1-cyclohexyl-1-(2-hydroxy-2-phenylethyl)hydrazine (137).

$$2\ HONO \rightleftharpoons O{=}N{-}O{-}N{=}O + H_2O$$

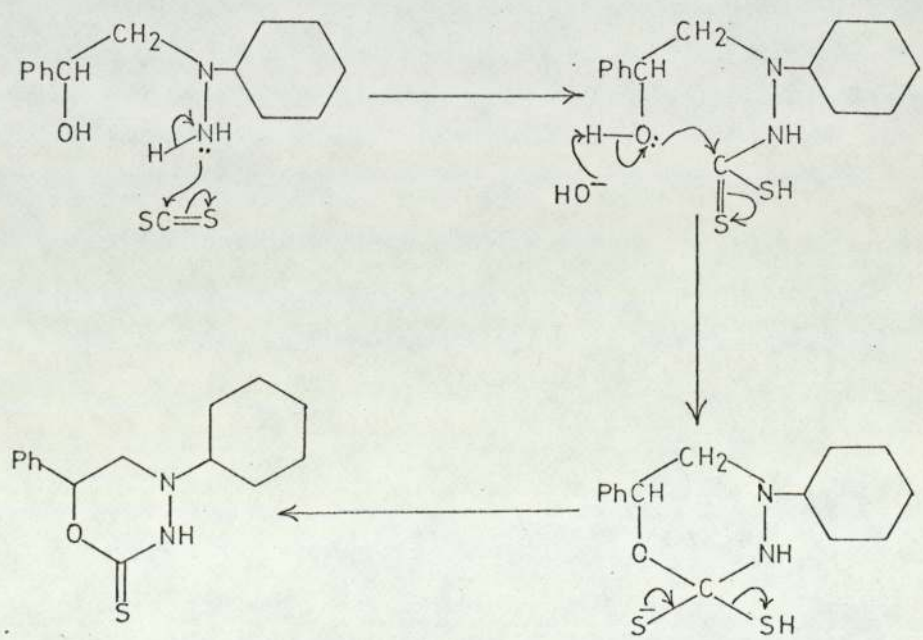
(135)



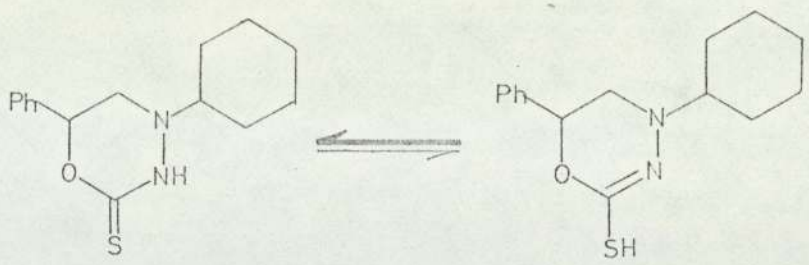
(137) (136)

(b) Attempted cyclisation reactions

The hydrazine (137) was cyclised with carbon disulphide in ethanolic potassium hydroxide to give 4-cyclohexyl-6-phenyl-3,4,5,6-tetrahydro-2H-1,3,4-oxadiazine-2-thione (138).[40] A possible mechanism for the reaction would be :



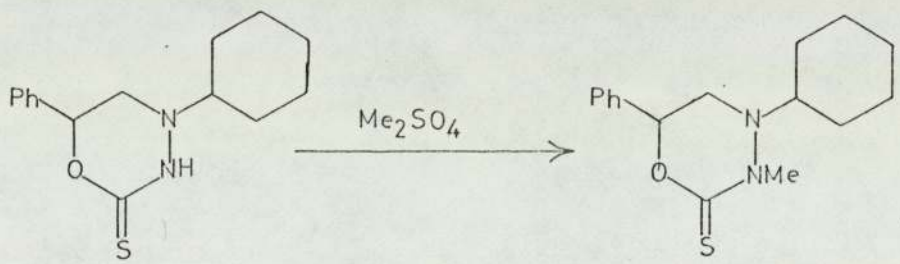
(138)



(138) (139)

The thione (138) could also exist as its thiol tautomer (139) but the infrared spectrum of the product showed an absorption at 1190 cm.$^{-1}$ due to the C:S stretch and an NH absorption at 3160 cm.$^{-1}$ No C:N or SH abscrptions were visible which indicated that the equilibrium lay towards the thione (138).

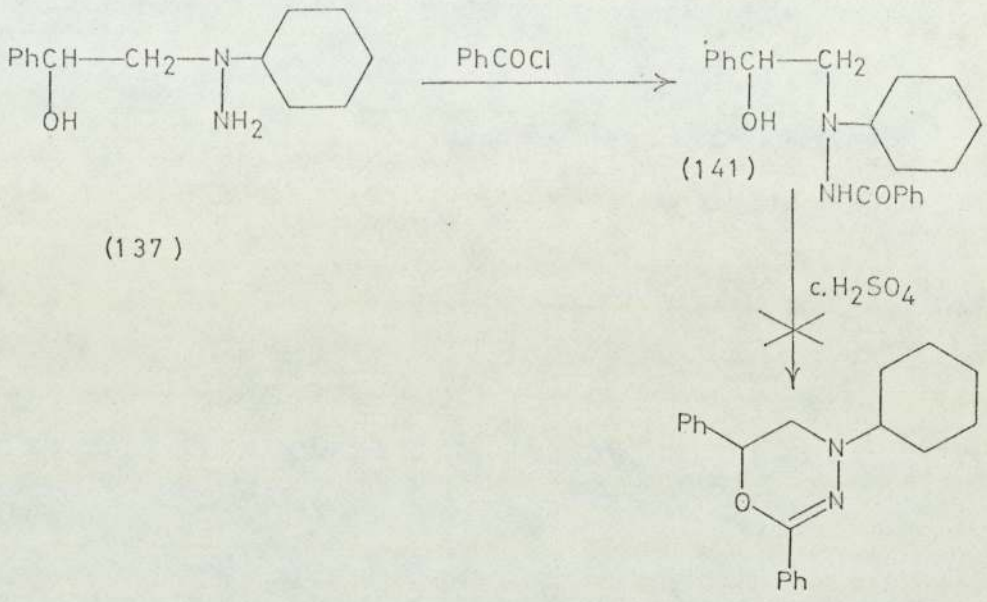
The thione (138) was methylated with alkaline dimethyl sulphate to give 4-cyclohexyl-3-methyl-6-phenyl-3,4,5,6-tetrahydro-2H-1,3,4-oxadiazine-2-thione (140).



(138) (140)

The reaction of the hydrazine (137) with benzoyl chloride gave 1'-benzoyl-1-cyclohexyl-1-(2-hydroxy-2-phenylethyl)hydrazine (141). Trepanier and Sprancmanis have prepared various 5,6-dihydro-4H-1,3,4-oxadiazines by the sulphuric acid dehydration of aroyl hydrazines.[133] Various attempts were made to cyclise the benzoyl hydrazine (141) with conc. sulphuric acid but the product was contaminated with charred material

from which it proved impossible to isolate a pure fraction.



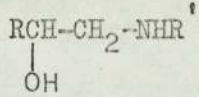
(137)

(141)

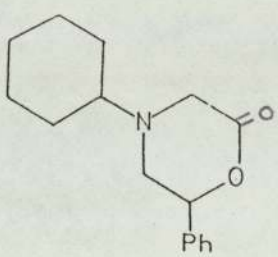
C. SYNTHESIS AND PROPERTIES OF SOME 1-SUBSTITUTED PYRROLES.

1. Introduction

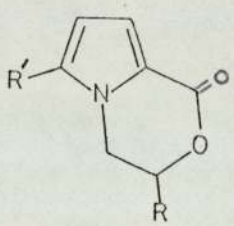
A common feature of the compounds discussed in the previous section was the ethanolamine structural unit (142), from which was obtained many different ring systems. As an extension to this work, compounds were synthesised in which the nitrogen atom formed an integral part of a pyrrole ring. Thus the analagous compound to 4-cyclohexyl-6-phenylmorpholin-2-one (128) would be 3-phenyl-1H-3,4-dihydropyrrolo [2,1-c] [1,4] oxazin-1-one (143).



(142) R = Ph; R' = Ph; -c-C_6H_{11}; CH_2CH_2Ph



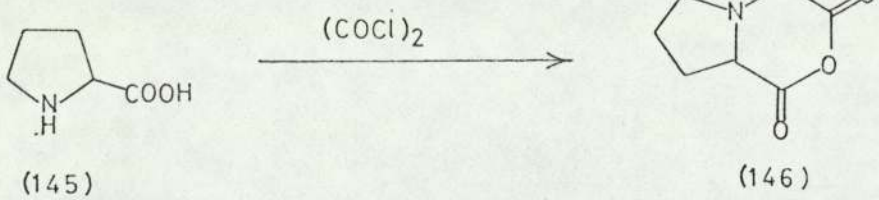
(128)



(143) R = Ph; R' = H

(144) R = H; R' = NO_2

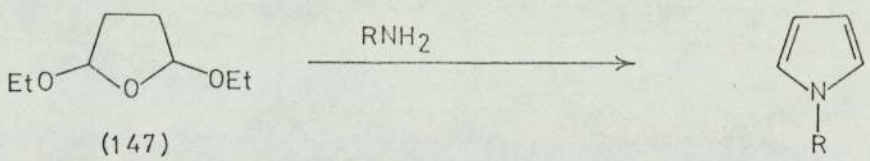
When this work was commenced the majority of known examples of the 1H-pyrrolo [2,1-c] [1,4] oxazine ring system were saturated derivatives prepared from proline.[136] More recently, the 1,3,4-trione (146) has been prepared by the reaction of proline (145) and oxalyl chloride,[137] and a partially aromatic pyrrolo [2,1-c] [1,4] oxazin-1-one (144) has been reported (see page 25).[62]



(145) (146)

Two routes to the 1H-pyrrolo[2,1-c][1,4]oxazine ring system were investigated, one involving the synthesis of the pyrrole ring, and the other requiring the alkylation of a substituted pyrrole.

1-Substituted pyrroles (148) have been obtained directly from the reaction of primary amines with 2,5-diethoxytetrahydrofuran (147).[138] The attempted reaction of 2-amino-1-phenylethanol (149) with 2,5-diethoxytetrahydrofuran in 1,2-dimethoxyethane yielded starting material, whereas with acetic acid as solvent a product was obtained which showed the presence of pyrrole protons in the n.m.r. spectrum. The dark coloured product was obtained in low yield, however, and proved difficult to purify.



(147) (148)

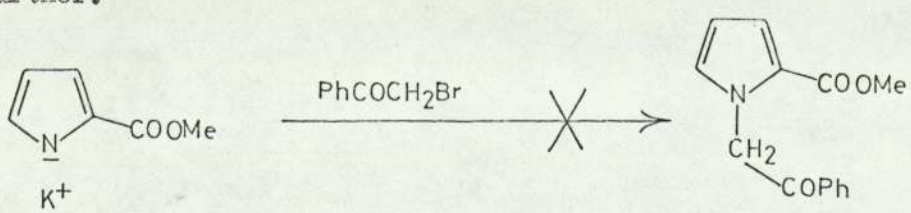
$PhCHCH_2NH_2$
|
OH

(149)

(a) Direct alkylation of pyrrole

(i) With phenacyl bromide.

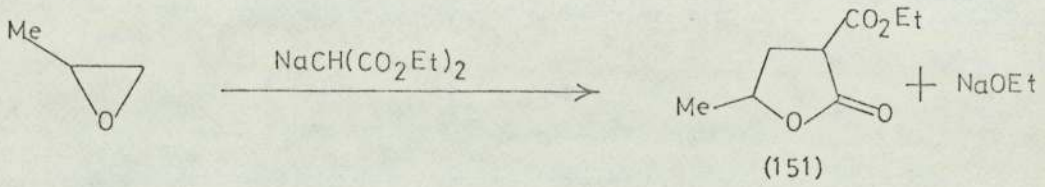
The difficulties involved in the preparation of 1-alkylated pyrroles have been discussed earlier (see page 20). The potassium salt (150) of methyl pyrrole-2-carboxylate was reacted with phenacyl bromide in 1,2-dimethoxyethane. It was hoped that the 2-ester group would decrease the reactivity of the ring and lessen the chance of dialkylated products. The product from the reaction mixture was a dark brown tar which could not be identified further.



(150)

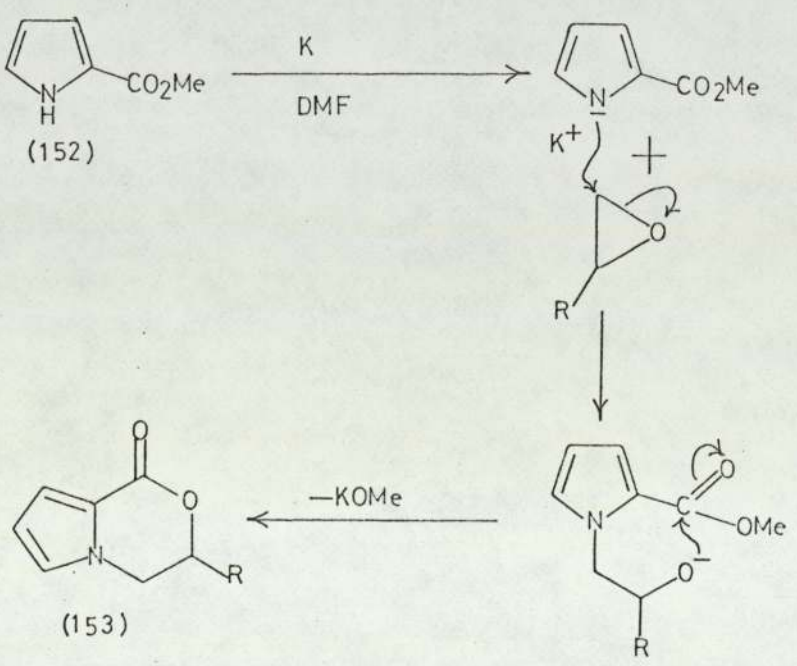
(ii) With epoxides.

The reactions of carbanions with epoxides which yield γ-lactones have been extensively studied and reviewed.[139] Diethylsodiomalonate has been reacted with propylene oxide to yield the butyrolactone (151). No evidence was found of abnormal fission of the epoxide, probably due to the bulky nature of the nucleophile.



(151)

The few reported reactions of pyrrole salts with epoxides have been mentioned earlier (see page 23). The reactions of the potassium salt of methyl pyrrole-2-carboxylate (152) with epoxides have been studied in an attempt to synthesise 1H-3,4-dihydropyrrolo [2,1-c] [1,4] oxazin-1-ones (153) according to the scheme in Figure 13.

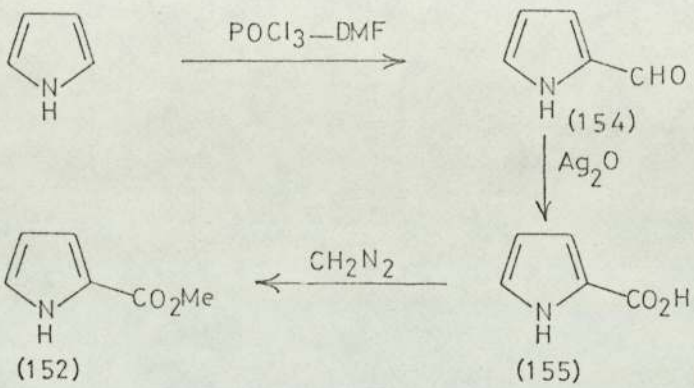


(152)

(153)

Figure 13

Methyl pyrrole-2-carboxylate (152) was prepared by the Vilsmeier formylation of pyrrole[140] to give pyrrole-2-aldehyde (154) which was then oxidised[141] with moist silver oxide to yield pyrrole-2-carboxylic acid (155). Esterification with ethereal diazomethane gave methyl pyrrole-2-carboxylate (152).

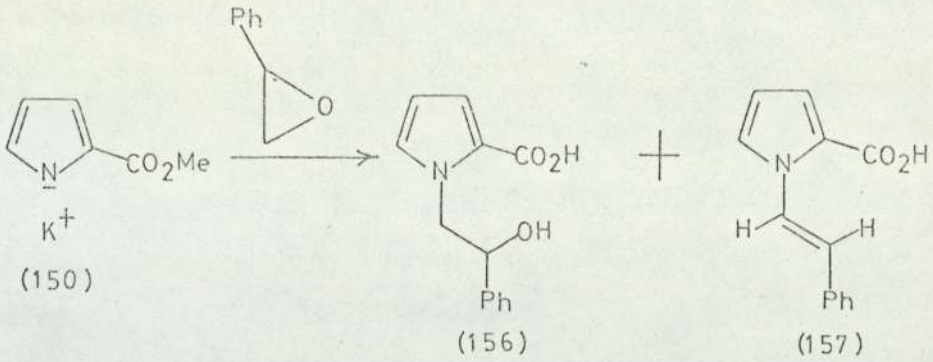


The preparation of the potassium salt (150) of methyl pyrrole-2-carboxylate was achieved under milder conditions than have previously been reported,[142] probably due to the increased solubility of the salt in dimethylformamide (DMF) compared to toluene.

2. Reactions of methyl pyrrole-2-carboxylate with epoxides.

(a) Styrene oxide

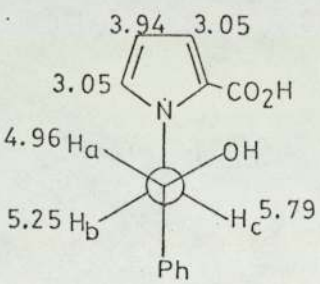
The reaction of styrene oxide with the potassium salt (150) in DMF under mild conditions gave a product which was shown by tlc to consist of two slow running polar components. The infrared spectrum of the crude product showed absorptions at 3400 (alcohol OH), 2700 (acid OH), 1670 (acid C:O), 1640 (vinyl C:C), and 950 (trans-vinyl CH)cm.$^{-1}$ The two products were identified as the alcoholpyrrole acid (156) and the styrylpyrrole acid (157).



(150) (156) (157)

When the reaction was performed under reflux conditions more of the fluorescent, faster running component was produced which suggested that it was the styrylpyrrole acid (157). With milder conditions it was possible to obtain a product which contained relatively little styrylpyrrole acid, and could be purified by recrystallisation to give 1-(2-hydroxy-2-phenylethyl)pyrrole-2-carboxylic acid (156).

The alcoholpyrrole acid (156) was not very soluble in deuterochloroform but an n.m.r. spectrum was obtained in acetone. The chemical shifts and coupling constants are shown on the projection formula in Figure 14.



$J_{b,c}$ = -13.0 Hz

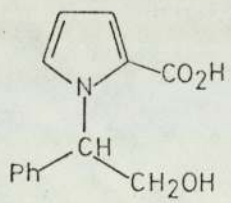
$J_{a,b}$ = 3.6 Hz

$J_{a,c}$ = 8.5 Hz

Figure 14

The three protons in the N·CH_2CH· group appeared as a typical AMX pattern consisting of twelve distinct lines. The vicinal coupling constants indicated a probable conformation in which the OH group was anti- to proton H_b.

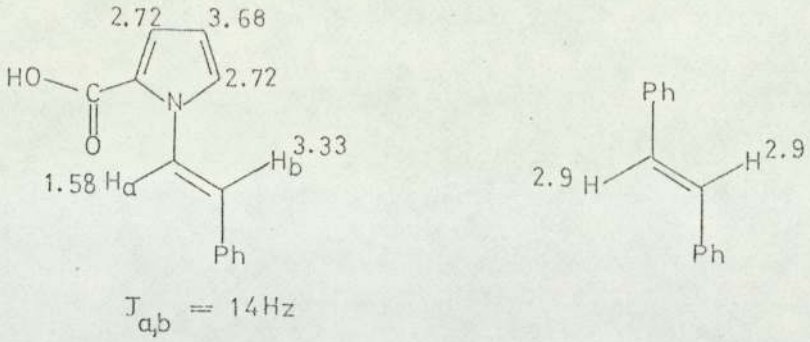
The preparation of a pure sample of the styrylpyrrole acid (157) proved difficult. Styrene oxide was reacted with the potassium salt (150) in DMF under reflux conditions, but even after 8 hr. reflux, the styrylpyrrole acid was contaminated with a small amount of a slow running polar component. The minor product which could not be removed by fractional crystallisation, may have resulted via abnormal fission of styrene oxide to give 1-(2-hydroxy-1-phenylethyl)pyrrole-2-carboxylic acid (158). Preparative tlc showed, however, that the minor product was the alcoholpyrrole acid (156).



(158)

The infrared spectrum of trans-1-styrylpyrrole-2-carboxylic acid (157) showed the out of plane CH deformation of the trans-CH:CH group at 950 cm.$^{-1}$

The nmr spectrum confirmed the trans-configuration of the styrylpyrrole acid (157) and the chemical shifts and coupling constants are shown in Figure 15, together with values for trans-stilbene.[143]



$J_{a,b} = 14$ Hz

Figure 15

The conjugation of the pyrrole nucleus with the trans-1-styryl group resulted in a deshielding of the pyrrole protons by ca. τ 0.3, compared to the alcoholpyrrole acid (156). The olefinic coupling constant of 14 Hz supported the trans-configuration of the molecule.

The substituted pyrrole ring exerted a strong deshielding effect on proton H_a which was partly due to the 2-carboxylic acid group. On decarboxylation with p-toluenesulphonic acid (see page 99), proton H_a absorbed at τ 2.77. The reported[144] conformation of pyrrole-2-aldehyde indicates that the carbonyl function is directed away from the pyrrole ring.

The electronic absorption spectra of the styrylpyrrole acid (157), cis- and trans-stilbene are shown in Table 4. The values for the styrylpyrrole acid (157) were similar to those of trans-stilbene which provided further evidence of a trans-configuration of the molecule.

Compound	λ max_{nm}	ε max
(157)	302	20,900
cis-stilbene[145]	278	9,350
trans-stilbene[145]	294	24,000

Table 4,

In order to define specific reaction conditions, the degree of moisture present in the reaction of the potassium salt (150) and styrene oxide was varied.

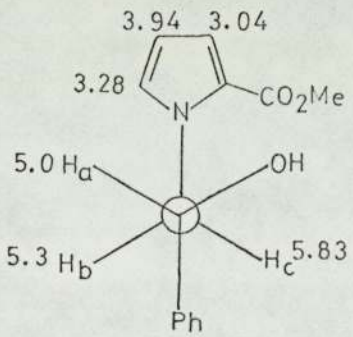
The reaction of the potassium salt (150) with styrene oxide in DMF under very humid conditions yielded the alcoholpyrrole acid (156). The product was shown by tlc to be free of any styrylpyrrole acid (157) although a mixture is produced under ordinary laboratory conditions.

The reaction of the potassium salt (150) with styrene oxide in DMF under dry nitrogen gave the styrylpyrrole acid (157) as the sole product.

The significance of these results is discussed later (see page 90).

(i) Esterification

Methyl 1-(2-hydroxy-2-phenylethyl)pyrrole-2-carboxylate (159) was obtained from the reaction of ethereal diazomethane and 1-(2-hydroxy-2-phenylethyl)pyrrole-2-carboxylic acid (156). The infrared spectrum of the product had absorptions at 3500 (secondary alcohol OH stretch) and 1675 (ester C:O) cm.$^{-1}$ The chemical shifts and coupling constants of the methyl ester (159) are shown in Figure 16, together with values for pyrrole-2-aldehyde (154).[146]



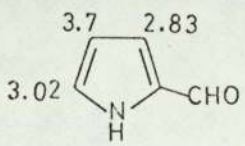
$J_{3,4}$ = 3.8 Hz

$J_{5,3}$ = $J_{5,4}$ = 2.0 Hz

$J_{b,c}$ = -14.0 Hz

$J_{a,b}$ = 4.0 Hz

$J_{a,c}$ = 8.0 Hz



(154)

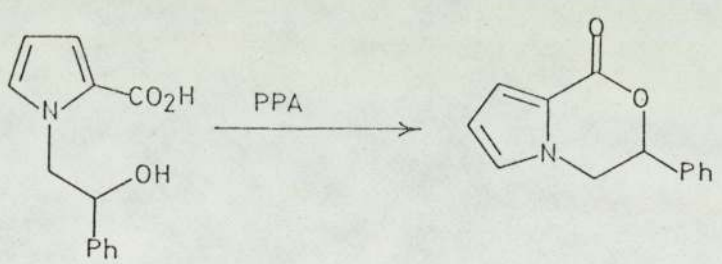
Figure 16

The assignment of the pyrrole protons was made on the basis of the observed coupling constants. Esterification has resulted in the shielding of the 5-H proton with respect to the same proton in the alcoholpyrrole acid (156). A similar chemical shift disposition exists in pyrrole-2-aldehyde (154) where the 5-H proton absorbs at τ 3.02 and the 3-H proton absorbs at τ 2.83.

The geminal and vicinal coupling constants obtained were consistent with the indicated projection formula.

(ii) Lactonisation

1-(2-Hydroxy-2-phenylethyl)pyrrole-2-carboxylic acid (156) was cyclised with polyphosphoric acid to yield 1H-3-phenyl-3,4-dihydropyrrolo[2,1-c][1,4]oxazin-1-one (143). The infrared spectrum of the product showed the lactone carbonyl (C:O) absorption at 1710 $cm.^{-1}$, which was lower than the normal range,[71] 1750-1735 $cm.^{-1}$ probably due to conjugation with the pyrrole ring.[147]

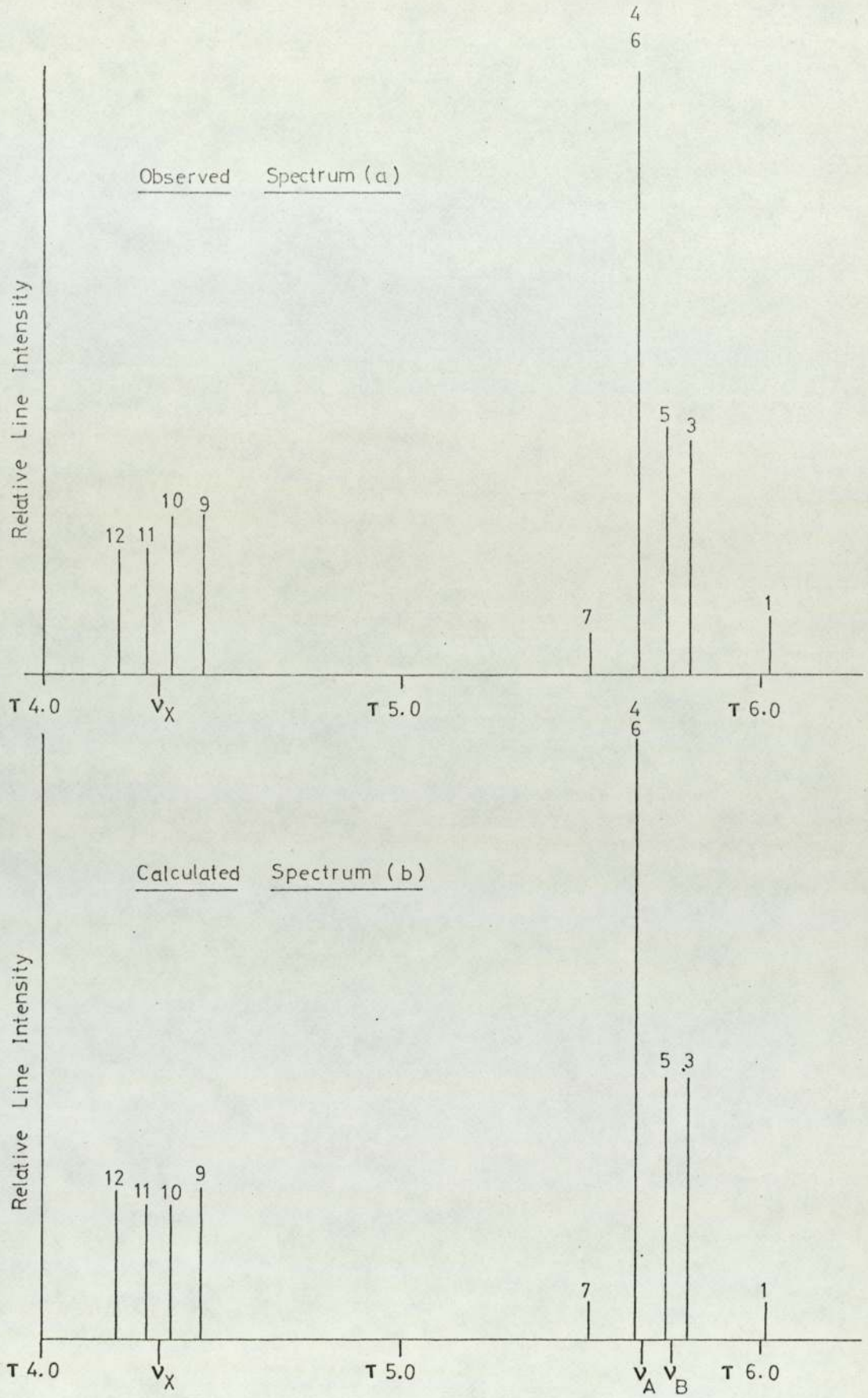


(156) (143)

The n.m.r. spectrum of the lactone (143) showed the 3-H and 4-H_2 protons as a complex ABX pattern which is reproduced diagramatically in Figure 17a. A first order analysis of the spectrum gave the following values:

$$\left| J_{AX} + J_{BX} \right| = \text{Line Sep.}^{n}\ 9\text{-}12 = 14.0\ \text{Hz}$$

$$J_{AB} = 13.0\ \text{Hz}$$



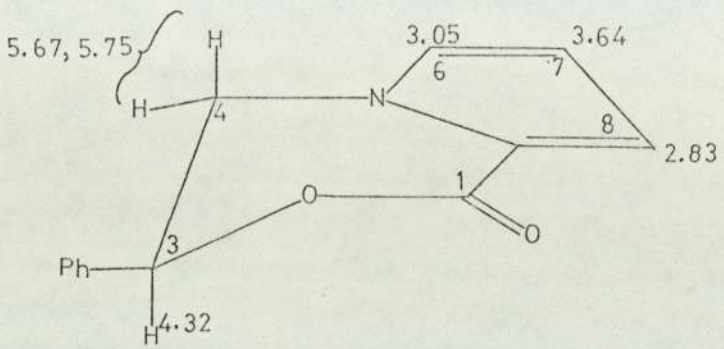
J_{AB} = -13.0 Hz $\quad$ τ_X = 4.32

J_{AX} = 1.5 Hz $\quad$ τ_A = 5.67

J_{BX} = 12.5 Hz $\quad$ τ_B = 5.75

Figure 17

The calculated chemical shifts[130,131] and relative line intensities of the ABX portion of the spectrum are shown in Figure 17b. The requirement of a planar C-O-CO-C group[124] indicated an approximate envelope conformation as shown in Figure 18.



$J_{4ax\,4eq}$ = -13.0 Hz

$J_{3ax\,4ax}$ = 12.5 Hz

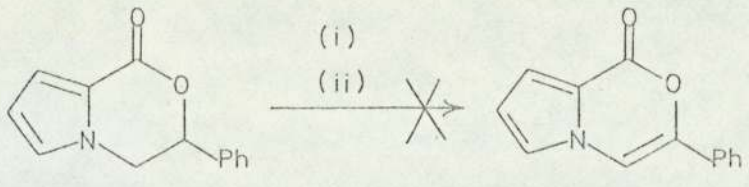
$J_{3ax\,4eq}$ = 1.5 Hz

Figure 18.

The calculated vicinal coupling constants of 12.5 and 1.5 Hz were consistent with the proposed envelope conformation.

(iii) Attempted dehydrogenation of 1H-3-phenyl-3,4-dihydropyrrolo[2,1-c][1,4]oxazin-1-one (143).

Using a variety of reagents and experimental conditions it was not possible to dehydrogenate the 3,4-dihydrolactone (143) to give the fully aromatic pyrrolo[2,1-c][1,4]oxazin-1-one (160)



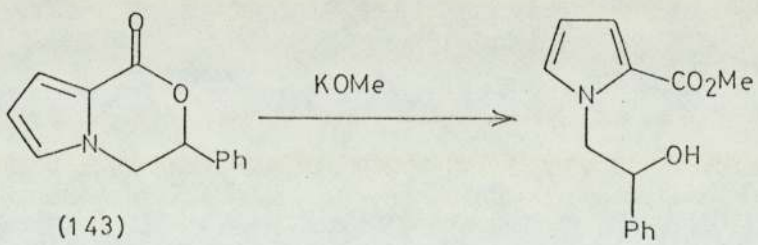
(143) (160)

Reagents: (i) 10% P_d-C[148]

(ii) DDQ[149]

(iv) Methanolysis of the pyrrolo[2,1-c][1,4]oxazinone (143).

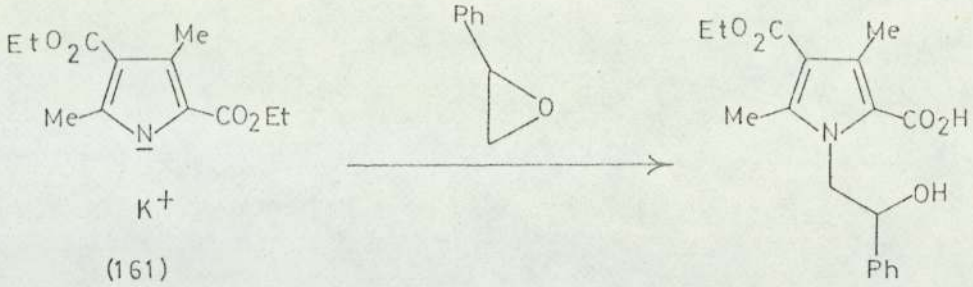
1H-3-Phenyl-3,4-dihydropyrrolo[2,1-c][1,4]oxazin-1-one (143) was reacted with potassium methoxide overnight at room temperature to give methyl 1-(2-hydroxy-2-phenylethyl)pyrrole-2-carboxylate (159). The product was identical with that obtained from the esterification of the alcoholpyrrole acid (156) with diazomethane.



(143) (159)

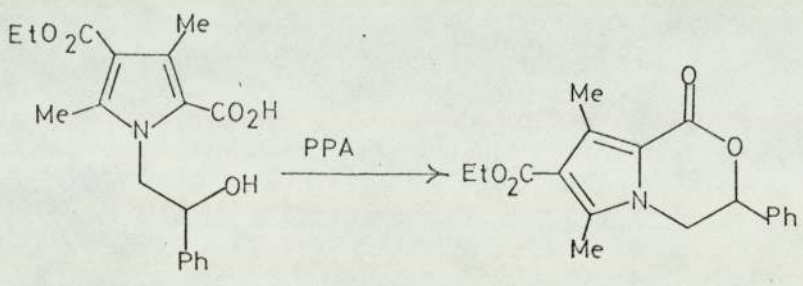
(v) Reaction of styrene oxide with Knorr's pyrrole.

The potassium salt (161) of Knorr's pyrrole (3,5-dimethyl-2,4-diethoxycarbonylpyrrole)[150] was reacted with styrene oxide in DMF under reflux to give 3,5-dimethyl-4-ethoxycarbonyl-1-(2-hydroxy-2-phenylethyl)pyrrole-2-carboxylic acid (162). When the reaction was done at room temperature, unchanged Knorr's pyrrole was isolated. The decreased reactivity of Knorr's pyrrole towards styrene oxide was probably due to the electron-withdrawing 4-ethoxycarbonyl group, which reduced the nucleophilicity of the pyrrole anion, and also to the steric effect of the 5-Me group.



(161) (162)

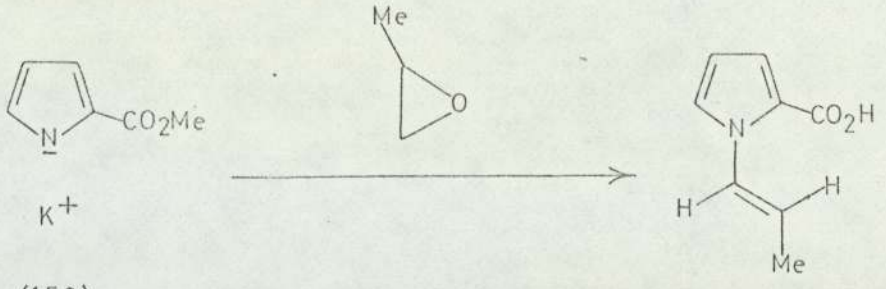
The n.m.r. spectrum of the product showed the presence of the 4-ethoxycarbonyl group superimposed on the $N{\cdot}CH_2$ protons. Partial hydrolysis of the 4-ethoxycarbonyl group was suspected because of a low carbon analytical result. An accurate mass of the molecular ion showed, however, that the alcoholpyrrole acid (162) was present in the product. The presence of the alcoholpyrrole acid (162) as the major component of the product was demonstrated by cyclising it with polyphosphoric acid to give 1H-6,8-dimethyl-3,4-dihydro-7-ethoxycarbonyl-3-phenylpyrrolo[2,1-c][1,4]oxazin-1-one (163). The infrared spectrum of the product showed the lactone carbonyl absorption at 1700cm.$^{-1}$



(162) (163)

(b) Propylene oxide.

The reaction of propylene oxide with the potassium salt (150) in DMF yielded trans-1-(2-methylvinyl)pyrrole-2-carboxylic acid (164).



(150) (164)

The infrared spectrum of the product showed the CH deformation of the trans-CH:CH group at 950 cm.$^{-1}$, the carboxylic acid (C:O) and the vinyl (C:C) stretching absorptions at 1680 cm.$^{-1}$

The n.m.r. spectrum of the vinylpyrrole acid (164), see Figure 19, showed N·CH: proton at τ 2.42 due to deshielding by the pyrrole ring. It consisted of eight lines containing the J_{trans} 14 Hz coupling and the ^{4}J 1.6 Hz coupling with the cis-methyl group. The Me·CH: proton appeared at τ 4.16 and consisted of seven lines (the eighth line was hidden under the absorption of the 4-H pyrrole proton) containing the J_{trans} 14 Hz, and the ^{3}J 7 Hz coupling with the methyl group.

The electronic absorption spectrum of the vinylpyrrole acid (164) (Table 5) showed a bathochromic shift relative to pyrrole-2-carboxylic acid due to conjugation with the 1-vinyl group.

Compound	λ max nm	ε max
Pyrrole-2-carboxylic acid	254	11,300
(164)	267	12,100

Table 5

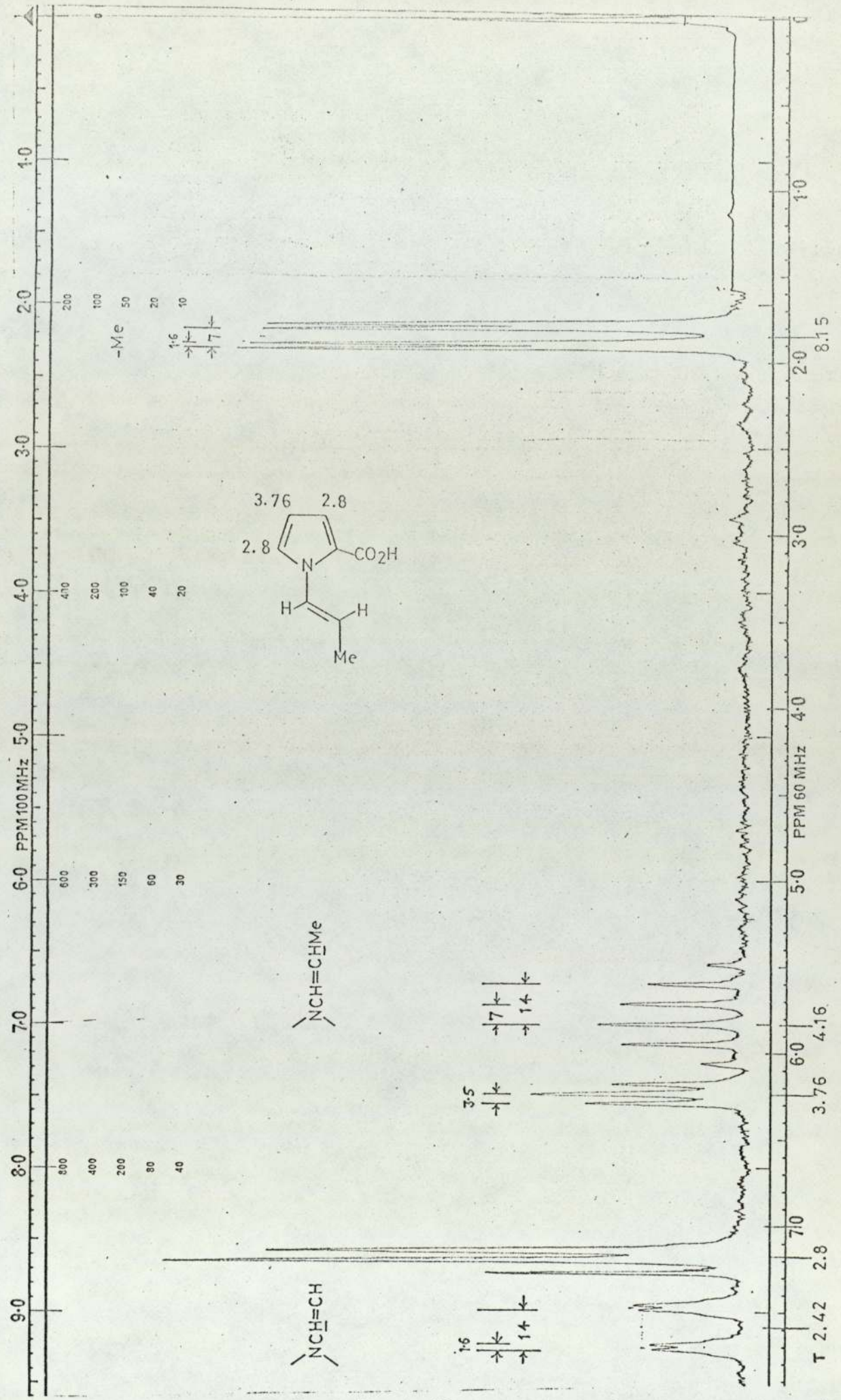

PPM 100 MHz
PPM 60 MHz
-Me
1·6
7
3·5
14
NCH=CHMe
NCH=CH
T 2.42
2.8
7·0
3.76
4.16
8.15
3.76
2.8
2.8
CO2H
N
H
H
Me

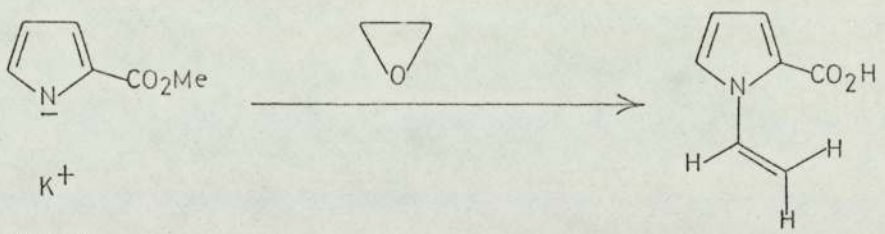
Figure 19

(i) Esterification

The reaction of trans-1-(2-methylvinyl)pyrrole-2-carboxylic acid (164) with methyl iodide in the presence of potassium carbonate[141] gave methyl trans-1-(2-methylvinyl)pyrrole-2-carboxylate (165). The infrared and n.m.r. spectra were consistent with the assigned structure.

(c) Ethylene oxide

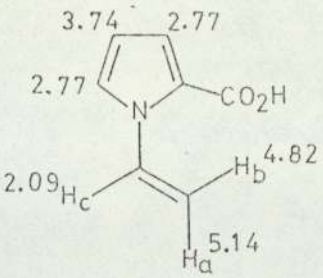
The reaction of ethylene oxide with the potassium salt (150) in DMF yielded 1-vinylpyrrole-2-carboxylic acid (166).



(150) (166)

The infrared spectrum of the product showed the CH deformation of the vinyl group at 980 cm.$^{-1}$, with the acid (C:O) and vinyl (C:C) stretching absorptions at 1680 cm.$^{-1}$

The chemical shifts and coupling constants of the vinylpyrrole acid (166) are shown in Figure 20. The geminal and vicinal coupling constants obtained were consistent with the proposed structure.



$J_{b,c}$ = 16.0 Hz

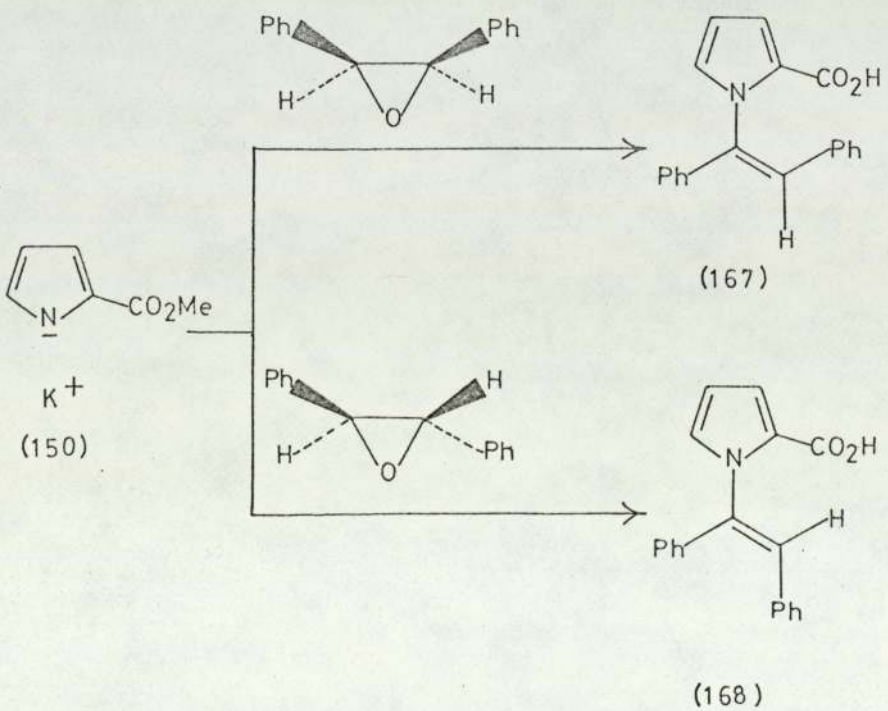
$J_{a,c}$ = 9.0 Hz

$J_{a,b}$ = ca. 0.3 Hz

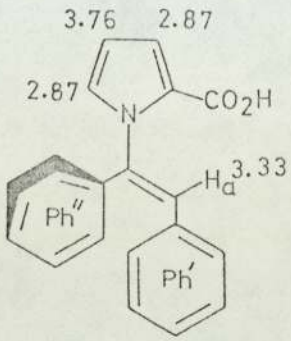
Figure 20.

(d) Stilbene oxides

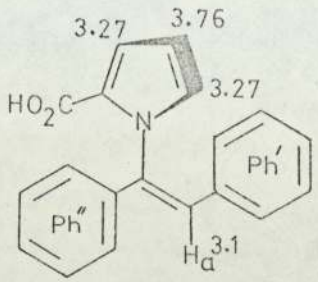
The reaction of the potassium salt (150) with cis-[151] and trans-stilbene oxide in DMF gave 1-(trans-1,2-diphenylvinyl)pyrrole-2-carboxylic acid (167) and 1-(cis-1,2-diphenylvinyl)pyrrole-2-carboxylic acid (168) respectively.



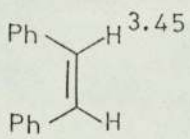
The structure of the products was confirmed by their n.m.r. and electronic absorption spectra. Figure 21 shows the chemical shifts of the two vinylpyrrole acids (167 and 168) together with those of cis- and trans-stilbene.[143]



(168)



(167)



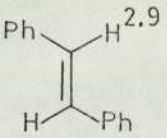
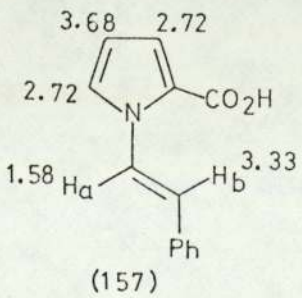


Figure 21

The chemical shift of proton H_a in each of the vinylpyrrole acids (167 and 168) was similar to that obtained with the stilbene analogues, indicating that inversion of configuration had occurred during the reaction (see page90). The cis-diphenyl acid (168) showed considerable deshielding of the 3-H and 5-H protons compared to the trans-diphenyl acid (167). This indicated that the diphenylvinyl group was conjugated with the pyrrole ring in the former but not in the latter case.



(157)

Figure 22

A comparison of the chemical shifts of the cis-diphenyl acid (168) with trans-1-styrylpyrrole-2-carboxylic (157) (see Figure 22) showed a close similarity with protons H_a and H_b, respectively, having identical absorptions. This indicated that Ph' in the cis-diphenyl acid (168) was conjugated, and therefore coplanar, with the pyrrole ring, leaving Ph" out of plane.

Conversely, the shielding of the 3-H and 5-H protons in the trans-diphenyl acid (167) indicated that Ph' and Ph" were coplanar, leaving the pyrrole ring out of plane.

The electronic absorption spectra of the diphenylvinyl acids are shown in Table 6.

Compound	λ max$_{nm}$	ε max
trans-stilbene[145]	294	24,000
(167)	299	25,000
cis-stilbene[145]	278	9,350
(168)	292	9,800
(157)	302	20,900

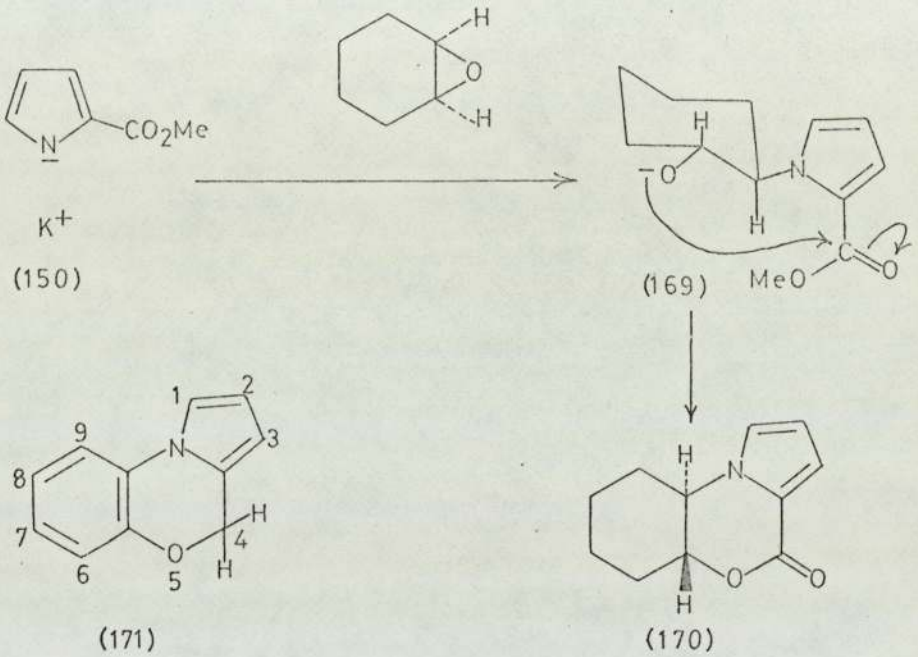
Table 6

The trans-diphenyl acid (167) had a very similar absorption to trans-stilbene which indicated that the two phenyl rings, Ph' and Ph" were coplanar.

It was expected that in support of the n.m.r. evidence cited above, the cis-diphenyl acid (168) would have an absorption similar to trans-1-styrylpyrrole-2-carboxylic acid (157). Decreased values were obtained, however, which indicated that interaction between the ortho-hydrogens of the phenyl groups was occurring which hindered coplanarity of Ph' with the pyrrole ring.[152]

(e) Cyclohexene oxide

The reaction of cyclohexene oxide with the potassium salt (150) in DMF yielded 4H-5a,6,7,8,9,9a-hexahydropyrrolo[2,1-c][1,4]benzoxazin-4-one (170) which is the first reported example of the 4H-pyrrolo[2,1-c][1,4]benzoxazine ring system (171). The infrared spectrum of the product showed the lactone carbonyl (C:O) absorption at 1700 cm.$^{-1}$



The n.m.r. spectrum of the product showed the 5a-H and 9a-H protons as a broad singlet at τ 6.06. The stereochemistry of the ring opened intermediate (169) indicated that the lactone (170) possessed a trans-fused bridge although the coupling between protons 5a and 9a could not be measured.

(ii) Attempted methanolysis of the pyrrolo[2,1-c][1,4]benzoxazinone (170)

The lactone (170) did not react with potassium methoxide under previously described conditions (see page 82).

3. Mechanism of the reaction between epoxides and pyrrole salts.

The mechanism of the reaction of pyrrole salts with epoxides should explain the following experimental evidence:

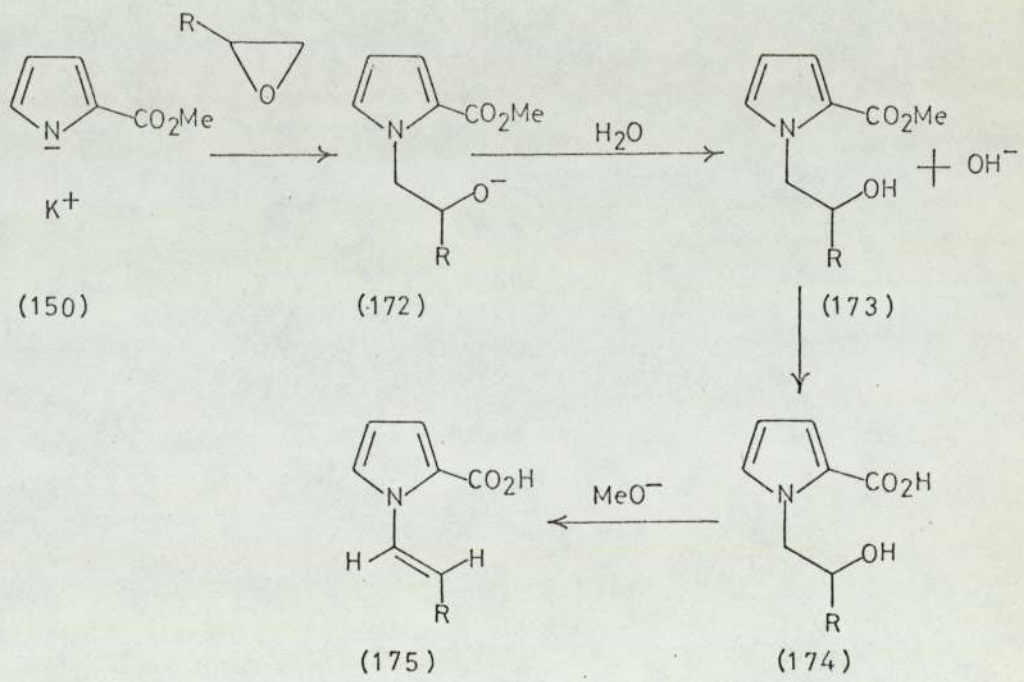
(a) Direct lactone formation with cyclohexene oxide.

(b) Production of different products with styrene oxide under humid and dry conditions.

(c) The stereospecific nature of the reaction products obtained with cis- and trans-stilbene oxide.

(d) The stability of the pyrrolobenzoxazinone (170) to methanolysis relative to the pyrrolooxazinone (143).

A possible scheme involves the cleavage of the epoxide by the pyrrole salt (150) to give the alkoxide (172), which then becomes protonated to give the alcoholpyrrole ester (173). Hydrolysis of the ester yields the alcoholpyrrole acid (174) which then undergoes base catalysed E2 elimination to give the vinylpyrrole acid (175)



This mechanism fails to explain why the reaction of Knorr's pyrrole and styrene oxide resulted only in the hydrolysis of the 2-ethoxycarbonyl group whereas a mixture of the 2- and 4-carboxylic acids

may be expected. Neither does it explain the reluctance of 1-(2-hydroxy-2-phenylethyl)pyrrole-2-carboxylic acid (156) to undergo elimination with potassium methoxide (under reflux conditions) when 1-styrylpyrrole-2-carboxylic acid (157) was obtained directly under dry conditions at room temperature (see pages 76 and 78). No alcoholpyrrole esters (173) were isolated from the reaction of the pyrrole salt (150) with epoxides. This susceptibility to cleavage of the 2-methoxycarbonyl group, and the direct production of the pyrrolobenzoxazinone (170) suggested that all of the epoxide reactions involved a lactone intermediate.

The modified mechanism is shown in Figure 23, with the alkoxide (172) existing in equilibrium with the lactone (153). Under humid conditions (i) the lactone will be hydrolysed to yield the alcoholpyrrole acid (174), whilst base catalysed elimination of the lactone may occur under dry conditions (ii) yielding the vinylpyrrole acid (175).

The reaction of the potassium salt (150) with cyclohexene oxide, which yielded the pyrrolobenzoxazinone (170), was the only case in which a lactone was isolated from the reaction mixture. The resistance of this lactone to undergo elimination was due to the unfavourable cis- axial-equatorial disposition of the hydrogen and oxygen atoms. The lactone intermediates in the other epoxide reactions eliminated easily to give vinylpyrrole acids (175).

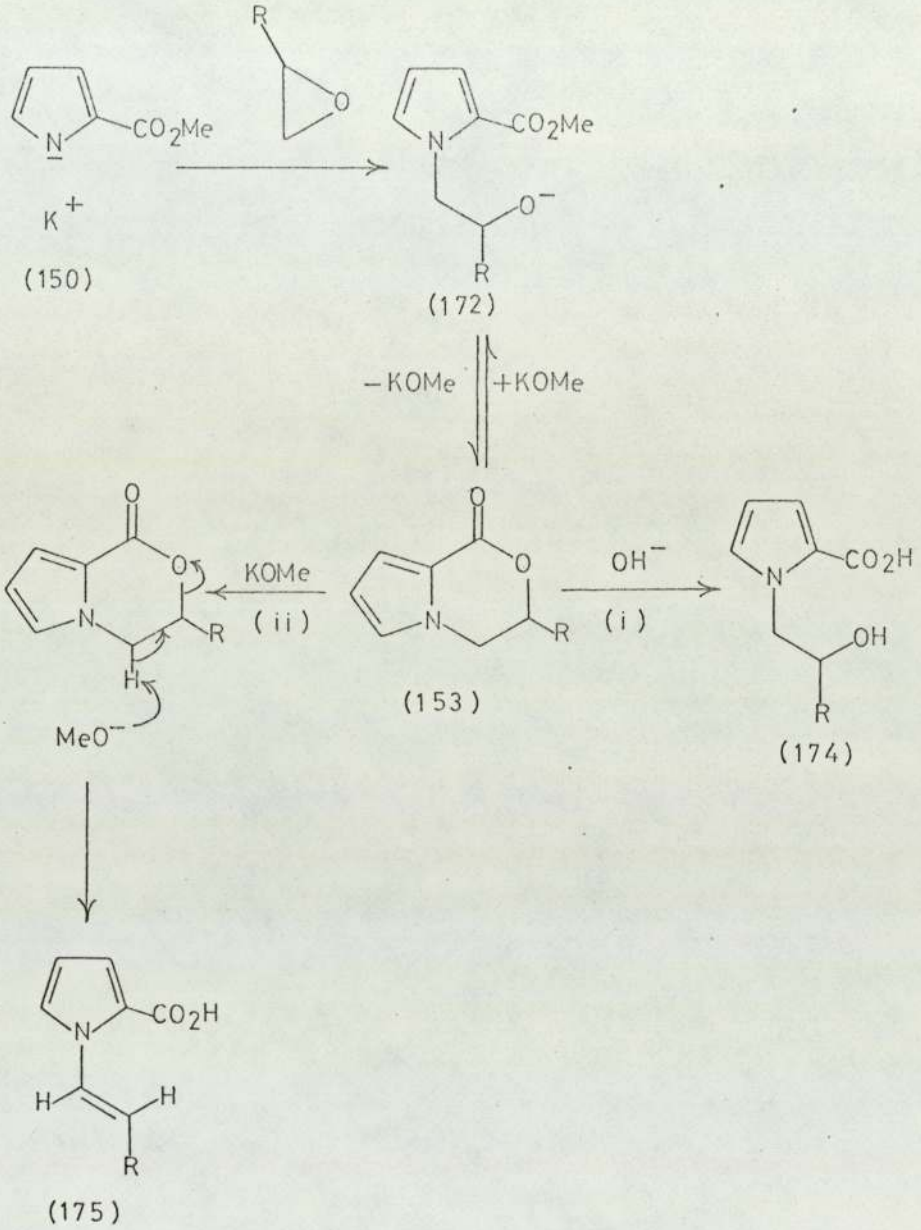

R
CO2Me
N
K+
(150)
O
CO2Me
N
O−
R
(172)
−KOMe
+KOMe
O
O
N
R
KOMe
(ii)
(153)
OH−
(i)
CO2H
N
OH
R
(174)
MeO−
CO2H
N
H
H
R
(175)

Figure 23

The stereospecific reaction of the potassium salt with cis- and trans-stilbene oxide can be explained by this mechanism (Figure 24). cis-Stilbene oxide is cleaved by the potassium salt, with inversion of configuration at the point of attack, to give the rotational isomers (176 and 177). Rotamer (176) gives rise to lactone (178), containing the hydrogen and oxygen atoms in a trans-configuration, which then undergoes methoxide catalysed elimination to give 1-(trans-1,2-diphenylvinyl)pyrrole-2-carboxylic acid (167). A similar series of reactions, with rotamer (177) yields the lactone (179) in which the hydrogen and oxygen atoms are in a cis-configuration. Elimination will not occur and cleavage of the lactone by methoxide will reverse the reaction pathway to yield eventually the vinylpyrrole acid (167).

trans-Stilbene oxide reacted in a similar manner to give 1-(cis-1,2-diphenylvinyl)pyrrole-2-carboxylic acid (168).

Treatment of the pyrrolooxazinone (143) and the pyrrolobenzoxazinone (170) with methoxide at room temperature showed that the former reacted to give methyl 1-(2-hydroxy-2-phenylethyl)pyrrole-2-carboxylate (159), whereas the latter was stable under these conditions.

(continued on page 96)

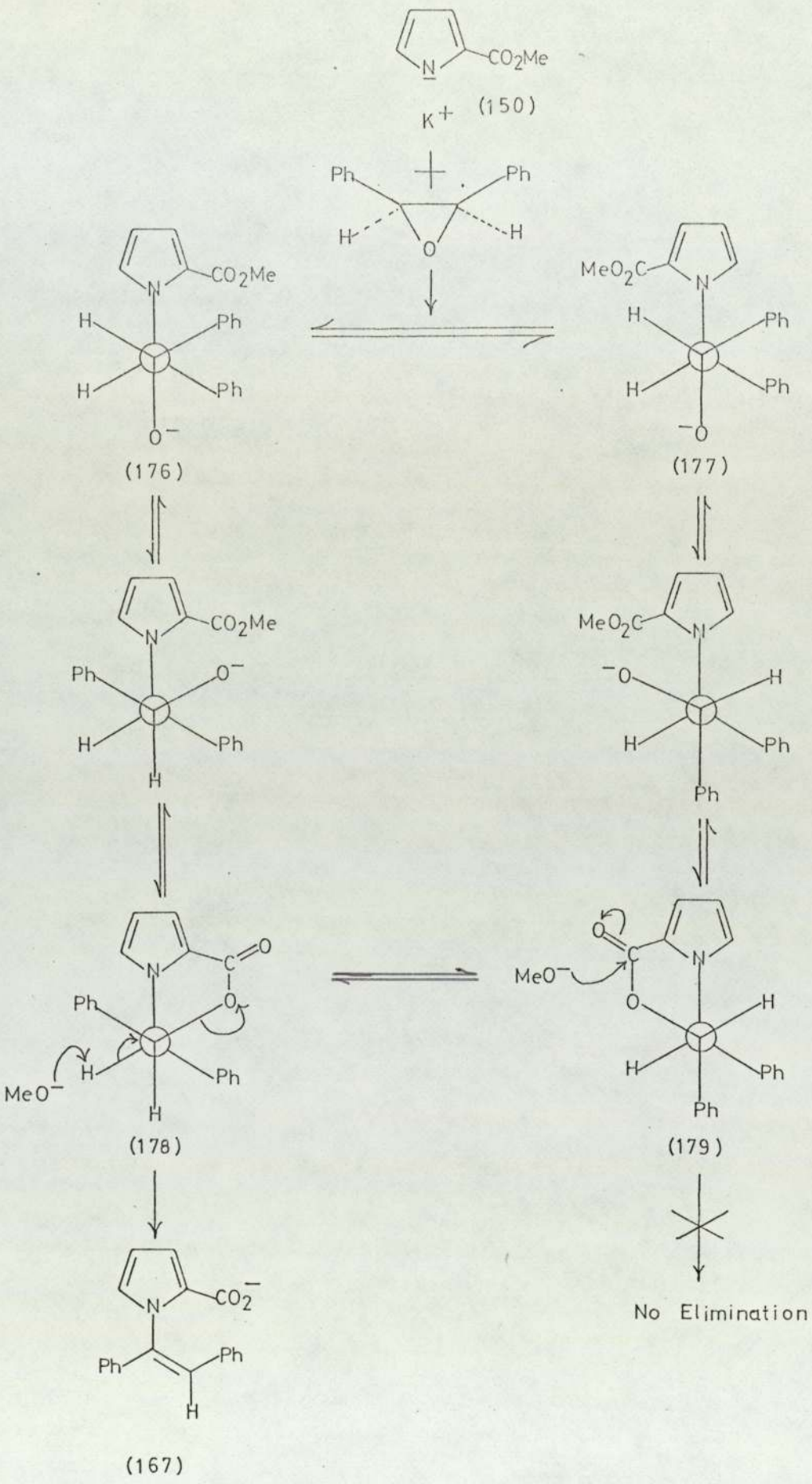
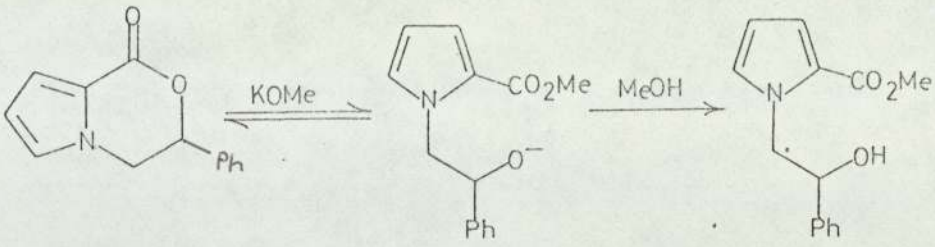
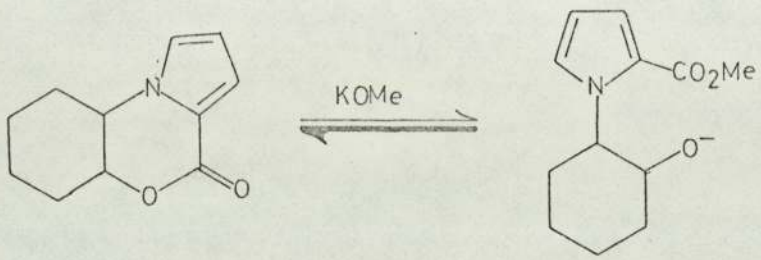

CO2Me
K+
(150)
Ph
Ph
H
H
O
Y
CO2Me
H
Ph
H
Ph
O−
(176)
MeO2C
H
Ph
H
Ph
−O
(177)
CO2Me
Ph
O−
H
Ph
H
MeO2C
−O
H
H
Ph
Ph
O
C
N
Ph
O
H
MeO−
H
Ph
H
(178)
MeO−
O
C
N
O
H
H
Ph
Ph
(179)
CO2−
N
Ph
Ph
H
(167)
No Elimination

Figure 24



(143) (180) (159)



(170) (181)

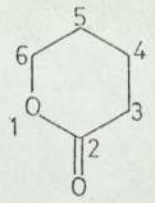
An indication of the relative stability of the two lactones (143 and 170) may be obtained by comparing the rates of hydrolysis of benzyl and cyclohexyl acetate (Table 7).

Compound	k (acid)
Benzyl acetate[153]	1675×10^6
Cyclohexyl acetate[154]	0.38×10^6

Table 7

These rates support the finding that the pyrrolooxazinone (143) was more susceptible to methanolysis than the pyrrolobenzoxazinone (170).

The ease of formation[155] of some δ-lactones has been shown to depend on the number and position of substituents in the alkyl chain (Table 8).



Substituent	% Lactone at Equilibrium	k (min.$^{-1}$)
None	9.0	0.24
3-Me	16.5	0.36
6-Me	21.2	0.56
4-Me-6,6-Me_2	95.5	3.02

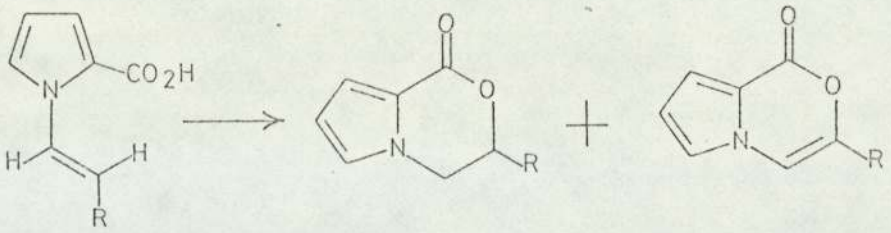
Table 8

The presence of larger numbers of alkyl groups increased both the rate of formation of the lactone and the proportion of lactone present at equilibrium. The cyclohexane ring will impart a degree of rigidity to the alkoxide (181) not found in the phenyl alkoxide (180), which will favour the lactone (170) in the equilibrium reaction.

4. Attempted cyclisation of 1-substituted vinylpyrrole-2-carboxylic acids.

The cyclisation of suitably substituted olefinic acids to give γ- and δ-lactones, has been extensively studied and reviewed.[156]

1-Substituted vinylpyrrole-2-carboxylic acids (157 and 164) were reacted with various reagents in an attempt to prepare derivatives of the 1H-pyrrolo[2,1-c][1,4]oxazin-1-one ring system.



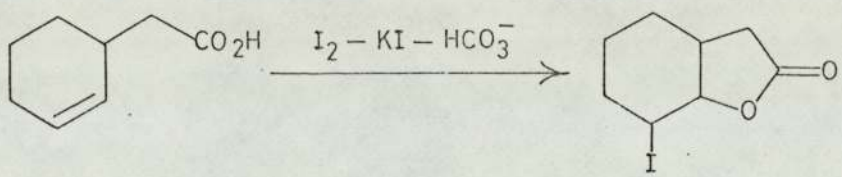
(164) R = Me

(157) R = Ph

To a large extent these attempts proved unsuccessful due to the lability of the 2-carboxylic acid group.[157] The replacement of the 2-carboxylic acid group occurs during halogenation and nitration reactions to such an extent that it may be used preparatively.[158]

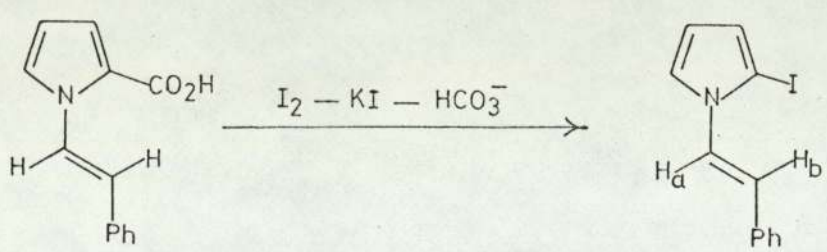
(a) Iodine-sodium bicarbonate.

The iodolactone (183) has been prepared by the reaction of iodine with the olefinic acid (182) under alkaline conditions.[159]



(182) (183)

trans-1-Styrylpyrrole-2-carboxylic acid (157) was reacted under similar conditions to give a product which was identified as trans-1-styryl-2-iodopyrrole (184). The product was unstable[160] and decomposed to a black mass on standing at room temperature for a few days.



(157) (184)

The infrared spectrum of the product showed the C:C absorption at 1650 cm.$^{-1}$ and the CH deformation of the trans CH:CH group at 950 cm.$^{-1}$

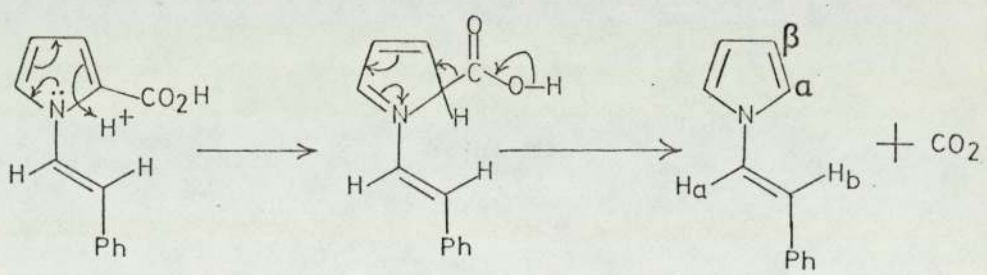
The n.m.r. spectrum showed proton Ha at τ 2.57 whereas it absorbed at τ 1.58 in the styrylpyrrole acid (157) illustrating the smaller amount of deshielding produced by the 2-iodo group.

The decarboxylation of pyrrole-2-carboxylic acids under these conditions has been reported elsewhere.[161]

(b) p-Toluenesulphonic acid

Suitably substituted olefinic acids have been cyclised to γ- and δ-lactones in the presence of strong acids such as p-toluenesulphonic acid.[156]

When trans-1-styrylpyrrole-2-carboxylic acid (157) was heated in benzene with p-toluenesulphonic acid the only product that could be identified was trans-1-styrylpyrrole (185). A possible mechanism may be as follows:



(157) (185)

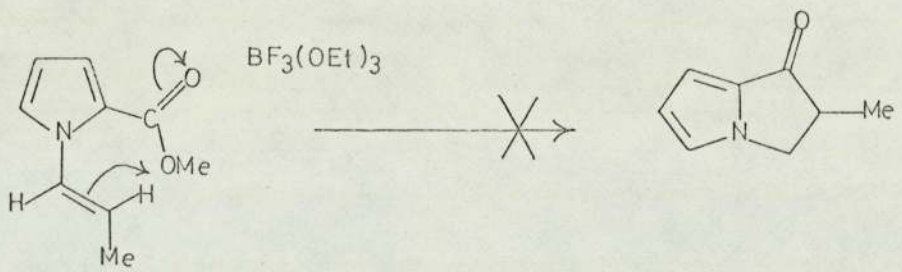
The infrared spectrum of the product showed the C:C absorption at 1645 cm.$^{-1}$ and the CH deformation of the trans CH:CH group at 950 cm.$^{-1}$

The chemical shift of proton H_a was τ 2.77 compared to τ 1.58 in the styrylpyrrole acid (157). The pyrrole protons appeared as two, two proton triplets at τ 3.14 (α) and τ 3.85 (β).

The tendency for pyrrole-2-carboxylic acids to undergo decarboxylation under mild acid conditions has been noted previously.[157]

(c) Boron trifluoride

The reaction of methyl trans-1-(2-methylvinyl)pyrrole-2-carboxylate (165) with boron trifluoride (triethyl etherate) failed to yield any of the expected ketone (186). The oily, intractable product could not be identified.



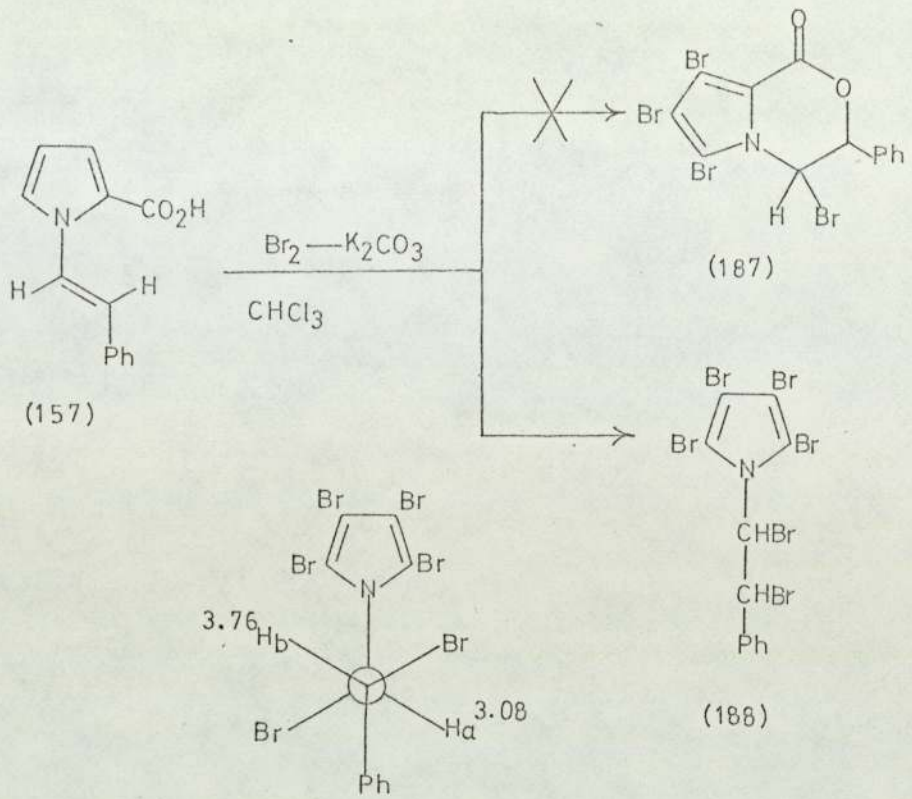
(165) (186)

Boron trifluoride has been used as an initiator in the cationic polymerisation of N-vinylindoles and carbazoles,[162] which probably accounts for the failure of the above reaction.

(d) Bromine

The reaction of trans-1-styrylpyrrole-2-carboxylic acid (157) with bromine[54] failed to give any of the expected bromolactone (187). The product was identified as 1-(1,2-dibromo-2-phenylethyl)-2,3,4,5-tetrabromopyrrole (188) and no styryl C:C stretching absorption was observed in the infrared spectrum.

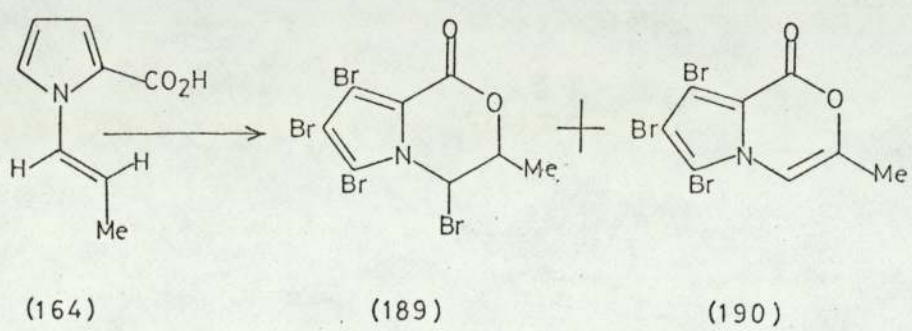
The chemical shifts of the bromopyrrole (188) are shown on the projection formula in Figure 25. The aliphatic protons, H_a and H_b were deshielded about τ 2 relative to the alcoholpyrrole acid (156). The vicinal coupling constant of 11.5 Hz indicated an anti-conformation of protons H_a and H_b.



$J_{a,b}$ = 11.5 Hz

Figure 25

The reaction of trans-1-(2-methylvinyl)pyrrole-2-carboxylic acid (164) with bromine in acetic acid under various conditions gave a mixture of the bromolactone (189) and the dehydrobrominated lactone (190). The infrared spectrum of the product showed lactone (C:O) absorptions at 1740 and 1720 $cm.^{-1}$

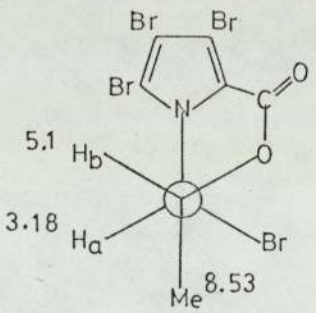


(164) (189) (190)

The n.m.r. spectrum of the product showed the presence of the two lactones in approximately equal proportions and the chemical shifts are shown in Figure 26.

In the bromolactone (189), proton H_a appeared as a doublet at τ 3.18 whilst proton H_b appeared as eight lines at τ 5.1. The vicinal coupling constants of 2 and 7 Hz were consistent with a conformation in which proton H_b was anti- to the 4-Br atom in order to facilitate elimination of hydrogen bromide. The vicinal coupling constant of 2 Hz was in close agreement with the calculated value of 1.5 Hz for the lactone (143, see page 81).

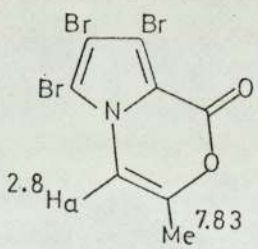
Proton H_a in the dehydrobrominated lactone (190) appeared as a singlet at τ 2.8 and the 3-methyl group as a singlet at τ 7.93. Aromatisation of the lactone had resulted in the deshielding of these absorptions.



$J_{a,b}$ = 2.0 Hz

$J_{Me,b}$ = 7.0 Hz

(189)



(190)

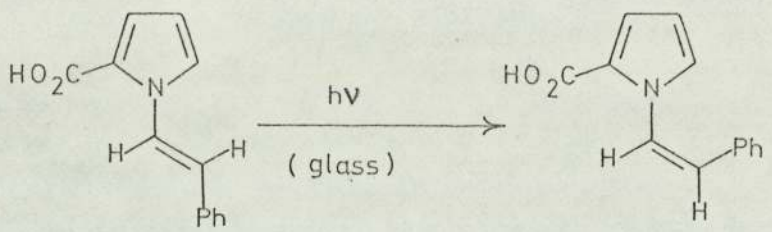
Figure 26

The lactones (189 and 190) had similar R_F values and could not be separated by tlc. The reaction of the mixture with lithium chloride in DMF[54] failed to dehydrobrominate the lactone (189).

5. Photochemical reactions

(a) Photochemical isomerisation

Irradiation of trans-1-styrylpyrrole-2-carboxylic acid (157) with filtered light from a low power UV lamp at 350 nm yielded cis-1-styrylpyrrole-2-carboxylic acid (191).[163] The infrared spectrum of the product showed the CH deformation of the cis CH:CH group at 700 $cm.^{-1}$



(157) (191)

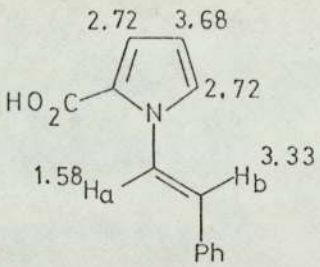
The electronic absorption spectra of the cis- and trans-isomers (157 and 191) and trans-2-styrylpyrrole[164] are shown in Table 9. The long wavelength absorption, due to conjugation between the two rings, occurred at 302 nm in the trans-isomer (157) but dropped to 270 nm in the cis-isomer (191). This hypsochromic shift was probably due to the phenyl and pyrrole rings being twisted slightly out of plane caused by interaction between the ortho-phenyl and α-pyrrole hydrogens.

Compound	λ_{max} nm	ε max
(157)	302	20,900
(191)	270	12,900
trans-2-styrylpyrrole[164]	333	31,200

Table 9.

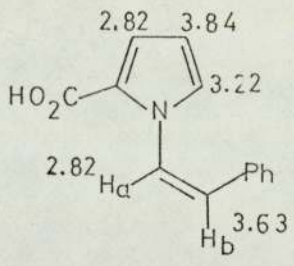
The absorption of trans-2-styrylpyrrole occurred at a longer wavelength than in trans-1-styrylpyrrole-2-carboxylic acid (157) indicating a greater degree of conjugation in the former compound.

The chemical shifts of the protons in cis- and trans-1-styrylpyrrole-2-carboxylic acids are shown in Figure 27. The smaller degree of conjugation present in the cis-isomer (191) caused a shielding of all the protons relative to the trans-isomer. This effect was most marked with proton H_a. The olefinic coupling constant of 8.5 Hz was consistent with a cis-configuration.



$J_{a,b}$ = 14.0 Hz

(157)



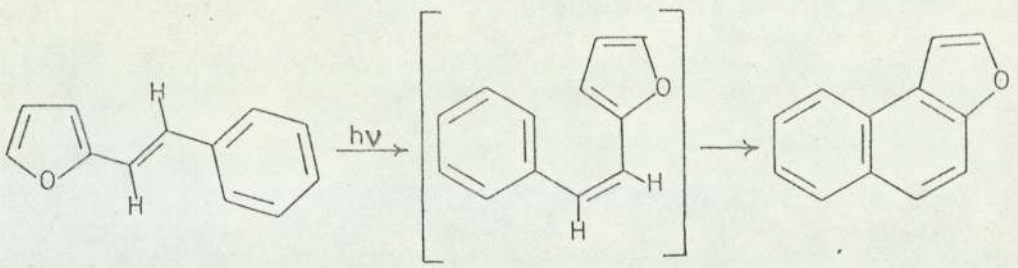
$J_{a,b}$ = 8.5 Hz

(191)

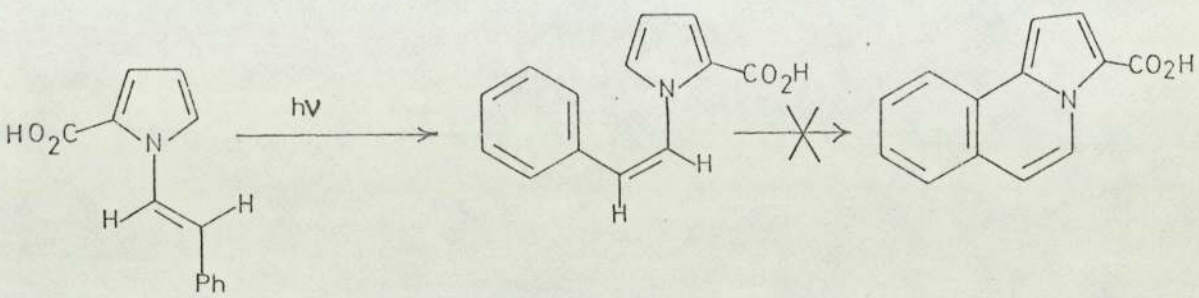
Figure 27

(b) Attempted photochemical cyclisation.

Loader and Timmons[165] have reported the photocyclisation of trans-2-styrylfuran (192) to yield the naphtho[2,1-b]furan (194) using ultraviolet light, presumably via the unisolated cis-intermediate (193). They also reported that 2-styrylpyrrole was destroyed under similar conditions.



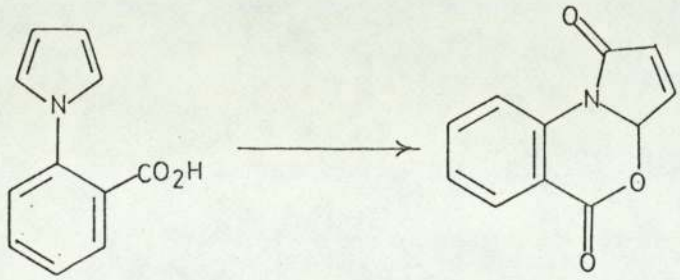
(192) (193) (194)



(157) (191)

Irradiation of trans-1-styrylpyrrole-2-carboxylic acid (157) with unfiltered light from a powerful lamp yielded the cis-isomer (191) almost immediately. Further irradiation of the solution resulted in a gradual destruction of the cis-isomer with no new absorption bands appearing. The product from the reaction mixture, which was contaminated with polymeric coloured material, could not be identified. This finding confirms earlier work on the difficulty of photocyclising pyrrole compounds.

The use of singlet oxygen has been reported[166] in the photooxidation of 1-(2-carboxyphenyl)pyrrole (195) to give the lactam-lactone (196). Pyrroles bearing electron-withdrawing substituents, however, did not undergo photooxidation.

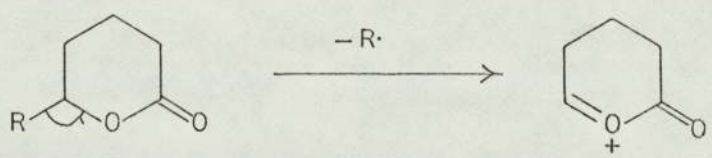


(195) (196)

6. Mass spectra

1H-3,4-Dihydro-3-phenylpyrrolo[2,1-c][1,4]oxazin-1-one (143).

The mass spectrum of the lactone (143) (Figure 28) showed a small molecular ion peak at m/e 213 (18%), a feature previously noted with other lactones.[167] The major fragmentation pathway from this ion yielded the base peak at m/e 107 (107.036960, C_6H_5NO)(M-PhCHO). The reported[167] mass spectra of δ-lactones (197) show a major decomposition due to fission α- to the ring oxygen atom but this fragmentation mode was not observed in the pyrrolooxazinone (143).



(197)

Fragmentation and rearrangement of the base peak ion yielded the pyridine ion at m/e 79 (79.042312, C_5H_5N) (107-CO), in common[168] with some other 1-substituted pyrroles, and then the ion at m/e 52 (79-HCN).

Loss of carbon dioxide from the molecular ion constituted a minor pathway yielding ions at m/e 169 (M-CO_2), m/e 168 (169-H) and m/e 167 (168-H). Fragmentation of this latter ion yielded ions at m/e 141 (167-C_2H_2) and m/e 140 (167-HCN).

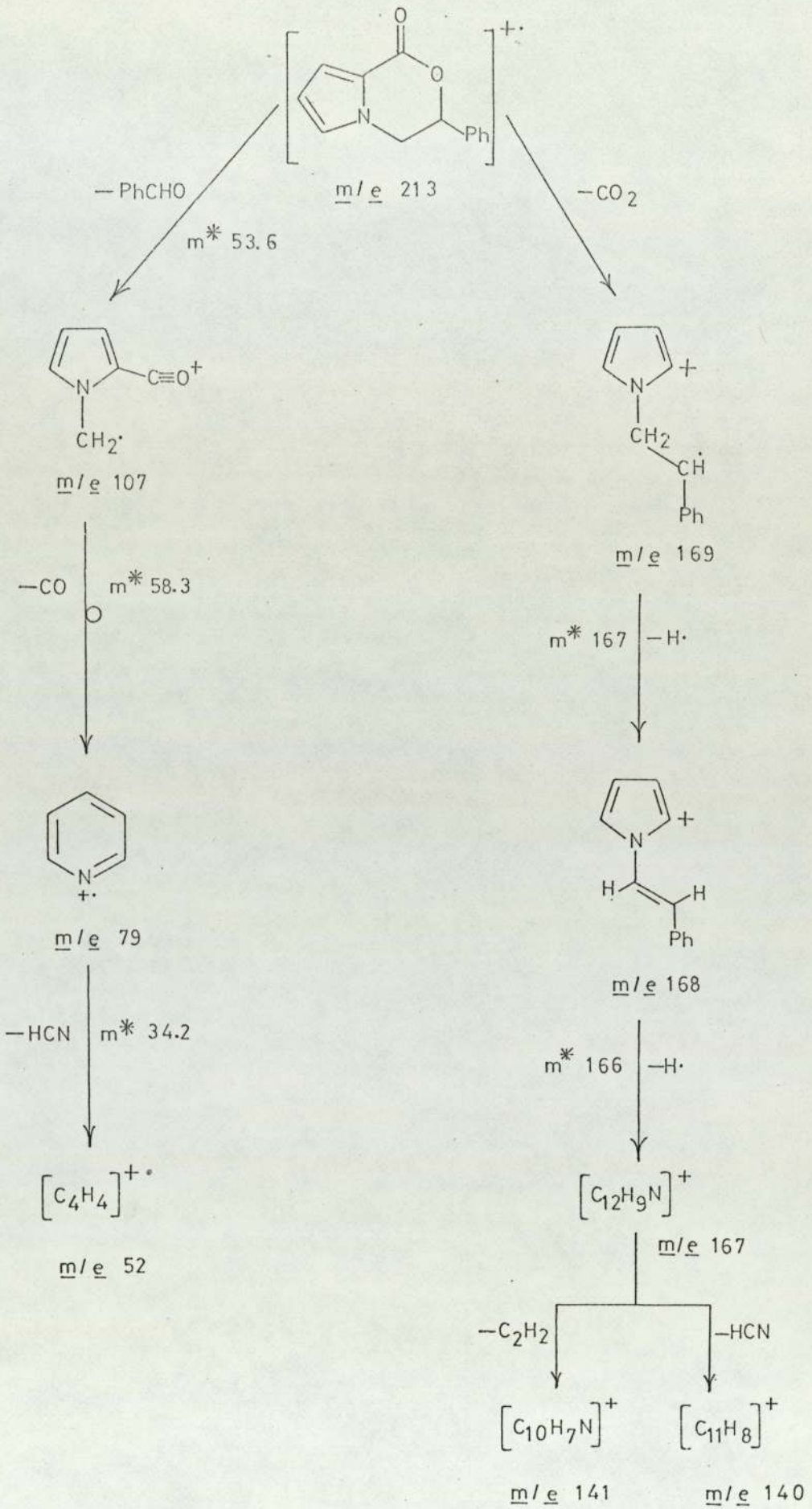
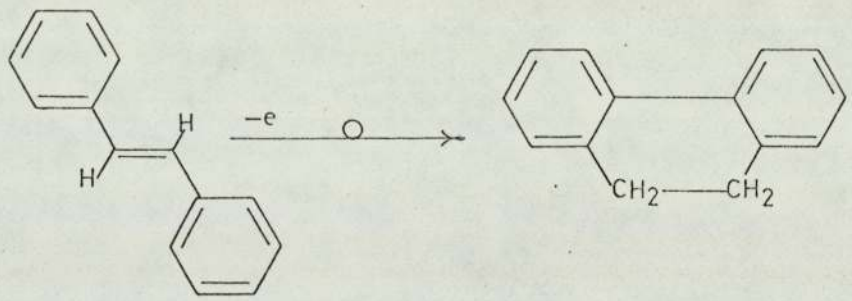

m/e 213
−PhCHO
m* 53.6
−CO2
m/e 107
−CO
m* 58.3
m/e 79
−HCN
m* 34.2
[C4H4]+·
m/e 52
m/e 169
m* 167
−H·
m/e 168
m* 166
−H·
[C12H9N]+
m/e 167
−C2H2
−HCN
[C10H7N]+
[C11H8]+
m/e 141
m/e 140

Figure 28

trans-1-Styrylpyrrole-2-carboxylic acid (157).

The mass spectrum of the vinylpyrrole acid (157) (Figure 29) showed a more intense molecular ion peak, at m/e 213 (39%), than was observed in the isomeric lactone (143).

The major fragmentation pathway from the molecular ion yielded the base peak at m/e 168 ($M-CO_2-H$). Decomposition and possible rearrangement of this ion yielded a fragment at m/e 167 (168-H). A similar rearrangement has been proposed[169] in the decomposition of stilbene (198) to account for the loss of a methyl radical.



(198)

Further fragmentation of the ion at m/e 167 gave ions at m/e 141 ($167-C_2H_2$) and m/e 140 (167-HCN).

Loss of carbon dioxide from the molecular ion yielded the 1-styrylpyrrole ion at m/e 169 ($M-CO_2$) which gave rise to ions at m/e 143 ($169-C_2H_2$) and m/e 142 (169-HCN).

Two minor pathways from the molecular ion yielded ions at m/e 212 (M-H) and m/e 94 (M-PhCCH-OH).

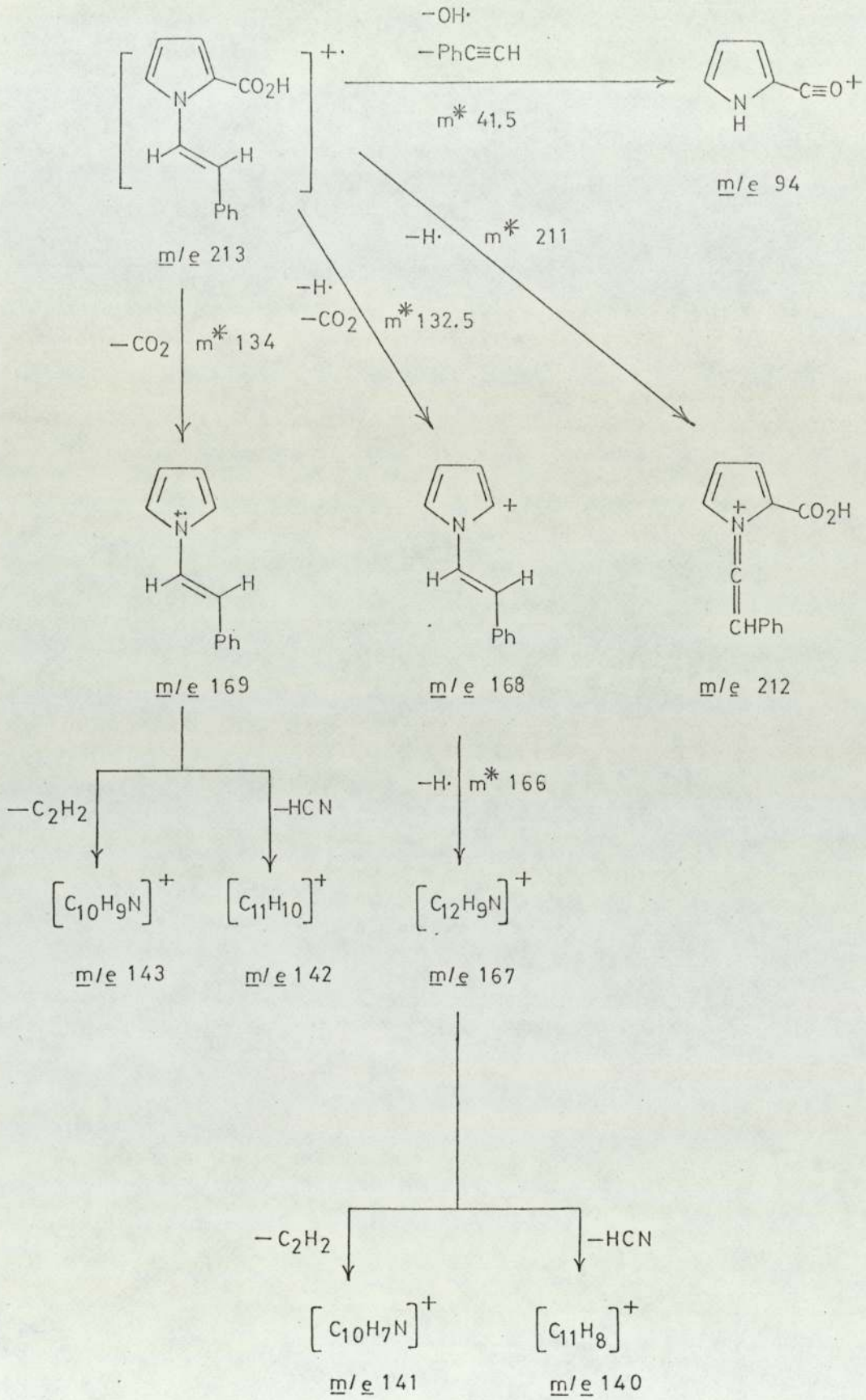

−OH·
−PhC≡CH
m* 41.5
m/e 94
m/e 213
−H·
m* 211
−H·
−CO2
m* 132.5
−CO2
m* 134
m/e 169
m/e 168
m/e 212
−C2H2
−HCN
−H·
m* 166
[C10H9N]+
[C11H10]+
[C12H9N]+
m/e 143
m/e 142
m/e 167
−C2H2
−HCN
[C10H7N]+
[C11H8]+
m/e 141
m/e 140

Figure 29

1-(2-Hydroxy-2-phenylethyl)pyrrole-2-carboxylic acid (156).

The mass spectrum of the alcoholpyrrole acid (156) (Figure 30) showed a small molecular ion peak at m/e 231 (5%) which decomposed by two major pathways.

Loss of water from the molecular ion gave the ion at m/e 213 ($M-H_2O$) which could be formulated as either the lactone (143) or the styrylpyrrole acid (157). Further fragmentation of this ion gave the base peak at m/e 107 (213-PhCHO) which is also the base peak in the mass spectrum of the lactone (143), but is absent from that of the styrylpyrrole acid (157). This suggests that the ion at m/e 213 had the lactone structure. Fragmentation of the base peak ion gave rise to ions at m/e 79 (107-CO) and m/e 52 (79-HCN).

Another fragmentation pathway from the molecular ion yielded the ion at m/e 125 (85%) (M-PhCHO) which gave rise to ions at m/e 81 ($125-CO_2$) and m/e 80 (125-OH-CO).

A minor fragmentation route yielded ions at m/e 169 ($M-CO_2-H_2O$) and m/e 168 (169-H).

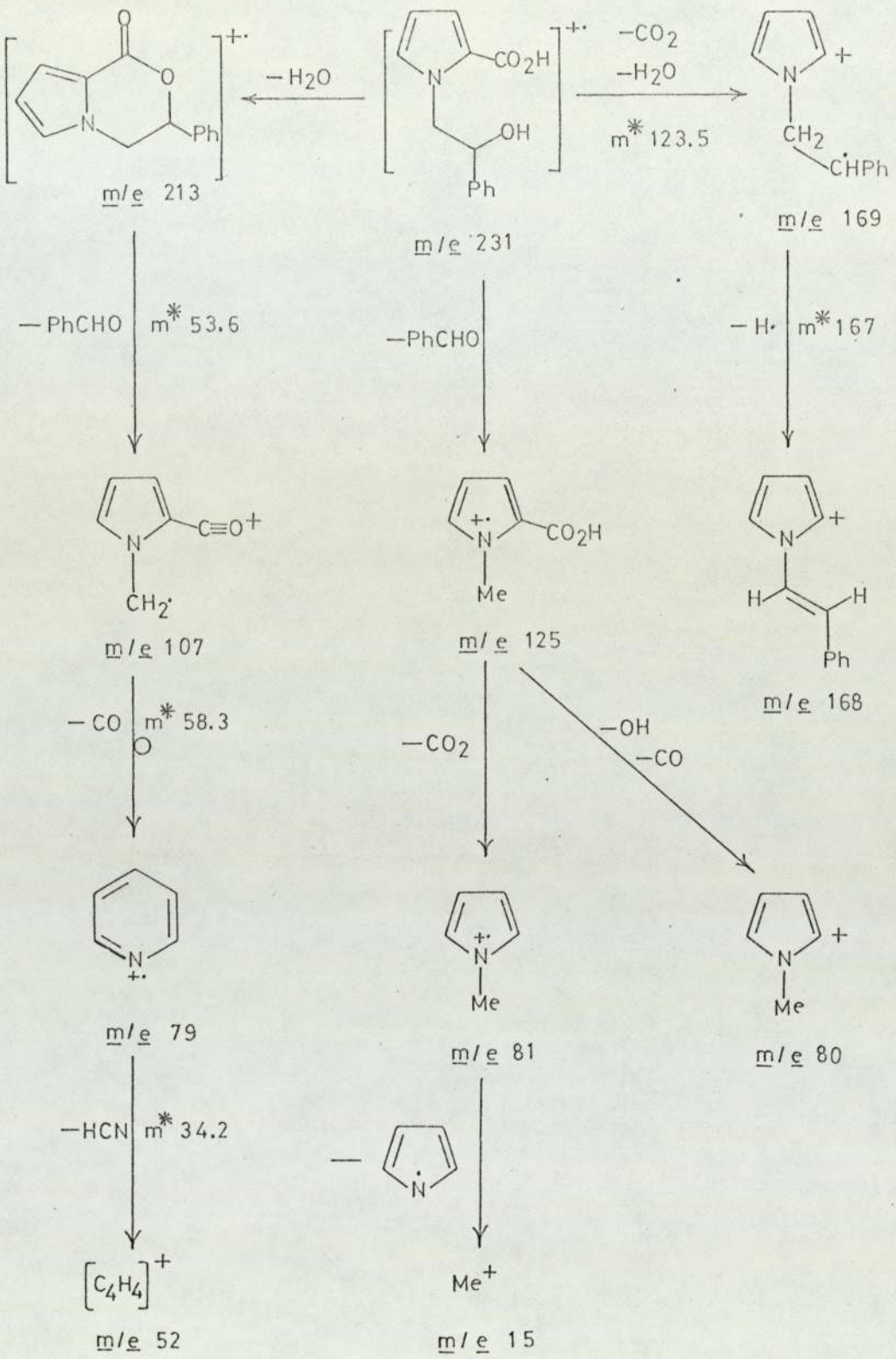

−H2O
−CO2
−H2O
m* 123.5
m/e 213
m/e 231
m/e 169
−PhCHO
m* 53.6
−PhCHO
−H·
m* 167
m/e 107
m/e 125
m/e 168
−CO
m* 58.3
−CO2
−OH
−CO
m/e 79
m/e 81
m/e 80
−HCN
m* 34.2
m/e 52
m/e 15

Figure 30

D. PHARMACOLOGICAL RESULTS

A selected number of compounds were submitted for preliminary pharmacological screening tests. These were all performed on mice and were designed to examine the presence of general C.N.S. activity.

(a) Acute toxicity

Large doses of the compound were administered by various routes and the LD 50's were measured and the symptoms they produced were noted.

(b) Phenylquinone induced writhing

This test has been used to detect narcotic analgesic antagonists which were inactive in the usual animal tests for analgesia (tail flick and hot plate). Blumberg, Wolf and Dayton[170] found a reasonable correlation between writhing prevention ED 50 values and analgesic properties in man, for a series of morphine antagonists. The test, however, lacks specificity[171] and will detect compounds with anti-inflammatory, analgesic, sedative, neuroleptic, anticholinergic, antihistaminic and antidepressant activity.

(c) Pentobarbitone sedation

A subthreshold dose of pentobarbitone was administered to the mice followed by a dose of the compound under test. A compound with neuroleptic, psychosedative or antihistaminic activity will potentiate the action of pentobarbitone, whereas the activity of other sedative compounds will only be additive.

(d) Five parameter neuropharmacological screen

(i) Mydriasis - a measure of anticholinergic activity

(ii) Rotating rod - a measure of muscular co-ordination

(iii) Grip strength - a measure of muscle tone and psychosedative activity

(iv) Hotplate - a measure of analgesia but the end point may be affected by other C.N.S. depressant activity and loss of muscle tone.

(v) Tonic extension and Death by Leptazol infusion - a measure of anticonvulsant activity

The following compounds were tested :

Tetrahydroisoquinolines

2-Cyclopropylmethyl-1,2,3,4-tetrahydroisoquinoline (69), 2-cyclobutylmethyl-1,2,3,4-tetrahydroisoquinoline (70) and 2-(3,3-dimethylallyl)-1,2,3,4-tetrahydroisoquinoline (71) were tested and found to possess little pharmacological activity.

Diphenylmethylpiperidines

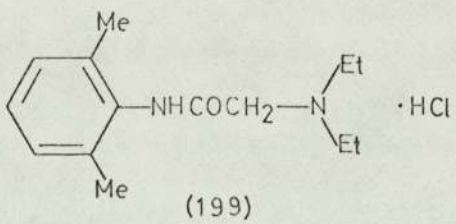
4-Diphenylmethylpiperidine (78), 1-cyclobutylcarbonyl-4-diphenylmethylpiperidine (79), 1-cyclobutylmethyl-4-diphenylmethyl piperidine (80), 1-cyclopropylmethyl-4-diphenylmethylpiperidine (81), 4-diphenylmethyl-1-trimethylacetylpiperidine (82) and 4-diphenylmethyl-1-neopentylpiperidine (83) were tested.

The amines (80 and 81) were active in the phenylquinone induced writhing test with ED 50's of 17.5 and 5.4 mg/Kg respectively, compared to pentazocine (3.8 mg/Kg) and cyclazocine (0.028 mg/Kg). The amines (78, 80 and 81) were active in tests for local anaesthetics but some histological work indicated that nerve damage had occurred.

Phenylpiperazines

1-Cyclopropylcarbonyl-4-phenylpiperazine (73), 1-cyclobutylcarbonyl-4-phenylpiperazine (75) and 1-cyclopropylmethyl-4-phenylpiperazine (74) were submitted for testing.

The phenylpiperazine derivatives had the most interesting pharmacological activities of all the compounds submitted for screening. Amine (74) was active in both the phenylquinone test (ED 50, 8.5 mg/Kg) and the pentobarbitone test (ED 50, 16.6 mg/Kg). At a dose of 30 mg/Kg it also protected 100% of the animals in the hot plate test. Tests for local anaesthetics have shown that amine (74) has an activity similar to lignocaine hydrochloride (199).



(199)

Further neuroleptic and psychosedative tests have shown that amine (74) has a similar pharmacological profile of action to chlorpromazine, both centrally and peripherally.

Work in other laboratories[172] has shown that amine (74) causes a sustained fall in blood pressure.

Miscellaneous compounds

2-Cyclohexylamino-1-phenylethanol (89), 2-phenethylamino-1-phenylethanol (90), 2-cyclohexylamino-O,N-diphenylacetyl-1-phenylethanol (94), 1-cyclohexyl-1-(2-hydroxy-2-phenylethyl)phenethylamine (95), 3-cyclohexyl-5-phenyloxazolidine (96), 3-phenethyl-5-phenyloxazolidine (97), 3-cyclohexyl-5-phenyloxazolidin-2-one (112), 4-cyclohexyl-6-phenylmorpholine-2,3-dione (129), 1-(2-hydroxy-2-phenylethyl)pyrrole-2-carboxylic acid (156), 1H-3-phenyl-3,4-dihydropyrrolo[2,1-c][1,4]oxazin-1-one (143), trans-1-(2-methylvinyl)pyrrole-2-carboxylic acid (164), 1-(cis-1,2-diphenylvinyl)pyrrole-2-carboxylic acid (168) and 4H-5a,6,7,8,9,9a-hexahydropyrrolo[2,1-c][1,4]benzoxazin-4-one (170) were found to possess little pharmacological activity in the above tests.

EXPERIMENTAL

Infrared spectra were recorded on a Unicam SP 200 spectrophotometer.

Ultraviolet spectra were recorded on a Unicam SP 800 spectrophotometer.

Nuclear magnetic resonance spectra were determined at 60 MHz using tetramethylsilane as internal standard on a Varian A60-A spectrometer. Abbreviations used in the interpretation of n.m.r. spectra: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad singlet; and J = coupling constant.

Mass spectra were determined with an A.E.I. MS9 spectrometer operating at 50 a and 70 eV. Mass spectral data is presented as m/e readings with the figures in parentheses representing the relative intensity of each peak. M^+ signifies the molecular ion peak; m^* denotes metastable peaks.

Melting points are uncorrected. Microanalyses were determined by Dr. F. B. Strauss, Oxford, England, or by Dr. A. Bernhardt, Max-Planck Institut fur Kohlenforschung, Mulheim, West Germany.

A. SYNTHESIS OF SOME TETRAHYDROISOQUINOLINE, PHENYLPIPERAZINE, AND DIPHENYLMETHYLPIPERIDINE DERIVATIVES.

General method for lithium aluminium hydride reduction of amides.

The amide in ether was added slowly to a stirred suspension of lithium aluminium hydride (1.5 g.) in ether, and the mixture was then heated under reflux for 18 hr. To the cooled mixture was added slowly, successive quantities of water (4 ml.), 30% aqueous sodium hydroxide solution (3 ml.) and sufficient water (ca. 10 ml.) to produce a granular precipitate. The ethereal mixture was filtered, dried ($MgSO_4$), and evaporated to give the product which either crystallised as the base or was converted to the hydrochloride salt with dry hydrogen chloride.

2-Cyclopropylmethyl-1,2,3,4-tetrahydroisoquinoline (69).

Cyclopropanecarboxylic acid chloride (5.0 g., 0.048 mole) in benzene (15 ml.) was added slowly to a stirred mixture of 1,2,3,4-tetrahydroisoquinoline (5.0 g., 0.038 mole) and sodium bicarbonate (7 g.) in benzene (15 ml.), and the mixture was then heated under reflux for 4 hr. The filtrate from the cooled reaction mixture was diluted with twice its own volume of ether, then washed successively with N-hydrochloric acid and water. Evaporation of the dried ($MgSO_4$) ethereal solution gave 2-cyclopropylcarbonyl-1,2,3,4-tetrahydroisoquinoline as a yellow oil (5.8 g.). The product was not purified further but was utilised in the next reaction.

2-Cyclopropylcarbonyl-1,2,3,4-tetrahydroisoquinoline (7.5 g., 0.037 mole) in ether (100 ml.) was added slowly to a stirred suspension of lithium aluminium hydride (2.5 g., 0.066 mole) in ether (100 ml.), and the mixture was then heated under reflux for 14 hr. The tetrahydroisoquinoline hydrochloride (69) (6.35 g., 76%) was isolated from the reaction mixture according to the general method. Recrystallisation from ethanol-ether gave colourless microprisms, m.p. 210-212°.

(Found: C, 69.9; H, 8.1; N, 6.1%; E.W., 226. $C_{13}H_{18}ClN$ requires C, 70.0; H, 8.1; N, 6.3%; E.W., 223).

$\nu_{max.}$ (Nujol) 2650, 2550, 2490 (tertiary amine salt NH), 1500 (aromatic nucleus), 1020 (cyclopropane skeletal stretch) and 760 (aromatic CH) $cm.^{-1}$

2-Cyclobutylmethyl-1,2,3,4-tetrahydroisoquinoline (70).

Cyclobutanecarboxylic acid chloride (7.1 g., 0.06 mole) in benzene (25 ml.) was added slowly to a stirred mixture of 1,2,3,4-tetrahydroisoquinoline (6.65 g., 0.05 mole) and sodium bicarbonate (5 g.) in benzene (25 ml.), and the mixture was then heated under reflux for 12 hr. The filtrate from the cooled reaction mixture was diluted with twice its own volume of ether, and then washed successively with N-hydrochloric acid and water. Evaporation of the dried ($MgSO_4$) ethereal solution gave 2-cyclobutylcarbonyl-1,2,3,4-tetrahydroisoquinoline as a yellow oil (7.2 g.). The product was not purified further but was utilised in the next reaction.

2-Cyclobutylcarbonyl-1,2,3,4-tetrahydroisoquinoline (6.45 g., 0.03 mole) in ether (100 ml.) was added slowly to a stirred suspension of lithium aluminium hydride (4.0 g., 0.105 mole) in ether (100 ml.), and the mixture was then heated under reflux for 14 hr. The tetrahydroisoquinoline hydrochloride (70) (5.2 g., 73%) was isolated from the reaction mixture according to the general method. Recrystallisation from ethanol-ether gave colourless microprisms, m.p. 193-194°.

(Found: C, 70.6; H, 8.3; N, 6.0%; E.W., 238. $C_{14}H_{20}ClN$ requires C, 70.7; H, 8.4; N, 5.9%; E.W., 237).

$\nu_{max.}$ (Nujol) 2700, 2500, 2420 (tertiary amine salt NH), 1510 (aromatic nucleus), 930 (cyclobutane skeletal stretch) and 770 (aromatic CH) $cm.^{-1}$

2-(3,3-Dimethylallyl)-1,2,3,4-tetrahydroisoquinoline (71).

1-Chloro-3-methyl-2-butene (6.25 g., 0.06 mole) in dimethylformamide (DMF) (20 ml.) was added slowly to a stirred mixture of 1,2,3,4-tetrahydroisoquinoline (6.65 g., 0.05 mole) and sodium bicarbonate (6 g.) in DMF (20 ml.), and the mixture was heated under reflux for 3 hr.[21,76] (DMF was used in preference to toluene because it gave improved yields and cleaner reactions). The brown mixture was stirred overnight at room temperature and then filtered. Evaporation of the DMF gave an oil which was dissolved in chloroform, and then washed with successive quantities of water to remove the last traces of DMF. The dried ($MgSO_4$) chloroform solution was evaporated to yield a purple oil which was dissolved in a little absolute ethanol and dry hydrogen chloride added. Addition of ether precipitated the tetrahydroisoquinoline hydrochloride (71) (8.3 g., 70%) as grey microprisms, m.p. 200-201° (from ethanol-ether).

(Found: C, 70.8; H, 8.3; N, 5.8%; E.W., 239. $C_{14}H_{20}ClN$ requires C, 70.7; H, 8.4; N, 5.9%; E.W., 237).

$\nu_{max.}$ (Hexachlorobutadiene) 2680, 2550, 2500 (tertiary amine salt NH), 1680 (allylC:C), 1460 (methyl CH bend) and 800 (aromatic CH) $cm.^{-1}$

The N-dimethylallyl amine (71) was regenerated from its hydrochloride and showed:

τ (CCl_4) 3.1 (4H, s, C_6H_4), 4.63 (1H, t, J 7Hz, C<u>H</u>:CMe_2), 6.46 (2H, s, 1-H_2), 6.94 (2H, d, J 7Hz, C<u>H</u>$_2$.CH:C), 7.1-7.5 (4H, m, 3-H_2 and 4-H_2), 8.3 (6H, 2br, C:C <u>Me</u>$_2$).

1-Cyclopropylcarbonyl-4-phenylpiperazine (73).

Cyclopropanecarboxylic acid chloride (1.05 g., 0.01 mole) in benzene (10 ml.) was added slowly to a stirred mixture of 1-phenylpiperazine (1.62 g., 0.01 mole), pyridine (1 drop) and sodium bicarbonate (2.0 g.) in

benzene (10 ml.), and the mixture was then heated under reflux for 18 hr. The cooled reaction mixture was diluted with twice its own volume of ether and washed three times with water. Evaporation of the dried ($MgSO_4$) ethereal solution gave a yellow oil (2.1 g.) which was dissolved in absolute ethanol and dry hydrogen chloride added. The piperazine hydrochloride (73) (2.1 g., 79%) was obtained on the addition of ether. Recrystallisation from methanol-ether gave colourless microprisms, m.p. 190-191°.

(Found: C, 62.9; H, 7.3; N, 10.7. $C_{14}H_{19}ClN_2O$ requires C, 63.0; H, 7.1; N, 10.5%).

$\nu_{max.}$(Nujol) 2400 (tertiary amine salt NH), 1625 (amide C:O), 1500 (aromatic nucleus), 1020 (cyclopropane skeletal stretch), 770 and 700 (aromatic CH) $cm.^{-1}$

1-Cyclopropylmethyl-4-phenylpiperazine (74).

1-Cyclopropylcarbonyl-4-phenylpiperazine (73) (4.2 g., 0.018 mole) in ether (50 ml.) was added slowly to a stirred suspension of lithium aluminium hydride (1.6 g., 0.042 mole) in ether (50 ml.) and the mixture was then heated under reflux for 18 hr. The piperazine dihydrochloride (74) (3.4 g., 64%) was isolated from the reaction mixture according to the general method. Recrystallisation from methanol-ether gave fine, colourless prisms, m.p. 187-188° (decomp.).

(Found: C, 58.0; H, 7.5; N, 9.8%; E.W., 147. $C_{14}H_{22}Cl_2N_2$ requires C, 58.1; H, 7.6; N, 9.7%; E.W., 148).

$\nu_{max.}$(Nujol) 2500 (tertiary amine salt NH), 1602, 1500 (aromatic ring), 1030 (cyclopropane skeletal stretch), 770 and 700 (aromatic CH)$cm.^{-1}$

1-Cyclobutylcarbonyl-4-phenylpiperazine (75).

Cyclobutanecarboxylic acid chloride (1.19 g., 0.01 mole) in benzene (10 ml.) was added slowly to a stirred mixture of 1-phenylpiperazine (1.62 g., 0.01 mole), pyridine (1 drop) and sodium bicarbonate (2.0 g.) in benzene (10 ml.), and the mixture was then heated under reflux for 4 hr. The cooled reaction mixture was diluted with twice its own volume of ether and washed three times with water. Evaporation of the dried ($MgSO_4$) ethereal solution gave a clear oil which crystallised on standing to give the piperazine (75) (1.2 g., 48%) as colourless prisms, m.p. 102-103° (from petrol b.p. 60-80°).

(Found: C, 73.6; H, 8.3; N, 11.6. $C_{15}H_{20}N_2O$ requires
C, 73.8; H, 8.2; N, 11.5%).

$\nu_{max.}$ (Nujol) 1620 (amide C:O), 1500 (aromatic nucleus),
910 (cyclobutane skeletal stretch), 770 and 700 (aromatic CH) $cm.^{-1}$

1-Cyclobutylmethyl-4-phenylpiperazine (76).

1-Cyclobutylcarbonyl-4-phenylpiperazine (75) (2.88 g., 0.011 mole) was added slowly to a stirred suspension of lithium aluminium hydride (1.0 g., 0.026 mole) in dry ether (100 ml.) and the mixture was then heated under reflux for 18 hr. The piperazine hydrochloride (76) (1.8 g., 67%) was isolated from the reaction mixture according to the general method. Recrystallisation from ethanol-ether gave colourless prisms, m.p. 218-219° (decomp.).

(Found: C, 68.1; H, 8.7; N, 10.4%; E.W., 145. $C_{15}H_{23}ClN_2$ requires
C, 67.6; H, 8.6; N, 10.5%; E.W., 134).

$\nu_{max.}$ (Nujol) 2600, 2500 (tertiary amine salt NH), 1602 (aromatic ring),
930 (cyclobutane skeletal stretch), 760 and 695 (aromatic CH) $cm.^{-1}$

1-(o-Chlorophenyl)-4-cyclopropylcarbonylpiperazine (77).

Cyclopropanecarboxylic acid chloride (1.05 g., 0.01 mole) in benzene (10 ml.) was added slowly to a stirred mixture of 1-(o-chlorophenyl) piperazine (1.97 g., 0.01 mole), pyridine (1 drop) and sodium bicarbonate (2.0 g.) in benzene (10 ml.), and the mixture was then heated under reflux for 18 hr. The cooled reaction mixture was diluted with twice its own volume of ether and washed three times with water. Evaporation of the dried ($MgSO_4$) ethereal solution gave a clear oil which crystallised on standing to give the piperazine (77) (1.45 g., 55%) as colourless needles, m.p. 86-87° (from petrol b.p. 60-80°).

(Found: C, 63.7; H, 6.5; N, 10.4. $C_{14}H_{17}ClN_2O$ requires C, 63.5; H, 6.4; N, 10.6%).

$\nu_{max.}$ (Nujol) 1630 (amide C:O), 1020 (cyclopropane skeletal stretch), 760, 730 and 680 (aromatic CH) $cm.^{-1}$

1-Cyclobutylcarbonyl-4-diphenylmethylpiperidine (79).

Cyclobutanecarboxylic acid chloride (3.85 g., 0.0325 mole) in benzene (50 ml.) was added slowly to a stirred mixture of 4-diphenyl methylpiperidine[173] (7.53 g., 0.03 mole) and sodium bicarbonate (3 g.) in benzene (50 ml.), and the mixture was then heated under reflux for 4 hr. The mixture was cooled and filtered. The filtrate was diluted with twice its own volume of ether and then washed successively with N-hydrochloric acid and water. Evaporation of the dried ($MgSO_4$) ethereal solution gave the piperidine (79) (6.2 g., 62%) as a clear oil which crystallised on trituration with petrol (b.p. 60-80°). Recrystallisation from acetone-petrol (b.p. 60-80°) gave colourless prisms, m.p. 121-122°.

(Found: C, 82.7; H, 7.9; N, 4.3. $C_{23}H_{27}NO$ requires C, 82.9; H, 8.1; N, 4.2%).

$\nu_{max.}$ (Nujol) 1630 (amide C:O), 1495 (aromatic nucleus), 920 (cyclobutane skeletal stretch), 780, 710 and 680 (aromatic CH) cm.$^{-1}$

1-Cyclobutylmethyl-4-diphenylmethylpiperidine (80).

1-Cyclobutylcarbonyl-4-diphenylmethylpiperidine (79) (2.15 g., 0.006 mole) in ether (50 ml.) was added slowly to a stirred suspension of lithium aluminium hydride (1.52 g., 0.04 mole) in ether (50 ml.), and the mixture was then heated under reflux for 18 hr. The piperidine hydrochloride (80)(1.43 g., 62%) was isolated from the reaction mixture according to the general method. Recrystallisation from ethanol-ether gave colourless microprisms, m.p. 248-249°.

(Found: C, 77.6; H, 8.2; N, 4.0%; E.W., 372. $C_{23}H_{30}ClN$ requires C, 77.7; H, 8.4; N, 3.9%; E.W., 355).

$\nu_{max.}$ (Nujol) 2600, 2500 (tertiary amine salt NH), 1600, 1505 (aromatic nucleus), 930 (cyclobutane skeletal stretch), 760, 745 and 700 (aromatic CH)cm.$^{-1}$

1-Cyclopropylmethyl-4-diphenylmethylpiperidine (81).

Cyclopropanecarboxylic acid chloride (2.35 g., 0.022 mole) in benzene (25 ml.) was added slowly to a stirred mixture of 4-diphenyl methylpiperidine (5.15 g., 0.02 mole) and sodium bicarbonate (3.0 g.) in benzene (25 ml.), and the mixture was then heated under reflux for 3 hr. The filtrate from the cooled reaction mixture was diluted with twice its own volume of chloroform and then washed successively with N-hydrochloric acid and water. Evaporation of the dried ($MgSO_4$) chloroform solution gave 1-cyclopropylcarbonyl-4-diphenylmethylpiperidine as a yellow oil (8.3 g.). The product was not purified further but utilised in the next reaction.

1-Cyclopropylcarbonyl-4-diphenylmethylpiperidine (8.3 g., 0.026 mole) in ether was added slowly to a stirred suspension of lithium aluminium hydride (2.5 g., 0.066 mole) in ether (100 ml.), and the mixture was then heated under reflux for 18 hr. The piperidine hydrochloride (81) (5.4 g., 79% overall from 4-diphenylmethylpiperidine) was isolated from the reaction mixture according to the general method as colourless platelets, m.p. 234-235 (from ethanol-ether).

(Found: C, 77.1; H, 8.1; N, 4.2%; E.W., 351. $C_{22}H_{28}ClN$ requires C, 77.3; H, 8.2; N, 4.1%; E.W., 342).

$\nu_{max.}$(Nujol) 2680, 2580, 2480 (tertiary amine salt NH), 1503 (aromatic nucleus), 1030 (cyclopropane skeletal stretch), 750, 740, 700 and 695 (aromatic CH) $cm.^{-1}$

4-Diphenylmethyl-1-trimethylacetylpiperidine (82).

Trimethylacetyl chloride (1.2 g., 0.01 mole) in benzene (10 ml.) was added slowly to a stirred mixture of 4-diphenylmethylpiperidine (2.51 g., 0.01 mole), pyridine (1 drop) and sodium bicarbonate (2.0 g.) in benzene (10 ml.), and the mixture was then heated under reflux for 18 hr. The filtrate from the cooled reaction mixture was diluted with twice its own volume of ether and washed three times with water. Evaporation of the dried ($MgSO_4$) ethereal solution gave a yellow oil which crystallised on standing to give the piperidine (82) (2.3 g., 68%) as colourless platelets, m.p. 140-141° (from acetone-petrol b.p. 40-60°).

(Found: C, 82.6; H, 8.8; N, 4.3. $C_{23}H_{29}NO$ requires C, 82.4; H, 8.6; N, 4.2%).

$\nu_{max.}$(Nujol) 1620 (amide C:O), 750, 710 and 695 (aromatic CH) $cm.^{-1}$

4-Diphenylmethyl-1-neopentylpiperidine (83).

4-Diphenylmethyl-1-trimethylacetylpiperidine (5.26g., 0.016 mole) in ether (50 ml.) was added slowly to a stirred suspension of lithium aluminium hydride (1.6 g., 0.042 mole) in ether (50 ml.), and the mixture was then heated under reflux for 18 hr. The piperidine hydrochloride (83) (4.0 g., 71%) was isolated from the reaction mixture according to the general method as colourless, crystalline prisms, m.p. 271-273° (decomp.) (from methanol-ether).

(Found: C, 77.1; H, 8.8; N, 3.9%; E.W., 361. $C_{23}H_{32}ClN$ requires C, 77.2; H, 8.9; N, 3.9%; E.W., 357).

$\nu_{max.}$ (Nujol) 2650, 2500 (tertiary amine salt NH), 750, 740 and 700 (aromatic CH) $cm.^{-1}$

4-(4-Diphenylmethylpiperid-1-yl)-4'-fluorobutyrophenone (84).

Ethyleneketal of 4-chloro-4'-fluorobutyrophenone.

Ethane-1,2-diol (3.1 g., 0.05 mole), 4-chloro-4'-fluorobutyrophenone (10 g., 0.05 mole) and p-toluenesulphonic acid (0.1 g.) in benzene (100 ml.) were heated under reflux in a Dean and Stark apparatus for 18 hr. After 4 hr. a further quantity of ethane-1,2-diol (3.1 g.) was added to the mixture and heating continued.[78] The cooled reaction mixture was washed successively three times with 5% aqueous sodium bicarbonate solution and water. Evaporation of the dried ($MgSO_4$) benzene solution gave 2-(3-chloropropyl)-2-(4-fluorophenyl)-1,3-dioxolane (86)[77] (12.2 g., 100%) as a clear, colourless oil. The infra-red spectrum showed no carbonyl absorption. The ketal was not purified further and was utilised in the following reaction.

4-Diphenylmethylpiperidine (2.51 g., 0.01 mole), ketal (86) (2.76 g., 0.011 mole) and potassium carbonate (2.5 g., 0.02 mole) in

n-butanol (40 ml.) were refluxed for 66 hr.[79] The filtrate from the cooled reaction mixture was evaporated to give an oil which was dissolved in methanol-water, acidified with 2N-hydrochloric acid and refluxed for 1 hr. The cooled mixture was diluted with water, basified and extracted with ether. Evaporation of the dried ($MgSO_4$) ethereal solution gave an oil (3.2 g.) which crystallised on trituration with petrol (b.p. 60-80°) to give the butyrophenone (84) (2.86 g., 69%) as fine, colourless needles, m.p. 130-131° (from ethanol).

(Found: C, 80.8; H, 7.4; N, 3.5%; E.W., 422. $C_{28}H_{30}FNO$ requires C, 80.9; H, 7.2; N, 3.4%; E.W., 415).

$\nu_{max.}$ (Nujol) 1680 (C:O), 1600, 1500 (aromatic nucleus), 760 and 710 (aromatic CH) $cm.^{-1}$

B. SYNTHESIS OF SOME β-PHENYLETHANOLAMINE DERIVATIVES.

1. β-Amino alcohols and acylated derivatives.

2-Cyclohexylamino-1-phenylethanol (89).[174]

Styrene oxide (2.4 g., 0.02 mole) and cyclohexylamine (2.18 g., 0.022 mole) were mixed together and allowed to stand at room temperature for two weeks. The crystalline product which had separated was collected. Recrystallisation from petrol (b.p. 60-80°) gave the amino alcohol (89) (2.48 g., 56%) as long colourless needles, m.p. 87-88° undepressed by an authentic sample.[175]

$\nu_{max.}$ (Nujol) 3250 (bonded OH), 3100 (bonded NH), 1500 (aromatic nucleus), 1120 (secondary C·OH) 750 and 700 (aromatic CH) $cm.^{-1}$

τ ($CDCl_3$) 2.9 (5H, br, Ph), 5.47 (1H, q, 1-H), 7.0-7.5 (2H, m, 2-CH_2), 8.0-9.3 (11H, m, C_6H_{11}).

2-Phenethylamino-1-phenylethanol (90).[176]

A mixture of phenethylamine (26.62 g., 0.22 mole) and styrene oxide (24 g., 0.2 mole) was allowed to stand for four days at room temperature. The solidified reaction mixture was washed with 50% benzene-petrol (b.p. 60-80°) and the crystalline material collected. Refrigeration of the evaporated filtrate gave more crystalline product. The amino alcohol (90) (19.8 g., 41%) was obtained as colourless needles, m.p. 90-91° (lit. 89.5-90°)[90] (from acetone-petrol b.p. 60-80°).

(Found: C, 79.6; H, 7.9; N, 6.0. $C_{16}H_{19}NO$ requires C, 79.7; H, 7.9; N, 5.8%).

$\nu_{max.}$ (Nujol) 1600 (aromatic nucleus), 1120 (secondary C·OH), 760, 750 and 710 (aromatic CH) $cm.^{-1}$

τ (C_6H_6) 5.3-5.6 (1H, m, 1-H), 7.4-7.6 (6H, m, 2-H_2 and N·$\underline{CH_2}\underline{CH_2}$·Ph).

2-Cyclohexylamino-O,N-diphenylacetyl-1-phenylethanol (94).

Phenylacetyl chloride (13.1 g., 11.2 ml., 0.085 mole) in dry benzene (50 ml.) was added slowly to a rapidly stirred mixture of 2-cyclohexylamino-1-phenylethanol (89) (8.7 g., 0.04 mole) and sodium bicarbonate (10 g.) in dry benzene (50 ml.), and the mixture was then heated under reflux for 4 hr. The cooled reaction mixture was diluted with twice its own volume of ether and washed with water. Evaporation of the dried ($MgSO_4$) ethereal solution gave the diphenylacetyl derivative (94) as a clear oil which crystallised from acetone-petrol (b.p. 60-80°) as colourless plates (8.6 g., 47%), m.p. 84-85° (from petrol b.p. 80-100°).

(Found: C, 78.9; H, 7.4; N, 3.3. $C_{30}H_{33}NO_3$ requires
C, 79.1; H, 7.3; N, 3.1%),

$\nu_{max.}$ (Nujol) 1730 (ester C:O), 1620 (amide C:O), 1500 (aromatic nucleus), 730 and 710 (aromatic CH) $cm.^{-1}$

1-Cyclohexyl-1-(2-hydroxy-2-phenylethyl) phenethylamine (95).

2-Cyclohexylamino-O,N-diphenylacetyl-1-phenylethanol (94) (26.45 g., 0.058 mole) in dry ether (150 ml.) was added slowly to a stirred suspension of lithium aluminium hydride (4.6 g., 0.121 mole) in dry ether (200 ml.), and the mixture was then heated under reflux for 18 hr. and stirred at room temperature for a further 48 hr. The reaction mixture was treated according to the general method to yield an ethereal solution of the product which was evaporated to 50 ml. The ethereal solution was washed successively with 6% aqueous sodium hydroxide solution and water. Evaporation of the dried ($MgSO_4$) ethereal solution gave a pale coloured oil (24.5 g.) which was dissolved in absolute ethanol and dry hydrogen chloride added. The amine hydrochloride (95) (19.8 g., 94%) precipitated as colourless microprisms, m.p. 163-164° (from ethanol-ether).

(Found: C, 73.3; H, 8.5; N, 3.9%; E.W., 364. $C_{22}H_{30}ClNO$ requires C, 73.4; H, 8,4; N, 3.9%; E.W., 359).

$\nu_{max.}$(Nujol) 3200 (alcohol OH), 2700, 2600, 2550 (tertiary amine salt NH), 1500 (aromatic nucleus), 765 and 705 (aromatic CH) $cm.^{-1}$

2. Oxazolidines.

3-Cyclohexyl-5-phenyloxazolidine (96).

2-Cyclohexylamino-1-phenylethanol (89) (2.19 g., 0.01 mole) and 40% formalin solution (1 ml.) in absolute ethanol (20 ml.) were heated under reflux for 12 hr.[99] Evaporation of the ethanolic solution gave an oil which was distilled, b.p. 126-130°/0.3 mm, to give the oxazolidine (96) (1.88 g., 81%) as a clear mobile liquid. The free base was dissolved in ether and hydrogen chloride added to give the hydrochloride (1.48 g., 64%) as fine colourless prisms, m.p. 158-159° (from ethanol-ether). The hydrochloride was stored in a desiccator.

(Found: C, 67.2; H, 8.2; N, 5.1%; E.W., 270. $C_{15}H_{21}ClNO$ requires C, 67.3; H, 8.2; N, 5.2%; E.W., 267).

$\nu_{max.}$ (Nujol) 2550, 2490 (tertiary amine salt NH), 1500 (aromatic nucleus), 1120 (O·C·N), 770 and 705 (aromatic CH) $cm.^{-1}$

3-Phenethyl-5-phenyl oxazolidine (97)

2-Phenethylamino-1-phenylethanol (90) (4.8 g., 0.02 mole) and 40% formalin solution (2.5 ml.) in absolute ethanol (40 ml.) were heated under reflux for 18 hr.[99] Evaporation of the ethanolic solution gave an oil which was dissolved in ether and dried ($MgSO_4$). Evaporation of the ethereal solution, and distillation, b.p. 162-168°/0.5 mm., of the resultant oil, gave the oxazolidine (97) (4.18 g., 82%) as a pale, straw-coloured oil. Addition of dry hydrogen chloride to a solution of the base in ether precipitated the hydrochloride (2.7 g., 53%) as colourless prisms, m.p. 130-131° (from methanol-ether). The hydrochloride was stored in a desiccator.

(Found: C, 70.3; H, 7.1; N, 5.0%; E.W., 291. $C_{17}H_{20}ClNO$ requires C, 70.5; H, 6.9; N, 4.8%; E.W., 289).

$\nu_{max.}$ (Nujol) 2500, 2450 (tertiary amine salt NH), 1104 (O·C·N), 760 and 700 (aromatic CH) $cm.^{-1}$

τ (Neat base) 2.88 (10H, 2br, 2Ph), 5.19 (1H, t, J 7.5 Hz, 5-H), 5.63 (2H, s, 2-H_2), 6.93 (1H, q, J 7.5 and 10.5 Hz, 4-H), 7.4 (4H, s, N·CH_2·CH_2-Ph) and 7.48 (1H, q, J 7.5 and 10.5 Hz, 4-H').

3-Cyclohexyl-2-(4-nitrophenyl)-5-phenyloxazolidine (98).

2-Cyclohexylamino-1-phenylethanol (89) (2.19 g., 0.01 mole) and 4-nitrobenzaldehyde (1.51 g., 0.01 mole) in benzene (50 ml.) were heated together under reflux for 1 hr. in a Dean and Stark apparatus. Samples taken every 15 min. showed by tlc (alumina/50% chloroform-petrol) the slow development of a third component running faster than either of the two starting materials. At the end of 1 hr. p-toluenesulphonic acid (0.2 g.) was added to the mixture and after a further 30 min. reflux, a sample showed only a trace of the starting materials remaining. Refluxing for a further 3 hr. followed by evaporation of the benzene solution gave a brown oil (3.1 g.) which failed to crystallise.

$\nu_{max.}$ (Thin liquid film) 2950, 2900 (CH stretch), 1600 (aromatic nucleus), 1530 (C·NO_2 asym. stretch), 1350 (C·NO_2 sym. stretch), 750, 700 and 690 (aromatic CH) $cm.^{-1}$

Distillation of the oil produced much charring and the separation of yellow crystals on the bulb of the thermometer.

The oxazolidine picrate (98) was obtained as bright yellow prisms, m.p. 144-146° (from water-ethanol).

(Found: C, 54.4; H, 5.0; N, 11.7. $C_{27}H_{27}N_5O_{10}$ requires C, 55.7; H, 4.6; N, 12.0%).

τ (Base in CCl_4) 1.8-2.4 (4H, m, 4-$NO_2C_6H_4$), 2.8 (5H, 2 br, Ph), 4.48 (1H, d, 2-H), 5.0 (1H, m, 5-H), 6.3-7.4 (2H, m, 4-H_2), 8.0-9.1 (11H, m, C6H11).

3-Cyclohexyl-2-(4-fluorophenyl)-5-phenyloxazolidine (101)

2-Cyclohexylamino-1-phenylethanol (89) (4.38 g., 0.02 mole), 4-fluorobenzaldehyde (2.48 g., 0.02 mole) and p-toluenesulphonic acid (0.2 g.) in benzene (60 ml.) were heated under reflux for 18 hr. Evaporation of the benzene solution gave an oil which was distilled, b.p. 182-186°/0.5 mm., to give the oxazolidine (101) (4.2 g., 65%) as a pale yellow oil. The oxazolidine ring underwent hydrolysis on standing for one week at room temperature.

$\nu_{max.}$ (Thin liquid film) 1600 (aromatic nucleus), 1140 (O·C·N), 760, 700 and 680 (aromatic CH) $cm.^{-1}$

τ (CCl_4) 2.4-3.2 (9H, m, Ph and 4-FC_6H_4), 4.63 (1H, s, 2-H), 5.1 (1H, q, J 7 and 14 Hz, 5-H), 6.5-7.5 (2H, m, 4-H_2) and 8.0-9.1 (11H, m, C_6H_{11}).

3-Cyclohexyl-2-methyl-5-phenyloxazolidine (99).

2-Cyclohexylamino-1-phenylethanol (89) (4.38 g., 0.02 mole) and acetaldehyde (0.97 g., 0.022 mole) in ether (100 ml.) were left at room temperature for 2 days.[101] Anhydrous potassium carbonate (4 g.) was added, and the mixture was then refluxed for 2 hr. Evaporation of the ethereal filtrate from the reaction mixture gave an oil which was distilled, b.p. 135-140°/0.6 mm., to give the oxazolidine (99) (4.2 g., 85%) as a clear oil which failed to crystallise. The preparation of the hydrochloride salt caused hydrolysis of the oxazolidine ring.

$\nu_{max.}$ (Thin liquid film) 1460 (Me C·H bend), 1385 (Me C·H bend), 1140 (O·C·N), 760 and 700 (aromatic CH) $cm.^{-1}$

τ (Neat base) 2.76 (5H, br, Ph), 4.98 (1H, q, J 6 and 9.5 Hz, 5-H), 5.28 (1H, q, J 5 Hz, 2-H), 6.6-7.7 (2H, m, 4-H_2), 8.0-9.2 (11H, m, C_6H_{11}) and 8.7 (3H, d, J 5 Hz, 2-Me).

2-Methyl-3-phenethyl-5-phenyloxazolidine (100).

2-Phenethylamino-1-phenylethanol (90) (7.23 g., 0.03 mole) and acetaldehyde (1.45 g., 0.033 mole) in ether (200 ml.) were left at room temperature for 2 days. Anhydrous potassium carbonate (5 g.) was added, and the mixture was then refluxed for 3 hr.[101] Evaporation of the ethereal filtrate from the reaction mixture gave an oil which was distilled, b.p. 175-180°/1.0 mm., to give the oxazolidine (100) (6.6 g., 82%) as a clear mobile liquid.

$\nu_{max.}$ (Thin liquid film) 1460 (Me C·H bend), 1390 (Me C·H bend), 1140 (O·C·N), 760 and 700 (aromatic CH) $cm.^{-1}$

τ (Neat base) 2.83 (10H, 2br, 2Ph), 4.8-5.2 (1H, m, 5-H), 5.78 (1H, q, J 5 Hz, 2-H), 6.59 (1H, q, J 6 and 9 Hz, 4-H), 6.9-8.0 (5H, m, 4-H' and $N.\underline{CH_2}.\underline{CH_2}$) and 8.74 (3H, d, J 5 Hz, 2-Me).

3. Oxathiazolidinone and Oxazolidinones.

3-Cyclohexyl-2-oxo-5-phenyl-1,2,3-oxathiazolidine (106).

Thionyl chloride (2.3 ml., 0.032 mole) in dichloromethane (50 ml.) was added over 15 min. to a mixture of 2-cyclohexylamino-1-phenylethanol (89) (6.57 g., 0.03 mole) and triethylamine (11 ml., 0.08 mole) in dichloromethane (150 ml.), and the mixture was then stirred at room temperature for 18 hr.[108] The mixture was washed five times with water, dried ($MgSO_4$), and evaporated to give an oil (8.7 g.) which crystallised on standing to give the 2-oxo-1,2,3-oxathiazolidine (106) (1.2 g., 15%) as colourless needles, m.p. 107-108° (from ethanol). Double development of the product on tlc showed two slightly separated components indicating the presence of diastereoisomers. The non-crystallisable oil broke down to the amino alcohol (89) on distillation.

(Found: C, 63.5; H, 7.3; N, 5.3; S, 12.0. $C_{14}H_{19}NO_2S$ requires C, 63.4; H, 7.2; N, 5.3; S, 12.1%).

$\nu_{max.}$ (Nujol) 1140, 1135 (S:O stretch), 770, 750, 710 and 700 (aromatic CH) $cm.^{-1}$

τ (C_6H_6) 4.83 (1H, q, $J|5,4 + 5,4'| = 17.0$ Hz, 5-H), 6.81 (1H, s, 4-H), 6.96 (1H, t, 4-H') and 7.6-9.2 (11H, m, C_6H_{11}).

3-Cyclohexyl-5-phenyloxazolidin-2-one (112).

Method A: Ethyl chloroformate (3.8 g., 0.035 mole) was added slowly to 2-cyclohexylamino-1-phenylethanol (89) (6.57 g., 0.03 mole) in pyridine (20 ml.), and the mixture was then heated under reflux for 3 hr. Evaporation of the pyridine solution gave an oil which was dissolved in chloroform and washed with water. The dried ($MgSO_4$) chloroform solution was evaporated to give the urethane (111) as an oil which failed to crystallise. The infrared spectrum of the urethane showed :

$\nu_{max.}$ (Thin liquid film) 3,400 (OH), 1680 (urethane C:O), 780, 760 and 710 (aromatic CH) $cm.^{-1}$

The urethane was distilled, b.p. 210-215°/1.0 mm., undergoing thermal-cyclisation, to give the oxazolidinone (112) (2.15 g., 29%) as a yellow oil which crystallised in the receiver. A sample recrystallised from petrol (b.p. 60-80°) as large colourless plates, m.p. 94-95° (lit. 95-96°).[177]

(Found: C, 73.4; H, 7.9; N, 5.8. $C_{15}H_{19}NO_2$ requires C, 73.5; H, 7.7; N, 5.7%).

$\nu_{max.}$ (Nujol) 1740 (cyclic C:O), 1020 (oxazolidinone ring) 760 and 700 (aromatic CH) $cm.^{-1}$

τ ($CDCl_3$) 2.66 (5H, br, Ph), 4.57 (1H, q, J 7.5 and 8.5 Hz, 5-H), 6.13 (1H, t, J 8.5 Hz, 4-H), 6.67 (1H, q, J 7.5 and 8.5 Hz, 4-H') and 7.9-9.1 (11H, m, C_6H_{11}).

Method B: Ethyl chloroformate (5.43 g., 0.05 mole) in 1,2-dimethoxyethane (10 ml.) was added slowly to a mixture of 2-cyclohexylamino-1-phenylethanol (89) (10.95 g., 0.05 mole) and triethylamine (15.18 g.,

0.15 mole) in 1,2-dimethoxyethane (20 ml.) and the mixture was refluxed for 18 hr. The cooled reaction mixture was diluted with water, and then extracted with ether. The dried ($MgSO_4$) ethereal solution was evaporated to give an oil (15.7 g.) which was heated on an oil bath at 210° for 18 hr. The infrared spectrum of a sample of the reaction mixture after four hours heating showed 50% conversion of the urethane into the oxazolidinone. The cooled reaction mixture was dissolved in hot petrol (b.p. 60-80°) and refrigerated to give the oxazolidinone (112) (5.4 g., 44%) as colourless plates, m.p. 93-95°.

3,5-Diphenyloxazolidin-2-one (118).

Phenyl isocyanate (5.95 g., 0.05 mole) in dimethylformamide (DMF) (10 ml.) was added over 30 min. to styrene oxide (6.0 g., 0.05 mole) and lithium chloride (0.5 g.) in refluxing DMF (40 ml.) under nitrogen. The mixture was heated under reflux for 6 hr., allowed to stand at room temperature for 2 days, and the solvent removed to yield an oil. Distillation of the oil (180-184°/0.3 mm) gave a mixture of oxazolidinones (6.0 g., 50%) as a yellow oil which slowly crystallised. Recrystallisation from chloroform-petrol (b.p. 60-80°) gave colourless needles, m.p. 69-71°. Tlc (silica gel - double development with 5% methanol in benzene) indicated two components which on glc analysis (2.5% SE 30 on 97.5% Chromosorb GAW-DMCS column, oven temperature 210° and injection temperature 245°) were shown to be in the ratio of 3.6 (13.5 min.) to 1 (9 min.). The sample was recrystallised three times from chloroform-petrol (b.p. 60-80°) and the crystals were mechanically separated each time to yield the 3,5-diphenyl isomer (118), as colourless needles, m.p. 78-79° and the 3,4-isomer, as colourless prisms, m.p. 128-129° (lit. 129°).[119] Glc analysis of the 3,5-diphenyl isomer showed that it was 97% pure.

(Found: M^+, 239.092221. $C_{15}H_{13}NO_2$ requires M^+, 239.094622).

$\nu_{max.}$ (KBr) 1735 (C:O), 1600 (aromatic nucleus), 1025 (oxazolidinone ring), 750 and 690 (aromatic CH) $cm.^{-1}$

τ (CCl_4) 2.8 (10H, 2br, 2Ph), 4.62 (1H, q, J 7.5 and 8.5 Hz, 5-H), 5.85 (1H, t, J 8.5 Hz, 4-H) and 6.35 (1H, q, J 7.5 and 8.5 Hz, 4-H').

2-Chloro-2-phenylethyl chloroformate (124)

Styrene oxide (1.2 g., 0.01 mole) was added slowly to an ice-cold solution of phosgene (20 ml., 12.5% w/w, 0.025 mole) in benzene containing pyridine (1 drop), and the stirred mixture was allowed to warm up to room temperature over 24 hr. The benzene solution was evaporated to give an oil which was distilled, 0.1 mm., to give the chloroformate (124) (1.2 g., 55%).

τ ($CDCl_3$) 2.62 (5H, br, Ph), 4.89 (1H, t, J 7 Hz, Ph·C<u>H</u>) and 5.38 (2H, d, J 7 Hz, CH·C<u>H_2</u>).

2-Chloro-2-phenylethyl-N-phenylcarbamate (125).

Aniline (0.82 g., 0.009 mole) was added slowly to a stirred solution of 2-chloro-2-phenylethyl chloroformate (124) (1.0 g., 0.0046 mole) in benzene (10 ml.). After 15 min. the aniline hydrochloride was removed and evaporation of the benzene filtrate gave an oil which was triturated with petrol (b.p. 60-80°) to give the carbamate (125) (1.1 g., 87%) as colourless prisms, m.p. 94-95°.

τ ($CDCl_3$) 2.7 (10H, br, 2Ph), 4.89 (1H, t, J 7 Hz, Ph·C<u>H</u>), 5.5 (2H, d, J 7 Hz, CH·C<u>H_2</u>) and 6.63 (1H, s, Ph·N<u>H</u>).

3,4-Diphenyloxazolidin-2-one (121).

Potassium hydroxide (0.07 g., 0.012 mole) in ethanol (3 ml.) was added to 2-chloro-2-phenylethyl-N-phenylcarbamate (125) (0.33 g., 0.012 mole) in ethanol (3 ml.) and the mixture was heated for 10 min. on a steam-bath. The solution was filtered hot to remove the potassium chloride and evaporation of the filtrate gave an oil which crystallised to give the oxazolidinone (121) (0.27 g., 96%). Recrystallisation from chloroform-petrol (b.p. 60-80°) gave colourless prisms, m.p. 129-130° (lit.[119] 129°)

τ (CCl_4) 2.85 (10H, m, 2Ph), 4.8 (1H, q, J 6.0 and 8.5 Hz, 4-H), 5.5 (1H, t, J 8.5 Hz, 5-H) and 6.12 (1H, q, J 6.0 and 8.5 Hz, 5-H').

4. Morpholinone and Morpholinedione

4-Cyclohexyl-6-phenylmorpholin-2-one (128).

Ethyl bromoacetate (3.34 g., 0.02 mole) in 1,2-dimethoxyethane (5 ml.) was added slowly to a stirred mixture of 2-cyclohexylamino-1-phenylethanol (89) (4.38 g., 0.02 mole) and sodium bicarbonate (2.0 g.) in 1,2-dimethoxyethane (20 ml.), and the mixture was then heated under reflux for 66 hr. The cooled reaction mixture was diluted with twice its own volume of ether, filtered and the filtrate washed with water. Evaporation of the dried ($MgSO_4$) ethereal solution gave a yellow oil (4.4 g.) which failed to crystallise. The oil was shown by tlc to consist of three components. Distillation of the oil, b.p. 150-160°/0.7 mm., gave one major fraction as a yellow oil (2.1 g., 40%) which failed to crystallise. The base oil was heated in ethanol with a 10% molar excess of picric acid to give the morpholin-2-one picrate (128) as yellow prisms, m.p. 180-181° (from benzene).

(Found: C, 54.5; H, 5.1; N, 11.4%; E.W., 520. $C_{22}H_{24}N_4O_9$ requires C, 54.1; H, 4.9; N, 11.4%; E.W., 488).

$\nu_{max.}$ (Nujol) 1740 (lactone C:O), 790, 760, 740 and 700 (aromatic CH) $cm.^{-1}$

τ (Base in CCl_4) 2.66 (5H, s, Ph), 4.62 (1H, q, J 3.5 and 9.0 Hz, 6-H), 6.37 (1H, d, J 17.0 Hz, 3-H), 6.82 (1H, d, J 17.0 Hz, 3-H'), 6.91 (1H, q, J 3.5 and 12.5 Hz, 5-H), 7.52 (1H, q, J 9.0 and 12.5 Hz, 5-H') and 7.9-9.2 (11H, m, C_6H_{11}).

4-Cyclohexyl-6-phenylmorpholine-2,3-dione (129).

2-Cyclohexylamino-1-phenylethanol (89) (6.57 g., 0.03 mole) and diethyl oxalate (4.38 g., 0.03 mole) in toluene (150 ml.) were heated under reflux for 18 hr. during which time the toluene was slowly distilled out of the reaction mixture.[42] Evaporation of the residual toluene yielded an oil which crystallised from acetone-cyclohexane to give the morpholine-2,3-dione (129) (5.96 g., 73%) as colourless microprisms, m.p. 126-127° (from acetone-cyclohexane).

(Found: C, 70.3; H, 6.9; N, 5.0. $C_{16}H_{19}NO_3$ requires C, 70.3; H, 7.0; N, 5.1%).

$\nu_{max.}$ (Nujol) 1745 (lactone C:O), 1665 (lactam C:O), 780 and 700 (aromatic CH) $cm.^{-1}$

τ ($CDCl_3$) 2.65 (5H, br, Ph), 4.35 (1H, t, J 6.5 Hz, 6-H), 6.33 (2H, d, J 6.5 Hz, 5-H_2) and 7.9-9.1 (11H, m, C_6H_{11}).

τ (C_6H_6) 4.35 (1H, m, $|J_{6,5} + J_{6,5'}| = 13.0$ Hz, 6-H), 6.36 (1H, q, J 15.0 Hz, 5-H), 6.47 (1H, s, 5-H') and 7.9-9.1 (11H, m, C_6H_{11}).

5. Hydrazines

1-Cyclohexyl-1-(2-hydroxy-2-phenylethyl)hydrazine (137).

2-Cyclohexylamino-1-phenylethanol (89) (21.9 g., 0.1 mole) and N-hydrochloric acid (100 ml.) were heated together on a steam-bath until dissolved. The stirred solution was cooled to about 50° (further cooling precipitated the hydrochloride salt), and sodium nitrite (10.0g.) in water (30 ml.) was then added slowly.[134] A turbidity was produced which became a yellow oil during 2 hr. stirring. The mixture was extracted with ether and the dried ($MgSO_4$) ethereal solution was evaporated to give the N-nitrosamine (136) as a yellow oil (20.2 g., 81%). The infrared spectrum of the oil showed:

$\nu_{max.}$ (Thin film) 3400 (free OH), 1460 (N:O stretch), 760 and 700 (aromatic CH) $cm.^{-1}$

The N-nitrosamine (136) (20.2 g., 0.081 mole) in ether (150 ml.) was added slowly to a stirred suspension of lithium aluminium hydride (8.0 g., 0.21 mole) in ether (100 ml.) and the mixture was then heated under reflux for 66 hr. The reaction mixture was treated according to the general method yielding an oil (18.4 g.) which crystallised on standing to give the hydrazine (137) (10.1 g., 43% overall from the amino alcohol) as colourless microprisms, m.p. 82-83°, (from petrol b.p. 60-80°). The hydrazine hydrochloride was obtained as colourless prisms, m.p. 121-122° (from ethanol-ether).

(Found: C, 62.2; H, 8.5; N, 10.2. $C_{14}H_{23}ClN_2O$ requires C, 62.1; H, 8.5; N, 10.4%).

$\nu_{max.}$ (Nujol) 3200 (OH), 2730, 2650, 2550 (primary amine salt NH), 1600, 1500 (aromatic nucleus), 780 and 700 (aromatic CH) $cm.^{-1}$

4-Cyclohexyl-6-phenyl-3,4,5,6-tetrahydro-2H-1,3,4-oxadiazine-2-thione (138).

A cold solution of potassium hydroxide (1.12 g., 0.02 mole) in water (4 ml.) and ethanol (20 ml.) was added to a mixture of 1-cyclohexyl-1-(2-hydroxy-2-phenylethyl)hydrazine (137) (2.34 g., 0.01 mole) and carbon disulphide (1.52 g., 0.02 mole), and the stirred mixture was then heated under reflux for 4 hr.[40] The colour of the solution changed from yellow to dark green during the reaction. The cooled solution was diluted with water (50 ml.) and made just acid with N-hydrochloric acid. The solid which separated was collected and recrystallised to give the oxadiazinethione (138) (1.0 g., 36%) as colourless prisms, m.p. 182-183° (from chloroform-petrol b.p. 60-80°).

(Found: C, 65.3; H, 7.2; N, 10.2. $C_{15}H_{20}N_2OS$ requires C, 65.2; H, 7.2; N, 10.1%).

$\nu_{max.}$ (Nujol) 3160 (bonded NH), 1530 (C·N stretch in N·C:S), 1190 (C:S), 765 and 705 (aromatic CH) $cm.^{-1}$

Basification and extraction of the filtrate gave on evaporation 2-cyclohexylamino-1-phenylethanol (89) (125 mg.) resulting from hydrolysis of the hydrazine (137).

4-Cyclohexyl-3-methyl-6-phenyl-3,4,5,6-tetrahydro-2H-1,3,4-oxadiazine-2-thione (140).

Dimethyl sulphate (0.4 g., 0.003 mole) was added slowly to 4-cyclohexyl-6-phenyl-3,4,5,6-tetrahydro-2H-1,3,4-oxadiazine-2-thione (138) (0.27 g., 0.001 mole) in 5% aqueous sodium hydroxide (5 ml.). A creamy emulsion was formed immediately and the mixture was stirred at room temperature for 1.5 hr. The mixture was extracted with chloroform and evaporation of the dried ($MgSO_4$) chloroform extracts gave an oil which

failed to crystallise. The infrared spectrum showed :

$\nu_{max.}$ (Thin film) 1610 (aromatic nucleus), 1460 (Me CH bend), 1140 (C:S), 760 and 700 (aromatic CH) $cm.^{-1}$

A crystalline hydrochloride (140) (0.160 g., 49%) was obtained as colourless prisms, m.p. 148-149° (from ethanol-ether).

(Found: C, 58.6; H, 7.0; N, 8.4. $C_{16}H_{23}ClN_2OS$ requires C, 58.8; H, 7.0; N, 8.6%).

$\nu_{max.}$ (Nujol) 2200 (tertiary amine salt NH), 1600 (aromatic nucleus), 1170 (C:S), 760, 700 and 680 (aromatic CH) $cm.^{-1}$

1'-Benzoyl-1-cyclohexyl-1-(2-hydroxy-2-phenylethyl)hydrazine (141).

Benzoyl chloride (1.41 g., 0.01 mole) in benzene (10 ml.) was added slowly with stirring to a mixture of 1-cyclohexyl-1-(2-hydroxy-2-phenylethyl)hydrazine (137) (2.34 g., 0.01 mole) and pyridine (0.8 g., 0.01 mole) in benzene (20 ml.), and the mixture was then heated under reflux on a steam-bath for 6 hr. with occasional swirling. To the cooled mixture was added 10% aqueous sodium hydroxide solution (50 ml.), and then it was extracted with chloroform. The dried ($MgSO_4$) chloroform solution was evaporated to give a brown oil (2.8 g.) which crystallised on trituration with petrol (b.p. 60-80°) to give the benzoylhydrazine (141) (2.63 g., 78%) as colourless needles, m.p. 165-166° (from ethanol-petrol b.p. 60-80°). Sometimes crystallisation was prevented by the presence of O-acylated material, the infrared spectrum showing an ester (C:O) at 1710 $cm.^{-1}$ The ester contaminated material was dissolved in methanol and 8% aqueous sodium hydroxide, refluxed for 30 min., cooled, extracted with chloroform and evaporated to give the benzoylhydrazine (141).

(Found: C, 74.5; H, 7.5; N, 8.5. $C_{21}H_{26}N_2O_2$ requires C, 74.6; H, 7.7; N, 8.3%).

$\nu_{max.}$(Nujol) 3420 (OH), 3260 (NH), 1630 (amide C:O), 750, 720, 700 and 695 (aromatic CH) $cm.^{-1}$

Attempted cyclisation of 1'-benzoyl-1-cyclohexyl-1-(2-hydroxy-2-phenylethyl)hydrazine (141).[133]

The hydrazide (141) (2.63 g., 0.008 mole) was added with swirling to concentrated sulphuric acid (15 ml.) and the brown solution was allowed to stand at room temperature for 17 hr. The mixture was poured slowly onto crushed ice and the green oil which separated was extracted with chloroform. The chloroform extract was washed successively with 10% aqueous sodium carbonate solution and water. Evaporation of the dried ($MgSO_4$) chloroform solution gave an oil (2.0 g.) which showed the following infrared spectrum:

$\nu_{max.}$(Thin film) 1630 (C:N), 1500 (aromatic nucleus), 760 and 700 (aromatic CH) $cm.^{-1}$

Although the reaction seemed to have worked, with no sign of any starting material in the infrared spectrum, the brown oily product was contaminated with charred material from which it proved impossible to isolate any pure 5,6-dihydro-4H-1,3,4-oxadiazine.

C. SYNTHESIS AND PROPERTIES OF SOME 1-SUBSTITUTED PYRROLES

1. Synthesis of methyl pyrrole-2-carboxylate (152).

Pyrrole-2-aldehyde (154).

The method used was a combination of G.F. Smith's and R.M. Silverstein's[140] procedures.

Phosphorous oxychloride (50 ml., 0.55 mole) was added slowly with stirring over 30 min. to dimethylformamide (150 g., 2 mole) contained in a 1 L. flask and cooled *via* an ice bath to 10-20°. The ice bath was removed and stirring continued for 15 min. at room temperature. The ice bath was then replaced and freshly distilled pyrrole (33.8 g., 0.5 mole) was added slowly, with the exclusion of moisture, when the internal temperature was 10-15°. After heating at 35° for 30 min. the reddish viscous mixture was poured onto ice (300 g.) and the clear solution was extracted with ether (1 L.) to remove the unreacted pyrrole. To the cooled aqueous phase was slowly added sodium hydroxide (100 g.) in water (200 ml.) and the hot, 35-45°, alkaline solution was left for 20 min. The solution was made just acid with conc. hydrochloric acid and extracted with ether. The dried ($MgSO_4$) ethereal solution was evaporated to give an oil which was distilled at 78°/2 mm. to give pyrrole-2-aldehyde (42.2 g.). Redistillation of the product gave pyrrole-2-aldehyde (35.9 g., 75%) as colourless needles, m.p. 44-45°. (lit. 44-45°).[140]

Pyrrole-2-carboxylic acid (155).[141]

A suspension of silver oxide was prepared by adding, with mechanical stirring, silver nitrate (136 g., 0.8 mole) in water (250 ml.) to sodium hydroxide (68 g., 1.7 mole) in water (350 ml.). To the suspension was added pyrrole-2-aldehyde (36.4 g., 0.38 mole) in aqueous methanol (1:1, 50 ml.) with external cooling. After vigorous stirring for 2 hr. at room

temperature the mixture was filtered through Kieselguhr and washed with hot water. The combined filtrate and washings were extracted with ether and then acidified at 0° with conc. hydrochloric acid. The mixture was refrigerated for 30 min. and the product collected. Pyrrole-2-carboxylic acid (33.6 g., 81%) was obtained as pale brown prisms, m.p. 206-208° (lit. 207-209°).[141]

Methyl pyrrole-2-carboxylate (152).

To a mixture of ether (200 ml.) and 40% aqueous potassium hydroxide solution (150 ml.), cooled to 5°, was added in small portions N-nitrosomethylurea (22.5 g.). The ethereal solution of diazomethane (approx. 6 g.) was decanted off and dried over potassium hydroxide pellets.

Pyrrole-2-carboxylic acid (10 g., 0.09 mole) was added in small portions to the ice-cooled ethereal solution of diazomethane (approx. 6 g., 0.15 mole). The acid dissolved with the evolution of nitrogen. The solution was left stirring overnight at room temperature allowing the ether and excess diazomethane to evaporate. A solid brown mass was obtained which was dissolved in acetone and filtered hot through a bed of neutral alumina. Addition of petrol (b.p. 60-80°) and cooling caused methyl pyrrole-2-carboxylate (10.4 g., 93%) to precipitate as long, colourless needles, m.p. 71-73° (lit. 72-73°).[141]

2. Reaction of methyl pyrrole-2-carboxylate with epoxides:

(a) Styrene oxide

1-(2-Hydroxy-2-phenylethyl)pyrrole-2-carboxylic acid (156).

Potassium metal (0.16 g., 0.004 mole), cut under petrol, was added in small portions to methyl pyrrole-2-carboxylate (0.5 g., 0.004 mole) in dimethylformamide (5 ml.). When all the potassium had dissolved (10 min.),

styrene oxide (0.48 g., 0.004 mole) was added and the mixture was stirred at room temperature in a water saturated atmosphere for 18 hr. The water saturated atmosphere was produced by standing the open reaction flask in a petri dish of water, with a large beaker over both. The reaction mixture was added slowly to 0.5N-hydrochloric acid (20 ml.) and after refrigeration for 30 min. the precipitate was collected. Recrystallisation from acetone-petrol (b.p. 60-80°) gave the alcohol pyrrole acid (156) (0.46 g., 50%) as colourless prisms, m.p. 161-163°.

(Found: C, 67.7; H, 5.6; N, 6.2. $C_{13}H_{13}NO_3$ requires C, 67.5; H, 5.6; N, 6.1%).

$\nu_{max.}$ (Nujol) 3400 (bonded alcohol OH), 2700 (bonded acid OH), 1670 (C:O), 1120 (secondary C·OH), 770, 750, 730 and 700 (aromatic CH) $cm.^{-1}$

τ (Acetone) 2.65 (5H, m, ·CH·Ph), 3.05 (2H, d, J 3.4 Hz, 3-H and 5-H), 3.94 (1H, t, J 3.4 Hz, 4-H), 4.17 (1H, br, CHOH), 4.96 (1H, q, J 3.6 and 8.5 Hz, $\cdot CH_2 \cdot CH \cdot$), 5.25 (1H, q, J 3.6 and 13.0 Hz, ·CHH·CH) and 5.79 (1H, q, J 13.0 and 8.5 Hz, ·CHH·CH).

trans-1-Styrylpyrrole-2-carboxylic acid (157).

Method A: Potassium metal (0.16 g., 0.004 mole), cut under petrol, was added in small portions to methyl pyrrole-2-carboxylate (0.5 g., 0.004 mole) in dimethylformamide (5 ml.). When all the potassium had dissolved (10 min.), styrene oxide (0.48 g., 0.004 mole) was added and the mixture was stirred for 18 hr. in a dry nitrogen atmosphere. The reaction mixture was added slowly to 0.5N-hydrochloric acid (20 ml.) and after refrigeration for 30 min. the precipitate was collected. Recrystallisation from chloroform-petrol (b.p. 60-80°) gave the 1-styrylpyrrole acid (157) (0.17 g., 21%) as cream platelets, m.p. 178-179°.

(Found: C, 73.4; H, 5.2; N, 6.2. $C_{13}H_{11}NO_2$ requires C, 73.2; H, 5.2; N, 6.6%).

$\nu_{max.}$ (KBr) 2650 (bonded OH), 1670 (C:O), 1640 (C:C), 950 (trans-vinyl CH), 740, 730 and 690 (aromatic CH) $cm.^{-1}$

τ ($CDCl_3$) - 0.05 (1H, br, OH), 1.58 (1H, d, J 14 Hz, N·CH:CH), 2.61 (5H, s, Ph), 2.72 (2H, m, 3-H and 5-H), 3.33 (1H, d, J 14 Hz, N·CH:CH) and 3.68 (1H, t, J 3 Hz, 4-H)

$\lambda_{max.}$ (95% EtOH) 222 nm (log ε 4.19), 243 (4.05) and 302 (4.32).

Method B: Potassium metal (0.8 g., 0.02 mole), cut under petrol, was added in small portions to methyl pyrrole-2-carboxylate (2.5 g., 0.02 mole) in dimethylformamide (15 ml.). The flask was cooled during the addition so that the internal temperature did not rise above 30°. When the potassium had dissolved (15 min.) the mixture was further cooled to 0-5° and styrene oxide (3.6 g., 0.03 mole) was added. The stirred mixture was allowed to reach room temperature over 18 hr., heated under reflux for 4 hr., cooled and water (60 ml.) was then added. Unreacted epoxide was extracted with ether and the aqueous layer added slowly to 0.5N-hydrochloric acid (50 ml.). The acid mixture was refrigerated for 30 min., the yellow precipitate collected and dried to give the styrylpyrrole acid (157) (3.5 g., 82%).

Tlc on this product showed it to be a mixture of two components. The fast running, major component was fluorescent whilst the slow component was not. It was believed that the styryl pyrrole acid (157) was fluorescent and that the slow component was either the uneliminated pyrrole alcohol (156) or a product resulting from abnormal fission of the styrene oxide. Preparative tlc (silica gel and 0.5% g. acetic acid - 2% methanol - 97.5% benzene) enabled 50 mg. of the product mixture to be separated into 5 mg. of the slow component and 15 mg. of the fast component.

The slow component was identified by its infrared spectrum and mass spectrum as 1-(2-hydroxy-2-phenylethyl)pyrrole-2-carboxylic acid (156).

Purification of the Mixed Product: A pure sample of the styrylpyrrole (157) could not be obtained by fractional crystallisation because of the presence of the pyrrole alcohol (156).

The mixture was dissolved in benzene and run onto a neutral-alumina column. Methanol was used to elute impurities from the column. The styrylpyrrole (157), the position of which was noted using a small U-V lamp, was then eluted using methanol (containing a few ml. of 5% aqueous sodium hydroxide solution). Acidification of the eluent gave the styrylpyrrole (157).

(i) Esterification.

Methyl 1-(2-hydroxy-2-phenylethyl)pyrrole-2-carboxylate (159).

1-(2-Hydroxy-2-phenylethyl)pyrrole-2-carboxylic acid (156) (0.14 g., 0.0006 mole) was added slowly to a cold (0-5°) ethereal solution of diazomethane (0.42 g., 0.01 mole) and the mixture was allowed to evaporate overnight at room temperature. The residue was recrystallised from chloroform-petrol (b.p. 60-80°) to give the methyl ester (159) (0.11 g., 74%) as colourless prisms, m.p. 93-94°.

(Found: C, 67.9; H, 6.1; N, 5.6. $C_{14}H_{15}NO_3$ requires C, 68.5; H, 6.1; N, 5.7%).

$\nu_{max.}$(KBr) 3500 (OH), 1675 (ester C:O). 770, 740, 720 and 700 (aromatic CH) $cm.^{-1}$

$\tau(CDCl_3)$ 2.65 (5H, br, Ph), 3.04 (1H, q, J 2.0 and 3.8 Hz, 3-H), 3.28 (1H, t, J 2.0 Hz, 5-H), 3.94 (1H, q, J 2.0 and 3.8 Hz, 4-H), 5.0 (1H, q, J 4 and 8 Hz, Ph·C<u>H</u>·OH), 5.3 (1H, q, J 4 and 14 Hz, N·C<u>H</u>H), 5.83 (1H, q, J 8 and 14 Hz, N·CH<u>H</u>) and 6.2 (3H, s, Me).

(ii) Lactonisation.

1H-3-Phenyl-3,4-dihydropyrrolo[2,1-c][1,4]oxazin-1-one (143).

1-(2-Hydroxy-2-phenylethyl)pyrrole-2-carboxylic acid (156) (0.56 g.) was added with manual stirring to polyphosphoric acid (5 g.) and the mixture was left at room temperature for 18 hr. with occasional stirring. Ice-cold water (20 ml.) was added with stirring to the reaction mixture and the yellow oil was extracted with ether, dried ($MgSO_4$) and run through a 1" thick bed of neutral alumina. Evaporation of the ethereal solution gave an oil which crystallised on trituration with petrol to give the lactone (143) (0.4 g., 86%) as colourless platelets, m.p. 111-112° (from chloroform-petrol b.p. 60-80°).

(Found: C, 73.3; H, 5.2; N, 6.4. $C_{13}H_{11}NO_2$ requires C, 73.2; H, 5.2; N, 6.6%).

$\nu_{max.}$ (KBr) 1710 lactone C:O), 1100, 1090 (lactone C·O) 770, 760, 710 and 690 (aromatic CH) $cm.^{-1}$

τ ($CDCl_3$) 2.51 (5H, s, Ph), 2.83 (1H, q, J 1.5 and 4.0 Hz, 8-H) 3.05 (1H, q, J 1.5 and 2.5 Hz, 6-H), 3.64 (1H, q, J 2.5 and 4.0 Hz, 7-H), 4.32 (1H, q, $\left|J_{3,4} + J_{3,4'}\right|$ = 14 Hz, 3-H) and 5.7 (2H, m, $J_{4,4'}$ 13.0Hz, 4-H_2).

(iii) Attempted dehydrogenation of 1H-3-phenyl-3,4-dihydropyrrolo[2,1-c][1,4]oxazin-1-one (143).

Method A: The lactone (143) (0.1 g.) and 10% palladium-charcoal (0.05 g.)[148] in xylene (10 ml.) were heated under reflux for 18 hr. Evaporation of the filtered reaction mixture gave a residue which crystallised to give the unchanged lactone (143) (0.07 g.), m.p. 112-113°. Tlc on the product showed only one component present.

Method B: The lactone ($_{143}$) (0.21 g., 0.001 mole) and 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) (0.46 g., 0.002 mole) in dioxan (10 ml.) were heated under reflux for 4 days.[149] The cooled reaction mixture was diluted with 1,2-dichloroethane and filtered through neutral alumina. Evaporation of the filtrate gave an oil which crystallised to give the unchanged lactone (143) (0.07 g.). Tlc of the oil showed only one component present.

(iv) Methanolysis of 1H-3-phenyl-3,4-dihydropyrrolo[2,1-c][1,4]oxazin-1-one (143).

Potassium (0.02 g., 0.0005 mole) in dry methanol (2 ml.) was added to the lactone (143) (0.1 g., 0.0005 mole) in dimethylformamide (3 ml.), and the mixture was stirred at room temperature for 18 hr. in an atmosphere of nitrogen. The reaction mixture was added to 0.5 N-hydrochloric acid (15 ml.) and refrigerated to give a product which was identical to methyl 1-(2-hydroxy-2-phenylethyl)pyrrole-2-carboxylate (159) (0.06 g.).

(v) Reaction with Knorr's pyrrole.[150]

3,5-Dimethyl-4-ethoxycarbonyl-1-(2-hydroxy-2-phenylethyl)pyrrole-2-carboxylic acid (162).

Potassium metal (0.4 g., 0.01 mole), cut under petrol, was added in small portions to 3,5-dimethyl-2,4-diethoxycarbonylpyrrole (2.39 g., 0.01 mole) in dimethylformamide (10 ml.). The flask was cooled during the addition so that the internal temperature did not rise above 30°. When all the potassium had dissolved (15 min.), styrene oxide (2.4 g., 0.02 mole) was added and the mixture was then heated under reflux for 4 hr. The cooled reaction mixture was added slowly to 0.5 N-hydrochloric acid (50 ml.) and the yellow oil was extracted with ether. Evaporation of the

dried ($MgSO_4$) ethereal solution gave a yellow crystalline product (2.65 g.). Recrystallisation from chloroform-petrol (b.p. 60-80°) gave the pyrrole alcohol (162) (1.9 g., 57%) as fine colourless needles, m.p. 153-154°.

(Found: C, 62.3; H, 6.1; N, 4.0%; M^+, 331.141616. $C_{18}H_{21}NO_5$ requires C, 65.2; H, 6.3; N, 4.2%; M^+, 331.141962).

$\nu_{max.}$ (Nujol) 2650 (bonded acid OH), 1700, 1670 (C:O), 790, 750 and 700 (aromatic CH) $cm.^{-1}$

τ (Acetone) 2.65 (5H, m, Ph), 5.05 (1H, m, Ph.C<u>H</u>), 5.4-6.0 (4H, m, N·C<u>H</u>$_2$ and CH_3·C<u>H</u>$_2$), 7.48 (6H, 2s, 3-Me and 5-Me) and 8.73 (3H, t, C<u>H</u>$_3$·CH_2).

<u>1H-6,8-Dimethyl-3,4-dihydro-7-ethoxycarbonyl-3-phenylpyrrolo[2,1-c][1,4]oxazin-1-one (163)</u>.

3,5-Dimethyl-4-ethoxycarbonyl-1-(2-hydroxy-2-phenylethyl)pyrrole-2-carboxylic acid (162) (0.4 g.) was added with manual stirring to polyphosphoric acid (4 g.) and the mixture was left at room temperature for 6 hr. Ice-cold water (40 ml.) was added with stirring and the oily mixture was refrigerated overnight. The solid which separated was collected, dissolved in chloroform and run through a neutral alumina column. Evaporation of the chloroform solution gave an oil which crystallised on trituration with petrol. Recrystallisation from chloroform-petrol (b.p. 60-80°) gave the lactone (163) (0.12 g., 32%) as colourless microprisms, m.p. 180-181°.

(Found: C, 69.3; H, 6.2; N, 4.3. $C_{18}H_{19}NO_4$ requires C, 69.0; H, 6.1; N, 4.5%).

$\nu_{max.}$ (Nujol) 1700 (C:O), 790, 780, 740 and 700 (aromatic CH) $cm.^{-1}$

τ ($CDCl_3$) 2.6 (5H, s, Ph), 4.46 (1H, q, J 4.0 and 10.0 Hz, 3-H), 5.5-6.2 (4H, m, 4-H_2 and $CH_3 \cdot CH_2$), 7.45 (6H, 2s, 6-Me and 8-Me) and 8.65 (3H, t, $CH_3 \cdot CH_2$).

(b) Propylene oxide.

trans-1-(2-Methylvinyl)pyrrole-2-carboxylic acid (164).

Potassium metal (0.8 g., 0.02 mole), cut under petrol, was added in small portions to methyl pyrrole-2-carboxylate (2.5 g., 0.02 mole) in dimethylformamide (10 ml.). The flask was cooled so that the internal temperature did not rise above 30°. When the potassium had dissolved (15 min.), propylene oxide (2.3 g., 0.04 mole) was added and the mixture was heated under reflux for 2 hr, and then stirred overnight at room temperature. The reaction mixture was added slowly with stirring to 0.5 N-hydrochloric acid (70 ml.) and then refrigerated for 30 min. The brown floccular precipitate was collected and recrystallised from chloroform-petrol (b.p. 60-80°) to give the vinylpyrrole acid (164) (1.57 g., 52%) as colourless needles, m.p. 152-153°.

(Found: C, 63.3; H, 6.1; N, 9.3. $C_8H_9NO_2$ requires C, 63.6; H, 6.0; N, 9.3%).

$\nu_{max.}$ (Nujol) 2650 (bonded OH), 1680, (C:O and C:C), 950 (trans-vinyl CH) and 740 (aromatic CH) $cm.^{-1}$

τ ($CDCl_3$) -0.58 (1H, br, OH), 2.42 (1H, m, J 1.6 and 14 Hz, ·NCH:CH·), 2.8 (2H, d, J 3.5 Hz, 3-H and 5-H), 3.76 (1H, t, J 3.5 Hz, 4-H), 4.16 (1H, m, J 7.0 and 14 Hz, ·NCH:CH·) and 8.15 (3H, q, J 1.6 and 7.0 Hz, :CH·Me).

$\lambda_{max.}$ (95% Et OH) 219 nm (log ε 3.75) 267 (4.08).

(i) Esterification.

Methyl trans-1-(2-methylvinyl)pyrrole-2-carboxylate (165).

trans-1-(2-Methylvinyl)pyrrole-2-carboxylic acid (164) (1.01 g., 0.007 mole), methyl iodide (1.9 g., 0.014 mole) and potassium carbonate (6.0 g.) in acetone (20 ml.) were heated under reflux for 4 hr.[141] The cooled reaction mixture was filtered and the filtrate evaporated to give an oil which was dissolved in chloroform and washed with water. Evaporation of the dried ($MgSO_4$) chloroform solution gave the methyl ester (165) (1.4 g., 100%) as a pale yellow oil. Tlc showed the product to consist of one component.

(Found: M^+, 165.076847. $C_9H_{11}NO_2$ requires M^+, 165.078973).

$\nu_{max.}$ (Thin liquid film) 1710 (ester C:O), 1455 (Me·CH bend), 770, 750 and 690 (aromatic CH) $cm.^{-1}$

τ (CCl_4) 2.3 (1H, q, J 1.7 and 14.0 Hz, NCH:CH), 2.93 (1H, t, J 2.0 and 2.5 Hz, 5-H), 3.1 (1H, q, J 2.0 and 4.0 Hz, 3-H), 3.9 (1H, t, J 2.5 and 4.0 Hz, 4-H), 4.3 (1H, m, J 7 and 14 Hz, NCH:CH), 6.27 (3H, s, OMe) and 8.2 (3H, q, J 1.7 and 7.0 Hz, :CH·Me).

(c) Ethylene oxide

1-Vinylpyrrole-2-carboxylic acid (166).

Potassium metal (0.4 g., 0.01 mole), cut under petrol, was added in small portions to methyl pyrrole-2-carboxylate (1.25 g., 0.01 mole) in dimethylformamide (10 ml.). The flask was cooled during the addition so that the internal temperature did not rise above 30°. The reaction mixture was poured into a Carius tube and then cooled with Drikol. Ethylene oxide (3.5 g., 4 ml., 0.08 mole) was added slowly to the cold

mixture and the tube was then sealed. The tube was heated in a sand bath for 6 hr., during which time the temperature rose to 100°, and then left at room temperature overnight. The reaction mixture was acidified with 0.5 N-hydrochloric acid and extracted with ether. The dried ($MgSO_4$) ethereal solution was evaporated to give an oil which crystallised on standing for 3 days. Recrystallisation from chloroform-petrol (b.p. 60-80°) gave the vinylpyrrole (166) (0.28 g., 20%) as colourless needles, m.p. 137-138°.

(Found: C, 61.4; H, 5.3; N, 10.2%; M^+, 137.044531. $C_7H_7NO_2$ requires C, 61.3; H, 5.1; N, 10.2%; M^+, 137.047675).

$\nu_{max.}$ (KBr) 2700 (bonded OH), 1680 (C·O and C:C) 980 (vinyl CH bend), 780, 760, 740 and 690 (aromatic CH) $cm.^{-1}$

τ ($CDCl_3$) -2.11 (1H, s, OH), 2.09 (1H, q, J 9.0 and 16.0 Hz, N·C<u>H</u>:), 2.77 (2H, m, 3-H and 5-H), 3.74 (1H, t, 4-H), 4.82 (1H, q, J ca. 0.3 and 16.0 Hz, N·CH:C<u>H</u>H) and 5.14 (1H, q, J ca. 0.3 and 9.0 Hz, N·CH:CH<u>H</u>).

(d) <u>Stilbene oxides</u>

<u>1-(trans-1,2-Diphenylvinyl)pyrrole-2-carboxylic acid (167)</u>.

Potassium metal (0.16 g., 0.004 mole), cut under petrol, was added in small portions to methyl pyrrole-2-carboxylate (0.5 g., 0.004 mole) in dimethylformamide (5 ml.). When the potassium had dissolved (10 min.), <u>cis</u>-stilbene oxide[151] (0.78 g., 0.004 mole) was added and the mixture was then heated under reflux for 6 hr. The cooled reaction mixture was slowly added to 0.5 N-hydrochloric acid (20 ml.) and the floccular precipitate was extracted with ether. The dried ($MgSO_4$) ethereal solution was evaporated to give an oil which crystallised on trituration with petrol to give the <u>vinylpyrrole</u> (167) (0.25 g., 21%) colourless prisms,

m.p. 193-194° (from chloroform-petrol b.p. 60-80°).

(Found: C, 78.8; H, 5.2; N, 4.8. $C_{19}H_{15}NO_2$ requires C, 78.9; H, 5.2; N, 4.8%).

$\nu_{max.}$ (Nujol) 2650 (bonded OH) 1680 (C:O and C:C), 760, 740 and 690 (aromatic CH) $cm.^{-1}$

τ ($CDCl_3$) 1.2 (1H, br, OH), 2.86 (10H, s, 2Ph), 3.1 (1H, s, :CHPh), 3.27 (2H, m, 3-H and 5-H) and 3.76 (1H, t, 4-H).

$\lambda_{max.}$ (95% Et OH) 226 nm (log ε 4.35) and 299 (4.4).

1-(cis-1,2-Diphenylvinyl)pyrrole-2-carboxylic acid (168).

Potassium metal (0.8 g., 0.02 mole), cut under petrol, was added in small portions to methyl pyrrole-2-carboxylate (2.5 g., 0.02 mole) in dimethylformamide (10 ml.). The flask was cooled so that the internal temperature did not rise above 30°. When all the potassium had dissolved, trans-stilbene oxide (3.92 g., 0.02 mole) was added, and the stirred mixture was heated under reflux for 8 hr. Water (80 ml.) was added and the mixture then heated for 30 min. on a steam-bath. The alkaline solution was washed with ether to remove any unreacted epoxide. Acidification of the aqueous layer with N-hydrochloric acid gave a precipitate which was collected, dissolved in ether and run through a 1" thick bed of acidic alumina. Evaporation of the dried ($MgSO_4$) ethereal solution gave the vinylpyrrole (168) (2.3 g., 40%) as pale brown crystals. Recrystallisation from chloroform-petrol (b.p. 60-80°) gave colourless prisms, m.p. 164-165°.

(Found: C, 78.8; H, 5.2; N, 5.0. $C_{19}H_{15}NO_2$ requires C, 78.9; H, 5.2; N, 4.8%).

$\nu_{max.}$ (KBr) 2650 (bonded OH), 1670 (C:O and C:C), 790, 770, 750, 720 and 700 (aromatic CH) $cm.^{-1}$

τ ($CDCl_3$) - 0.87 (1H, br, OH), 2.87 (12H, m, 3-H, 5-H and 2Ph, 3.33 (1H, s, :CHPh) and 3.76 (1H, q, 4-H).

$\lambda_{max.}$ (95% Et OH) 227 nm (log ε 4.30) and 292 (3.99).

(e) Cyclohexene oxide

4H-5a,6,7,8,9,9a-Hexahydropyrrolo[2,1-c][1,4]benzoxazin-4-one (170).

Potassium metal (0.16 g., 0.004 mole) cut under petrol, was added in small portions to methyl pyrrole-2-carboxylate (0.5 g., 0.004 mole) in dimethylformamide (5 ml.). When all the potassium had dissolved (10 min.), cyclohexene oxide (0.39 g., 0.004 mole) was added, and the stirred mixture was then heated under reflux for 2 hr. in an atmosphere of dry nitrogen. The cooled reaction mixture was added slowly to 0.5 N-hydrochloric acid (20 ml.) and refrigerated for 1 hr. The precipitate was collected and recrystallised from chloroform-petrol (b.p. 60-80°) to give the lactone (170) (0.44 g., 58%) as cream platelets, m.p, 128-129°.

(Found: C, 69.3; H, 6.7; N, 7.5. $C_{11}H_{13}NO_2$ requires C, 69.1; H, 6.8; N, 7.3%).

$\nu_{max.}$ (Nujol) 1700 (lactone C:O), 780, 760 and 730 (aromatic CH) $cm.^{-1}$

τ (CCl_4) 3.15 (2H, m, 1-H and 3-H), 3.84 (1H, q, J 2.5 and 4.0 Hz, 2-H), 6.06 (2H, m, total band width 52 Hz, 5a-H and 9a-H) and 8.13 (8H, m, total band width 105 Hz, 6-H_2, 7-H_2, 8-H_2 and 9-H_2).

(i) Attempted methanolysis of 4H-5a,6,7,8,9,9a-hexahydropyrrolo[2,1-c][1,4]benzoxazin-4-one (170).

Under similar conditions to those described earlier (see p.147), the lactone (170) was obtained unchanged from the reaction mixture. Tlc and mass spectral data showed no other component present.

3. Attempted cyclisation reactions.

(a) Iodine-sodium bicarbonate

Attempted preparation of an iodolactone from trans-1-styrylpyrrole-2-carboxylic acid (157).

Iodine (0.127 g., 0.0005 mole) was dissolved in water (5 ml.) containing potassium iodide (0.25 g.) and the solution was added slowly over 45 min. to trans-1-styrylpyrrole-2-carboxylic acid (157) (0.106 g., 0.005 mole) in 0.5 N-sodium bicarbonate (5 ml.) and the mixture was stirred for 1 hr.[159] The precipitate was collected, dissolved in chloroform, dried ($MgSO_4$) and put down a neutral alumina column. Evaporation of the chloroform gave an oil which was dissolved in cyclohexane and filtered hot through basic alumina. Evaporation of the cyclohexane gave a product which was identified as trans-1-styryl-2-iodopyrrole (184) (0.03 g.), colourless prisms, m.p. 109-110° (from petrol b.p. 30-40°). The product was unstable and went black after a few days.

(Found: M^+, 295, m^* 95.7 (295 → 168). $C_{12}H_{10}IN$ requires M^+, 295).

$\nu_{max.}$ (KBr) 1650 (C:C) 950 (trans-vinyl CH), 770, 760, 730 and 700 (aromatic CH) $cm.^{-1}$

τ ($CDCl_3$) 2.57 (1H, d, J 14 Hz, N·CH:), 2.64 (5H, br, PH), 2.78 (1H, t, 5-H), 3.39 (1H, d, J 14 Hz, PhCH:), 3.53 (1H, q, 3-H) and 3.7 (1H, t, 4-H).

(b) Attempted cyclisation of trans-1-styrylpyrrole-2-carboxylic acid (157) with p-toluenesulphonic acid.

trans-1-Styrylpyrrole-2-carboxylic acid (157) (0.1 g.) and p-toluenesulphonic acid (0.01 g.) in benzene (10 ml.) were heated under reflux for 1 hr. Evaporation of the benzene solution gave a dark red oil

which was dissolved in ether and put down a neutral alumina column. The colourless ethereal solution was evaporated to give an oil which showed by tlc (silica gel-cyclohexane) one fast running component. The oil crystallised on standing to give a product which was identified as trans-1-styrylpyrrole (185) by infrared and nmr data.

$\nu_{max.}$ (Thin film) 1645 (C:C), 950 (trans-vinyl CH), 750, 730 and 690 (aromatic CH) $cm.^{-1}$

τ ($CDCl_3$) 2.77 (6H, m, Ph and N·CH:), 3.14 (2H, t, J 2 Hz, 2-H and 5-H), 3.5 (1H, d, J 14 Hz, PhCH:) and 3.85 (2H, t, J 2 Hz, 3-H and 4-H).

(c) Bromine.

Attempted cyclisation of trans-1-styrylpyrrole-2-carboxylic acid (157).

Bromine (1.2 g., 0.0075 mole) in chloroform (5 ml.) was added slowly to trans-1-styrylpyrrole-2-carboxylic acid (157) (0.31 g., 0.0015 mole) in chloroform (10 ml.). Potassium carbonate (0.9 g.) was added to the mixture which was then stirred for 24 hr. at room temperature.[54] The reaction mixture was filtered and the filtrate evaporated to give an oil which was dissolved in cyclohexane and run down a neutral alumina column. Decolourising charcoal was added to the eluent and the mixture boiled for 5 min. on a steam-bath. The cyclohexane solution was filtered and evaporated to give an oil which crystallised on standing to give 1-(1,2-dibromo-2-phenylethyl)-2,3,4,5-tetrabromopyrrole (188) (0.15 g., 16%) as colourless prisms, m.p. 209-210° (from chloroform-petrol b.p. 60-80°)

(Found: C, 22.6; H, 1.3; Br, 73.9; N, 2.3. $C_{12}H_7Br_6N$ requires C, 22.3; H, 1.1; Br, 74.4; N, 2.2%).

$\nu_{max.}$ (KBr) 1290 (strong), 800, 760 and 700 (aromatic CH) $cm.^{-1}$

τ ($CDCl_3$) 2.52 (5H, br, Ph), 3.08 (1H, d, J 11.5 Hz, NBr·CH·) and 3.76 (1H, d, J 11.5 Hz, PhBr·CH·).

Attempted cyclisation of trans-1-(2-methylvinyl)pyrrole-2-carboxylic acid (164).

Bromine (0.425 g., 0.0024 mole) in g. acetic acid (2 ml.) was added slowly to trans-1-(2-methylvinyl)pyrrole-2-carboxylic acid (164) (0.1 g., 0.0006 mole) in g. acetic acid (5 ml.) and the mixture was then heated under reflux for 4 hr.[178,179] The cooled reaction mixture was poured into water, neutralised with 10% aqueous sodium bicarbonate solution and refrigerated overnight. The precipitate was collected, dissolved in ether and put down a neutral alumina column. Evaporation of the ethereal solution gave a gummy solid.

$\nu_{max.}$ (KBr) 1740 and 1720 (C:O) $cm.^{-1}$

τ ($CDCl_3$) 2.8 (1H, s, N·CH:), 3.18 (1H, d, J 2 Hz, NBr·CH·), 5.1 (1H, m, J 2 and 7 Hz, Me.CH·), 7.83 (3H, s, Me C:) and 8.53 (3H, d, J 7 Hz, Me·CH).

Both the bromolactone (189) and the dehydrobrominated lactone (190) were present in the n.m.r. spectrum of the product. Although the reaction conditions were varied, it was not possible to prepare a pure sample of either of the two lactones. Tlc showed that the two lactones had very similar R_F values which made separation very difficult.

4. Photochemical reactions.

(a) Photochemical isomerisation.

cis-1-Styrylpyrrole-2-carboxylic acid (191).

trans-1-Styrylpyrrole-2-carboxylic acid (157) (0.15 g., 0.0007 mole) in benzene (100 ml.) was irradiated for 6 hr. with a "Camag" Universal UV lamp TL-900/U at 350 nm using a glass filter. Evaporation of the benzene solution gave a brown residue which was dissolved in chloroform and boiled for 5 min. with activated charcoal. Evaporation of

the chloroform filtrate, and trituration with petrol gave the styrylpyrrole acid (191)(0.12 g., 80%) as straw coloured prisms, m.p. 131-133° (from chloroform-petrol b.p. 60-80°).

(Found: C, 73.1; H, 5.2; N, 6.8. $C_{13}H_{11}NO_2$ requires C, 73.2; H, 5.2; N, 6.6%).

$\nu_{max.}$ (KBr) 2650 (bonded OH), 1670 (C:O and C:C), 780, 770, 740 (aromatic CH) and 700 (cis-vinyl CH) $cm.^{-1}$

τ ($CDCl_3$) - 1.04 (1H, br, OH), 2.82 (7H, m, 3-H, and N·CH:CH·Ph), 3.22 (1H, m, 5-H), 3.63 (1H, d, J 8.5 Hz, Ph·CH:) and 3.84 (1H, m, 4-H).

$\lambda_{max.}$ (95% EtOH) 222 nm (log ε 4.19) and 270 (4.11).

(b) Attempted photocyclisation of trans-1-styrylpyrrole-2-carboxylic acid (157).

trans-1-Styrylpyrrole-2-carboxylic acid (157) (0.2 g., 0.0009 mole) in 95% ethanol (1L) was irradiated with unfiltered light (quartz cooling jacket) from an Hanovia 1L-PCR fitted with a medium pressure arc tube. The reaction was monitored on a UV-spectrophotometer. After 20 min. the trans-acid had been completely isomerised to the cis-acid (191). During the next 5 hr. the spectra showed a slow decline in the absorbance of the cis-acid without the appearance of any new peaks. Evaporation of the pale yellow reaction mixture gave an oil which had a strong carboxylic acid (C:O) absorption in the infrared spectrum. Further purification of the oil did not yield any identifiable product.

D. MASS SPECTRAL TABLES

3-Cyclohexyl-2-oxo-5-phenyl-1,2,3-oxathiazolidine (106)

m/e (I%) 201 (23), 200 (45), 172 (8), 159 (37), 158 (23), 120 (14), 119 (16), 118 (65), 117 (6), 112 (27), 110 (33), 106 (20), 105 (27), 104 (23), 103 (12), 92 (17), 91 (63), 84 (6), 83 (91), 82 (22), 81 (10), 79 (8), 78 (18), 77 (43), 68 (17), 67 (12), 65 (8), 64 (32), 56 (13), 55 (100), 54 (22), 53 (10), 52 (6), 51 (24), 50 (10), 48 (18), 43 (6), 42 (11), 41 (65), 39 (25), 30 (30).

m^* 199 (201→200), 124 (201→158), 70.3 (118→91), 62.6 (110→83), 36.5 (83→55).

3-Cyclohexyl-5-phenyloxazolidin-2-one (112)

m/e (I%) 245 (68), 202 (20), 201 (6), 200 (15), 164 (38), 163 (12), 158 (33), 146 (9), 120 (24), 118 (15), 110 (48), 105 (13), 104 (100), 103 (9), 92 (11), 91 (46), 83 (22), 82 (13), 81 (9), 78 (6), 77 (13), 68 (11), 67 (10), 55 (59), 54 (24), 41 (42).

m^* 199 (201→200), 166.5 (245→202), 130 (164→146), 66.4 (163→104), 62.5 (110→83), 60.3 (201→110).

3,5-Diphenyloxazolidin-2-one (118)

m/e (I%)					
	239 (22),	196 (3),	195 (14),	194 (62),	193 (3),
	167 (3),	165 (3),	119 (3),	118 (3),	117 (3),
	116 (3),	113 (3),	105 (13),	104 (100),	103 (5),
	92 (12),	91 (27),	90 (3),	89 (3),	78 (10),
	77 (68),	65 (8),	64 (5),	63 (7),	52 (5),
	51 (20),	50 (6),	44 (4),	41 (4),	39 (10).

m^* 192.8 (195→194), 159 (239→195).

3,4-Diphenyloxazolidin-2-one (121)

m/e (I)					
	239 (92),	238 (6),	196 (4),	195 (6),	194 (7),
	187 (4),	182 (4),	181 (14),	180 (38),	162 (4),
	159 (4),	152 (3),	121 (3),	120 (18),	119 (21),
	118 (12),	117 (4),	105 (9),	104 (100),	103 (6),
	93 (3),	92 (15),	91 (35),	90 (6),	89 (6),
	78 (18),	77 (83),	76 (8),	75 (4),	74 (4),
	65 (11),	64 (8),	63 (8),	52 (8),	51 (30),
	50 (9),	39 (12).			

4-Cyclohexyl-6-phenylmorpholine-2,3-dione (129)

m/e (I%)					
	273 (5),	230 (2),	229 (2),	201 (1),	200 (2),
	199 (1),	193 (5),	192 (25),	182 (7),	174 (5),
	158 (2),	156 (1),	146 (8),	128 (5),	120 (5),
	119 (2),	118 (5),	110 (5),	107 (5),	106 (5),

105 (19), 104 (100), 103 (10), 102 (5), 91 (10), 83 (10), 82 (8), 81 (5), 79 (5), 78 (10), 77 (12), 55 (17), 41 (12).

m^* 192 (273→229), 157.5 (192→174), 61 (174→103), 47.5 (229→104).

1-(2-Hydroxy-2-phenylethyl)pyrrole-2-carboxylic acid (156).

m/e (I%) 231 (5), 214 (6), 213 (21), 188 (5), 187 (13), 185 (5), 169 (6), 168 (10), 167 (9), 166 (5), 156 (5), 154 (5), 141 (5), 139 (5), 126 (9), 125 (87), 124 (10), 120 (5), 116 (5), 115 (6), 109 (5), 108 (18), 107 (100), 106 (20), 105 (16), 104 (8), 103 (8), 102 (6), 97 (5), 94 (13), 93 (5), 92 (5), 91 (13), 90 (5), 89 (5), 82 (6), 81 (68), 80 (58), 79 (92), 78 (24), 77 (50), 76 (6), 75 (5), 74 (5), 68 (6), 67 (6), 66 (9), 65 (10), 64 (5), 63 (9), 62 (5), 55 (5), 54 (10), 53 (37), 52 (34), 51 (42), 50 (16), 45 (5), 44 (42), 43 (8), 42 (8), 41 (10), 40 (8), 39 (40), 38 (8), 37 (5),

m^* 167 (169→168), 123.5 (231→169), 58.3 (107→79), 53.6 (213→107), 34.2 (79→52).

trans-1-Styrylpyrrole-2-carboxylic acid (157).

m/e (I%) 214 (6), 213 (38), 212 (11), 194 (4), 170 (7),
169 (47), 168 (100), 167 (47), 166 (10), 154 (3),
143 (3), 142 (3), 141 (11), 140 (4), 139 (6),
128 (4), 120 (8), 115 (11), 103 (7), 102 (17),
101 (4), 94 (27), 93 (6), 91 (10), 89 (6),
77 (27), 67 (4), 65 (6), 63 (8), 51 (23),
39 (17).

m* 211 (213→212), 166 (168→167), 134 (213→169),
132.5 (213→168), 41.5 (213→94).

1H-3,4-Dihydro-3-phenylpyrrolo[2,1-c][1,4]oxazin-1-one (143).

m/e (I%) 213 (17), 169 (3), 168 (9), 167 (11), 166 (3),
156 (2), 154 (2), 141 (3), 140 (2), 139 (3),
128 (2), 115 (5), 108 (10), 107 (100), 106 (9),
105 (9), 104 (5), 103 (7), 102 (5), 94 (3),
91 (10), 89 (4), 80 (9), 79 (73), 78 (15),
77 (20), 65 (5), 63 (5), 53 (5), 52 (18),
51 (15), 50 (6), 39 (11).

m* 167 (169→168), 166 (168→167), 58.3 (107→79),
53.6 (213→107), 34.2 (79→52).

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