PHD

On the synthesis and stereochemistry of novel phenindamine and histryl analogues as potential H1-histamine antagonists

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ON THE SYNTHESIS AND STEREOCHEMISTRY OF NOVEL PHENINDAMINE AND HISTRYL ANALOGUES AS POTENTIAL H_1-HISTAMINE ANTAGONISTS.

Thesis

submitted by M. Jaffar, BSc.

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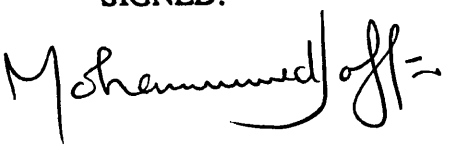
This research has been carried out in the School of Pharmacy and Pharmacology under the supervision of Dr. C. Upton.

SIGNED:



This thesis is dedicated to my Mother.

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SUMMARY.

A brief review of histamine antagonists is presented in Chapter 1 with particular reference to the importance of chirality in drug-receptor activity.

A main aim of the work described in this thesis was to synthesise novel phenindamine analogues as potential H_1-histamine antagonists. The syntheses and stereochemical analyses of novel N-2 substituted phenindamine analogues and their precursors are discussed in Chapter 2. It was found that analogues of phenindamine may be synthesised in which the indene double bond may be relocated from the 9,9a position to the more pharmacologically active 4a,9a site. Both 2-alkyl-9-phenyl-2,3,4,4a-tetrahydro-1*H*- indeno[2,1-c]pyridines and 2-alkyl-9-phenyl-2,3,4,9- tetrahydro-1*H*-indeno[2,1-c]pyridines were isolated. An investigation into the chiral separation of phenindamine analogues using HPLC techniques is also presented.

A route towards the synthesis of novel aryl-substituted phenindamine analogues is also presented in Chapter 2. Conformational analyses of the precursor piperidines are also discussed.

The ^{1}H NMR analysis of Histryl, a clinically useful antihistamine, showed that it exists as two clearly defined conformers. Chapter 3 deals with the syntheses and stereochemical studies of novel conformationally-restricted analogues of Histryl for the purpose of elucidating which conformer is the more biologically active. The synthesis and separation of *cis*-(*c* 3-Me r-4-OCHPh$_2$), *trans*-(*t*-3-Me-r-4-OCHPh$_2$)-1,3-dimethyl-4-benzhydryl ethers and α-1,2-dimethyl-4-benzhydryl ether are discussed.

Pharmacological results on a selection of the compounds synthesised in this work are presented in Chapter 4. The *in vitro* tests showed 3-benzoyl-1-ethyl-4-hydroxy-4-phenyl piperidine HCl, 2-ethyl-9-phenyl-2,3-dihydro-1*H*-indeno [2,1-c]pyridine HBr and 2-Benzyl-9-phenyl-2,3,4,9- tetrahydro-1*H*-indeno[2,1-c]pyridine HCl were the most active compounds. In *in vivo* test systems, the most active compounds were 2-methyl-9-phenyl-2,3,4,4a-tetrahydro- 1*H*-indeno[2,1-c]pyridine HBr and an isomeric mixture of 2-ethyl-9-phenyl-2,3,4,9- and 2,3,4,4a-tetrahydro-1*H*- indeno[2,1-c]pyridine HCl. Activity was also shown in 9-phenyl-2,3-dihydro-1*H*-indeno[2,1-c]pyridine HBr, 2-ethyl-9-phenyl-2,3,4,4a-tetrahydro-1*H*-indeno[2,1-c] pyridine HBr and 2-phenethyl-9-phenyl-2,3,4,4a-tetrahydro- 1*H*-indeno[2,1-c]pyridine HBr.

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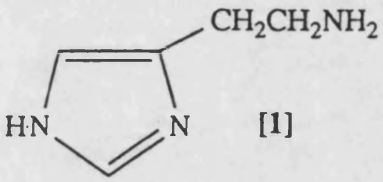
CHAPTER 1.
INTRODUCTION.

1. INTRODUCTION.

Histamine or 2-(imidazol-4-yl)ethylamine [1] was first reported by Windaus and Vogt[1] who synthesised it out of chemical interest as a partial structure of the naturally occurring α-amino acid histidine. They appeared to have no knowledge, however, of the biological implications of histamine, as it was not known at the time that it occurred in living organisms. In 1910, Dale and Laidlaw[2], published the first of a series of papers describing the pharmacological effects of histamine; in particular, they noted the powerful effects of histamine in stimulating contractions of smooth muscle, and its potent action in lowering blood pressure.



[1]

In the body, histamine is stored in vesicles in its inactive form histidine. It is activated by the enzyme histidine decarboxylase. Histamine is catabolised by diamine oxidase (Histaminase) and methyl transferase. Both enzymes are not specific to the degradation of histamine, indicating that histamine may be widely distributed in the body.

Histamine is closely associated with mast cells[3] and its long established role as a mediator of inflammation led to its general description as an autocoid (local hormone); produced by cells, is released to the tissue fluid, and only acts on adjacent cells. Much interest has been concentrated on a large list of pharmacological agents, in addition to immunogloblins, that can produce mast cell degradation and the biochemical events associated with histamine release[4,5,6]. However, not all tissue histamine is associated with mast cells, and, depending upon species, histamine has been detected in basophils, platelets[7], enterochromaffin-like cells[8], endothelial cells[9] and neurons[10]. There is also some evidence that histamine synthesis can be induced, and histamine made available

in an unstored diffusible form, in tissue undergoing rapid growth and repair[11]. These additional sites of histamine synthesis and storage suggest that there are alternative physiological roles for histamine.

Histamine has a dramatic effect when it is liberated into the tissue during allergic or anaphylactic reactions. Histamine has been shown to play a considerable part in gut motility, gastric acid secretion and in the stimulation of smooth muscles in the lungs and blood vessels.

1.1 HISTAMINE RECEPTORS.

It is well known that the majority, if not all, of the effects of histamine can be attributed to activation of either H_1-, H_2-, and recently H_3-histamine receptors, on the basis of quantitative *in vitro* studies in isolated peripheral tissue and brain slice preparations.

Histamine receptors were initially subdivided by Ash and Schild[12] when they introduced the term H_1-receptor to describe the class of histamine receptors that were sensitive to inhibition by low concentrations of classical antihistamines (synonymous with H_1-receptor antagonists). Prior to this, it was well established that only certain of the responses to histamine were sensitive to these agents.

Classic H_1-receptor-mediated responses include contractions of many visceral smooth muscles including guinea pig trachea, uterus, and the longitudinal smooth muscles of the ileum[12,13]. However, a number of responses to histamine, most notably stimulation of acid secretion from the gastric mucosa, the chronotropic responses of guinea pig right atrium, and the inhibition of electrically evoked contractions of rat uterine horn, were resistant to H_1- antagonists such as mepyramine[12,14]. The receptor responsible for

these latter responses was eventually defined as the H_2-receptor by Sir James Black and his colleagues[14], when they successfully developed a selective antagonist of this receptor, namely burimamide[14]. The third histamine receptor (H_3) was originally postulated in 1983 to explain the atypical pharmacological properties of the histamine autoreceptor responsible for controlling the release of histamine from rat cerebral cortical slices[15]. More recently, the H_1- and H_2-histamine receptors have been cloned[16,17]. A recent review on the histamine receptors has been published by Hill[18].

1.1.1 H_1-Receptor.

In most tissue, H_1-receptor stimulation leads to the hydrolysis of phosphatidylinositol-4,5-diphosphate with the consequent formation of inositol-1,4,5-triphosphate (IP_3) and 1,2-diacylglycerol (DG)[19]. IP_3 which is released into the cytosol, has been shown to mobilise calcium from intracellular stores[19]. The influx of calcium ions has a direct effect on the contractile apparatus. DG, which is retained within the membrane environment activates protein kinase C[19]. In many tissues, formation of inositol-1,3,4,5- tetrakisphosphate from IP_3 occurs and this molecule may have a role in controlling calcium influx and refilling of intracellular stores[19].

Histamine was first thought to stimulate, indirectly, the breakdown of membrane inositol phospholipids in rat brains[20] and guinea pig ileum[21]. This was later confirmed using [^{3}H] inositol phosphate accumulation in the presence of lithium ions, which inhibits inositol monophosphate, following prelabeling of tissues with [^{3}H] *myo*-inositol[22]. In guinea pig brain slices, the regional distribution and pharmacological characteristics of the inositol phosphate responses to histamine closely parallels that of the histamine H_1-receptor[22,23]. The guinea pig cerebellum contains the largest inositol

phosphate responses to histamine , and this is selectively inhibited by H_1-receptor antagonists[23]. Similar H_1-receptor-mediated responses have also been detected in rat cerebral cortex[24] and mouse cerebral cortex[25].

Histamine-stimulated inositol phospholipid hydrolysis has been demonstrated in a number of peripheral tissues, including canine and bovine trachea[26,27], bovine adrenalchromaffin cells[28], human umbilical endothelial cells[29], guinea pig ileum[23], guinea pig bladder[30], and guinea pig aorta[31]. In most of these tissues, pharmacological characterizations of the inositol phospholipid responses to histamine is consistent with an H_1-receptor-mediated response.

One of the pharmacological consequences of producing a raised intracellular level of inositol-1,4,5-triphosphate is mobilisation of intracellular calcium, although only small rises in the actual level of inositol-1,4,5- triphosphate following H_1-receptor stimulation have been demonstrated in a number of tissues[29]. The largest accumulation of the metabolites inositol-1,3,4-triphosphate and inositol-1,4-bisphosphate suggests that the flux through inositol-1,4,5-triphosphate may be large. A release of calcium from intracellular stores by histamine H_1-receptor stimulation has been shown in endothelial cells[29,32], airway smooth muscle[33] and rat aorta[34].

The effect of histamine H_1-receptor stimulation on the opening of plasma membrane ion channels is an area in which little, and often indirect, evidence is available. Most information has come from studies of the calcium dependence of histamine-induced contractile activity in various smooth muscle preparations, in particular guinea pig intestinal smooth muscle. Histamine can initiate smooth muscle contraction by releasing intracellular calcium or by opening either receptor-operated or voltage-operated calcium channels[35].

In intestinal smooth muscle, histamine can activate ion channels permeable to sodium, potassium and probably calcium ions leading to depolarisation, an increase in action potential discharge, and smooth muscle contraction[36]. It is likely that the depolarisation produced is sufficient to open voltage-operated calcium channels, which are partly responsible for smooth muscle contraction.

Histamine is one of the most potent stimulants of cyclic adenosine monophosphate (cAMP) accumulation in guinea pig and rabbit brain slices[37,38]. This elevation of cAMP levels produced by histamine appears to involve two separate mechanisms. One is *via* the H_1-receptor, the other through the H_2-receptor sites (see later). The H_1-receptor-mediated responses to cAMP depends upon the prior stimulation of the H_2-receptor. The H_1-receptor-mediated response is thought to be an indirect stimulation. It is likely that a secondary messenger is involved because the effects are lost in broken cell preparations[39].

It has been suggested that the indirect H_1-receptor stimulation of cAMP accumulation may be mediated at the levels of cAMP synthesis[40]. It has also been established that histamine H_1-receptors can elicit the release of catecholamines from adrenal glands[41]. Histamine (*via* the H_1-sites) has also been known to exert a powerful stimulant effect on the breakdown of glycolysis in mammalian brain slices, suggesting that it may have an important role to play in modulating carbohydrate metabolism in cerebral tissue[42].

As stated before, histamine is a potent stimulant of cAMP accumulation in many cells, and particularly those of the central nervous system (CNS)[43]. Pharmacological studies in brain slices[44] gastric mucosal cells and glands[45], dog fat cells[46], cardiac myocytes[47], vascular smooth muscle[48], basophils[49], and neutrophils[50] indicate that H_2-receptor

stimulation is intimately involved in those responses.

1.12 H_2-Receptor.

H_2-Receptor stimulation, leads to the influx of calcium ions, but, unlike H_1-receptor stimulation, this is secondary to the stimulation of the contractile apparatus. The influx of calcium ions regulates protein kinase C, which, in turn produces the desired agonist effect. The H_2-receptor also relies on the adenylate cyclase mechanism which is absent in H_1-receptor stimulation.

Histamine H_2-receptor-stimulated adenylate cyclase was first demonstrated by Klein and Levey[51] in broken cell preparation of guinea pig cardiac muscle, and in the brain by Hegstrand and co-workers[39]. It was later showed that guanine nucleotides were necessary for histamine induced activation of both of these tissues[52].

Histamine H_2-receptor stimulated adenylate cyclase activity in mammalian brain is sensitive to a range of psychotropic drugs[53]. Thus, a number of neutrophils[54], and D-lysergic acid diethylamide are potent inhibitors of the H_2-linked cyclase in broken cell preparations from mammalian brain. Many appear to act as competitive antagonists of the H_2-receptor in this system.

It has been proposed that H_2-receptor-mediated increase in intracellular cAMP levels leads to an increase in slow inward calcium ion current (I_{Ca}) as a result of cAMP-dependent phosphorylation of calcium channels which increases the number of channels that may open during depolarisation[55].

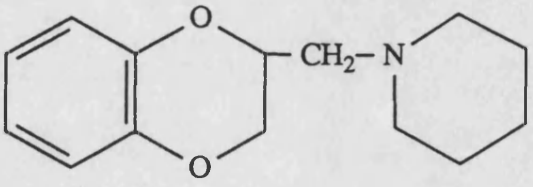
In isolated gastric mucosal parietal cells, histamine- stimulated secretion of

hydrochloric acid (HCl) has been associated with increased intracellular levels of cAMP[56], and is little altered by removal of extracellular calcium ions[57]. Furthermore, studies in single parietal cells have confirmed that H_2-receptor stimulation can release calcium from intracellular stores[58].

The potent effect of H_2-receptor stimulation on gastric acid secretion *in vivo* and the inhibitory effects of the H_2-receptor antagonists on pentagastrin-stimulated acid secretion indicates a physiological role for histamine in the control of gastric acid secretion[59,60]. Up to now, the mechanism of inhibition of the H_2-receptor with the antagonists has still not been resolved. Some hypotheses have been put forward. The first, by Black and Shankley[60], is that histamine acts as the final common mediator of the actions of acetylcholine and gastrin; the other, by Soll and Berglindh[56], suggested that potentiating interactions occur among histamine, gastrin, and acetylcholine at the levels of parietal cells.

1.2 HISTAMINE H_1-ANTAGONISTS.

The first compound reported capable of counteracting some of the effects of histamine in animals was 2-(1-piperidinomethyl)-1,4-benzodioxane [2] which protected guinea pigs from bronchial spasm induced by a histamine spray[61]. This led to the development of a wide range of clinically useful classical H_1-receptor drugs.

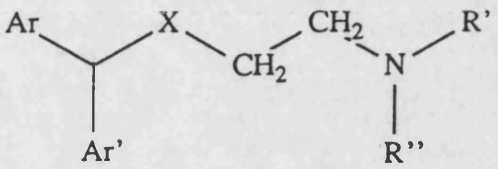


[2]

The classical histamine H_1-receptor antagonists are structurally very similar and are represented by the general formula shown in figure 1. A disubstituted terminal amino group (usually a dimethylamino substituent) is connected to an atom **X** *via* a short

carbon chain. This chain may be saturated, unsaturated, or part of a ring system, and where **X** can be an oxygen, nitrogen or a carbon atom; **X** links the side chain to an "aromatic head". This "aromatic head" contains two aromatic rings (e.g; Ph, CH_2Ph, 2-Py), which may be fused.

FIGURE 1.



Thus, most antihistaminics are chemically stable, no members contain labile ester or amide functionalities, and aryl substituents that facilitate oxidation such as phenolic hydroxy and amino are absent. The most important physical property of antihistaminic drugs is that of the equilibrium between the base and its conjugate acid, as measured by pKa[62].

In 1955, Marchall[63] measured the pKa values of a wide range of antihistaminic drugs which were representative of almost all classes of the drugs in clinical use. The pKa values ranged from Chlorocyclizine (pKa 8.15) to Antazoline (pKa 10.00). The range of magnitudes were such that all the compounds were extensively protonated (90% or greater) at physiological pH.

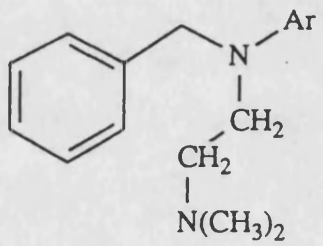
Because of their basic properties, the antihistamine drugs may be administered orally in the form of water-soluble salts. Hydrochloride and maleate salts are the most popular, but salts of citric, succinic, tartaric, and phosphoric acids are also used. In general, however, some fully ionised quaternary ammonium salts of antihistaminics are less effective than salts from acids, probably as a result of inferior absorption after oral administration and adverse differences in distribution after entry into the blood.

1.21 Classical Histamine H_1-Receptor Antagonists.

Based on the general formula in figure **1**, the classical H_1-receptor antagonists can be subdivided into several classes. This subject has been reviwed by Casy[64].

1.21.1 Ethylenediamines.

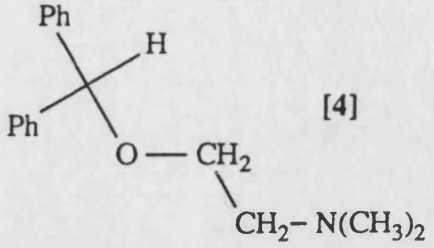
Halpern[65] synthesised the first clinically useful antihistaminic drug N-benzyl-N',N'-dimethyl-N- phenylethylenediamine **[3a]** (phenbenzamine, Antergan). A more potent and less toxic compound resulted when the N-phenyl group was replaced by 2-pyridyl and the discovery led to the development of mepyramine **[3b]** which is still in use clinically as the maleate salt[66,67]. Modifications of the parent structure have been synthesised with potential antihistaminic activity[68,69].



	Ar
[3a]	Ph
[3b]	2-Py

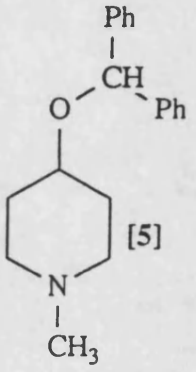
1.21.2 Tertiary-aminoalkyl Ethers.

In America, during the 1940s, the medicinal chemists investigated antihistamines in which the arylamino nitrogen was replaced by oxygen to give a series of basic ethers[70]. This work led to the introduction of 2-dimethylaminoethyl benzhydrylether **[4]** (diphenhydramine, Benadryl). This is not a potent antihistaminic drug and had a short duration of action as well as having anticholinergic activity. Sedative properties were also a side effect. Para substitution of the phenyl groups by methoxy, chloro, and bromo gave rise to antihistaminic drugs with reduced side effects respective to the parent drug[71,72].



[4]

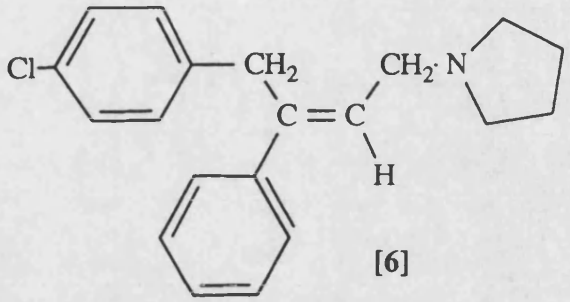
Knox and Knapp[73] varied the diphenhydramine structure by incorporating a piperidine ring instead of the alkylamino chain. This compound, known as diphenylpyraline [5] (Histryl) was considerably more potent than diphenhydramine[74]. Histryl is discussed in more detail in chapter 3.



[5]

1.21.3 1,2-Diaryl-4-Aminobut-2-enes.

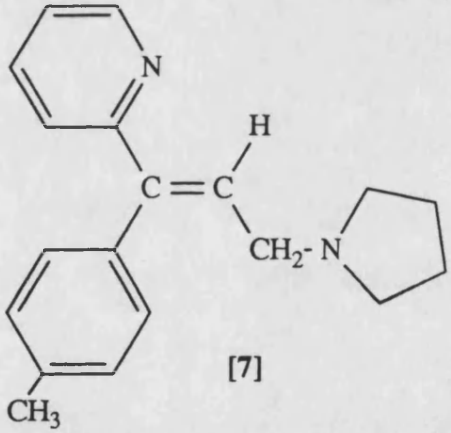
The clinically important member of this class is pyrrobutamine diphosphate [6] (Pyronil) which provided both structural and geometrical isomers that are of value in the investigation of the chemical and stereochemical requirements for the blockade of H_1-histamine receptors[75]. The antihistaminic potency of pyrrobutamine depends upon the rigidity and specific disposition of the alkenic bond. It was important to have a planar $ArCH.CH_2N$ unit and an aromatic substituent at C-1 in 1,2-diaryl-4-aminobut-2-enes for antihistaminic activity[76].



[6]

1.21.4 1,1-Diaryl-3-aminopropenes.

Investigation of 1,1-diaryl-3-aminopropenes was initially investigated by White and co-workers[77]. The 2-pyridyl group was introduced as one of the aryl groups present due to the elevated potency of this heterocycle in other classes of antihistamines[78]. This led to the synthesis of E-1-(2-pyridyl)-3-(1-pyrrolidino)-1-(4-tolyl)-prop-1-ene [7] (triprolidine, Actidil), a clinically very potent antihistaminic drug[79,80]. On the basis of PMR and UV data of salts, assignment of the *cis-trans* pair has been achieved[81].



[7]

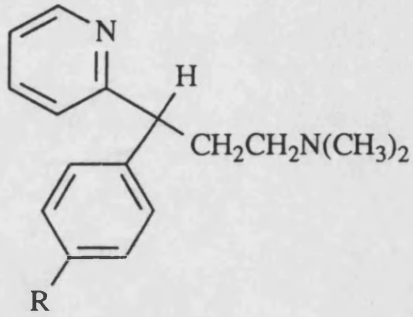
Observation of vinylic protons and other ^1H signals provided a convenient method for monitoring separation and consequent purification of isomeric mixtures. Stereochemical features of triprolidine itself have been confirmed by X-ray crystallography[82,83]. The special role of the pyrrolidino group in the blockade of H_1-histamine receptors is apparent in this series, as it is in the aminobutenes.

The positions of the aromatic system in 1,1-diaryl-3- aminopropenes is an important

factor for antihistaminic activity[84] and two geminal aryl substituents attached to C-1 alkenic carbon atoms are needed for antihistaminic activity.

1.21.5 3-Amino-1-Aryl-(2-Pyridyl)Propenes (Pheniramines).

The pheniramines are saturated analogues of 3-amino-1- aryl-1-(2-pyridyl)-propenes. The halogen derivatives **[8b]** (chloropheniramine) and **[8c]** (bromopheniramine) are more potent than pheniramine **[8a]** (trimiton) itself[85,86].



R

[8a] H

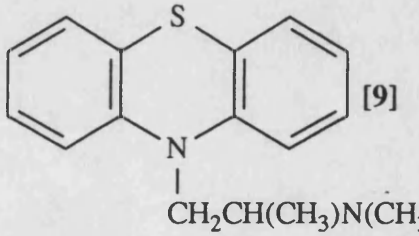
[8b] Cl

[8c] Br

The pheniramines are chiral molecules and potency differences between enantiomeric pairs have been reported[87] (See section **1.4**), although the racemates are clinically employed. The configuration of antipodal pheniramines has been established by a chemical method[88] and confirmed by X-ray crystallography[82,83].

1.21.6 Phenothiazine Derivatives.

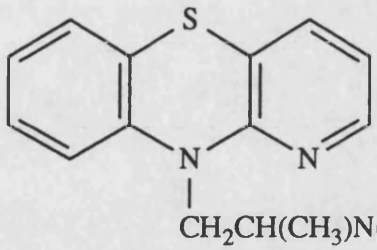
The best known member of this class is 10-(2-dimethylaminopropyl)phenothiazine **[9]** (promethazine) which is still a popular clinical drug[89].



[9]

Many variants of promethazine have been made. Antihistaminic activity is raised when

C-1 of the molecule is replaced by nitrogen to give 1-azaphenothiazine derivatives. Isothipendryl **[10]** has a shorter duration of action and less sedative properties than phenothiazine[90].

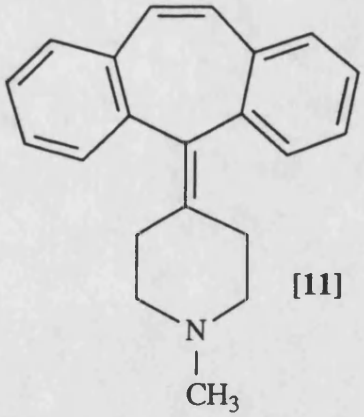


[10]

Both promethazine and isothiopendyl have been resolved[91]. Enantiomers of promethazine have similar antihistaminic and pharmacological properties in contrast to studies of pheniramines.

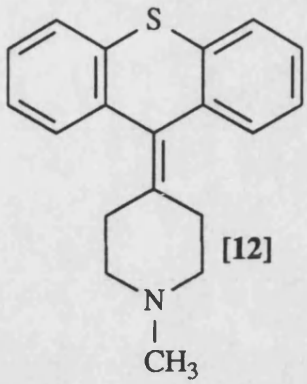
1.21.7 Other tricyclic derivatives.

Of this class, 5-(1-methylpiperidylidene-4)-5*H*-dibenzo- [a,d]-cycloheptene **[11]** (cyproheptadine) is a potent antagonist of histamine but lacks notable CNS effect[92].



[11]

Cyproheptadine and its thioxanthene congener **[12]** are the most potent of many analogues prepared; the sulphur derivative is also known to antagonise seratonergic, bradykininergic, cholinergic receptor sites as well as histaminic sites. The sulfoxide analogue raises the antihistaminic activity[93].

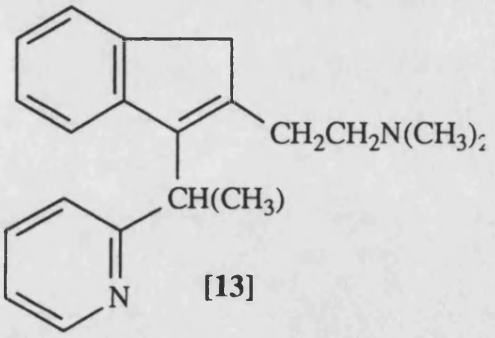


[12]

Other cyproheptadine analogues have been studied, most of which antagonise histamine at the H_1-receptors[94].

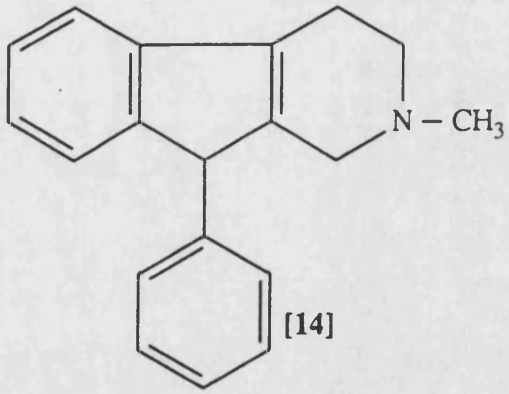
1.21.8 Miscellaneous Types.

Two indene derivatives are of importance as antihistamines. The first is 1-[1-(2-pyridylethyl)]-2- (2-dimethylaminoethyl)indene **[13]** (dimethindene, dimethpyrindene). The pharmacological activity is found to reside mainly in the *levo* isomer. Structurally it bears some resemblance to the 1,2-diaryl-4-aminobut-2-enes, in that the aromatic ring of the dimethpyrindene is *trans* to the aminoalkyl substituent[95,96].



[13]

The other clinically useful drug of interest is phenindamine **[14]** (Thephorin), which will be dealt with in more detail in chapter 2.



[14]

Many other ring system analogues with antihistaminic properties have been reported, mainly the derivatives of 1-phenylpyrrolidine, anthracene, and indole[97,98,99].

Therapeutic uses of the classical H_1-receptor antagonists have been the symptomatic treatment of several allergic responses where histamine release from mast cells is induced *via* immunological mechanisms. Histamine-induced contraction of smooth muscles and increase in capillary permeability can be antagonised *via* H_1-receptor blockade, resulting in an improvement of asthmatic conditions and a reduction in formation of oedema and cutaneous wheal. The classical H_1-receptor antagonists, however, are usually ineffective in bronchial asthma, but they can successfully be employed in allergic rhinitis, conjunctivitis, and dermatitis. This discrepancy may be explained by the fact that histamine probably plays an important part in dermatitis, whereas arachidonic acid metabolites appear to be primarily responsible for asthmatic diseases[100]. Another explanation is that some drug concentrations achieved in the target organ (lungs) are not high enough for effective H_1-receptor blockade.

Raising the applied dosage has limited interest due to unacceptable side-effects. At therapeutic doses, the classical H_1-receptor antagonists generally produce sedation. This usually unwanted effect is probably caused by H_1-receptor blockade in the CNS.

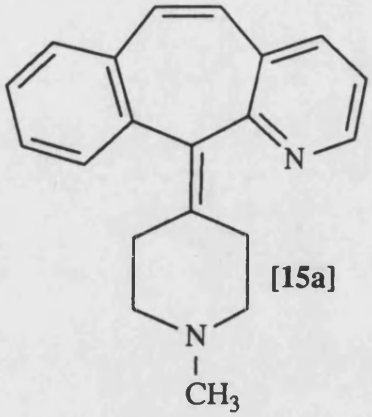
Recent data have shown that H_1-receptors are involved in the regulation of sleep and wakefulness in both the rat and in man[101]. Presently, however, it is not known if the H_1-receptor blockade increases the sleep duration or decreases the latency to sleep onset in man. Other observed side-effects are probably caused by anticholinergic activity of some of the compounds[102]. Such activity can result in dryness of the mouth.

Some of the classical H_1-receptor antagonists possess CNS stimulatory activity. This action may be explained by the fact that these compounds are able to interact with other neurotransmitter systems in the brain. Interaction with noradrenergic, seratonergic, and dopaminergic uptake systems have been reported, and these activities may play a role in behavioural effects of these antagonists[103,104].

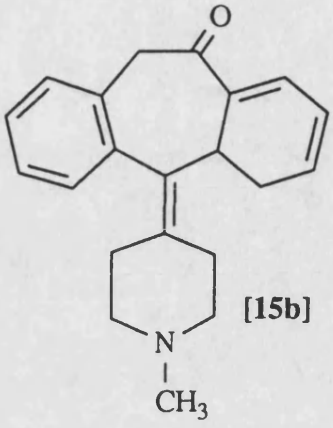
1.22 Modern H_1-Histamine Antagonists.

As a result of a greater understanding of the pharmacological aspects of the histamine receptors, modern H_1-receptor antagonists have been synthesised which combine H_1-antagonism with other clinically useful pharmacological activities in one molecule. This subject has been reviewed by Leurs *et al.*,[105].

Tozzi *et al.*,[106] reported the synthesis of Azatidine **[15a]** and Ketotifen **[15b]**, both of which are derivatives of the classical tricyclic compound, cyproheptadine.



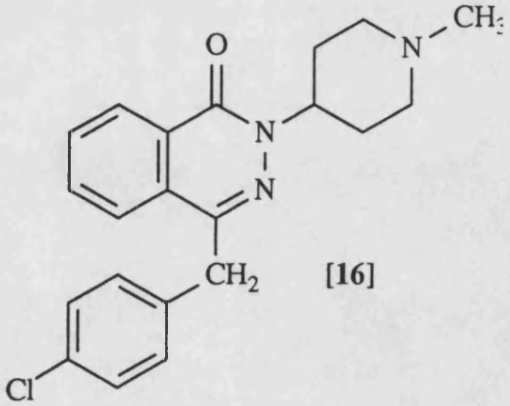
[15a]



[15b]

Azatidine is a potent antagonist of the H_1-receptor as well as the muscarinic, seratonergic, both in *in vitro* and in *in vivo* models. Azatidine is approximately nine times more potent than cyproheptadine. Ketotifen is a noncompetitive H_1-receptor antagonist with minor anticholinergic and seratonergic activity[107]. Clinically Ketotifen is employed for the treatment of asthma.

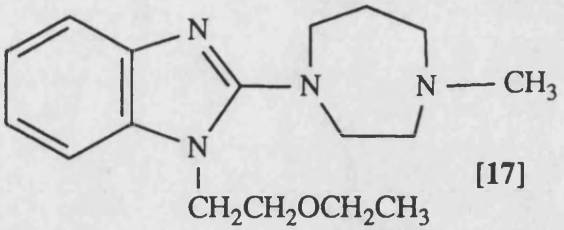
Azelastine **[16]**, a phthalazinone derivative is structurally unrelated to the classical H_1-antagonists. Azelastine has negligible anticholinergic activity, with moderate seratonergic antagonism[108]. In several *in vivo* test systems on allergic conditions, azelastine proved to be a long-lasting, orally effective agent[109].



[16]

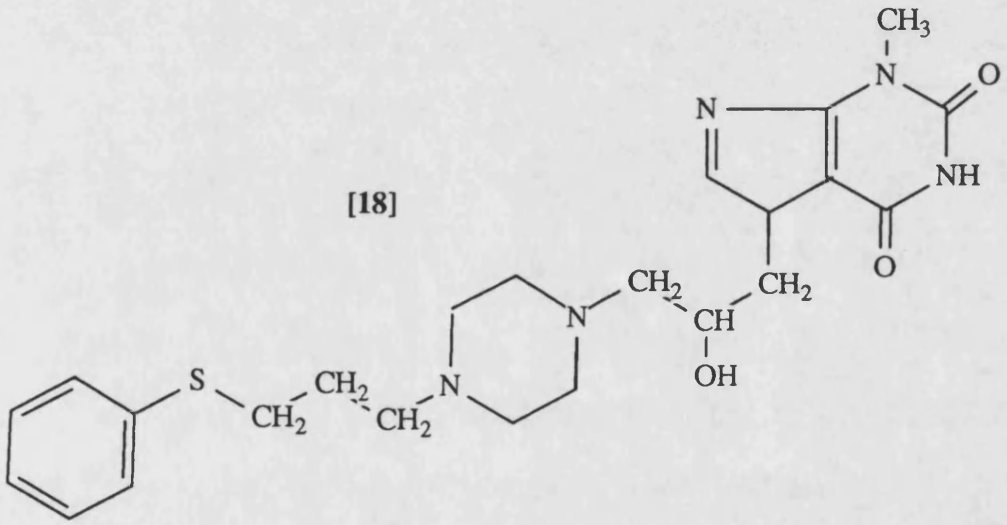
1-(2-Ethoxyethyl)-2-(4-methyl-1-homopiperazinyl)- benzimidazole **[17]** (KB-2413) is a selective potent H_1-receptor blocker. It is forty times more potent than chloropheniramine in *in vivo* studies. KB-2413 is highly effective in preventing

anaphylactic broncho-constriction in guinea pigs. KB-2413 is ineffective at acetylcholine, norepinephrine and serotonin receptors[110].



[17]

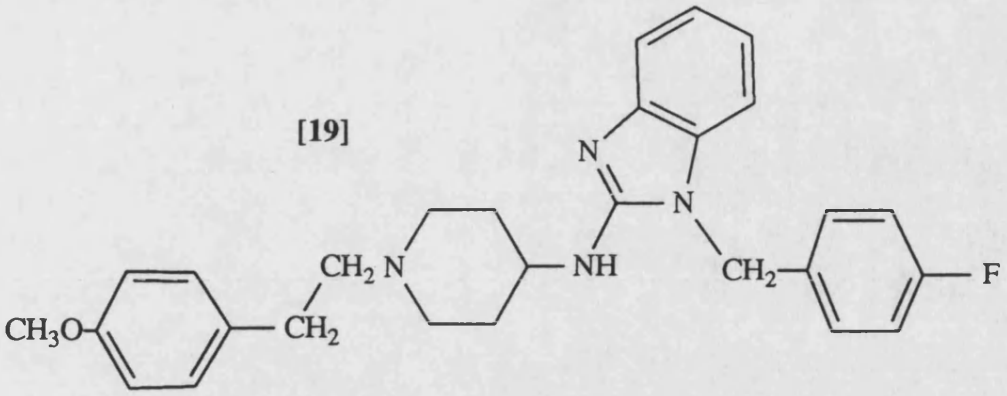
Tazifylline **[18]** is a selective H_1-blocker in both *in vivo* and *in vitro* test systems[111,112]. It has weak affinity towards adrenergic, saratonergic and muscarinic receptors[14]. As a consequence, tazifylline has few side-effects, and with a long duration of action, it might prove to be a very successful anti-allergic drug.



[18]

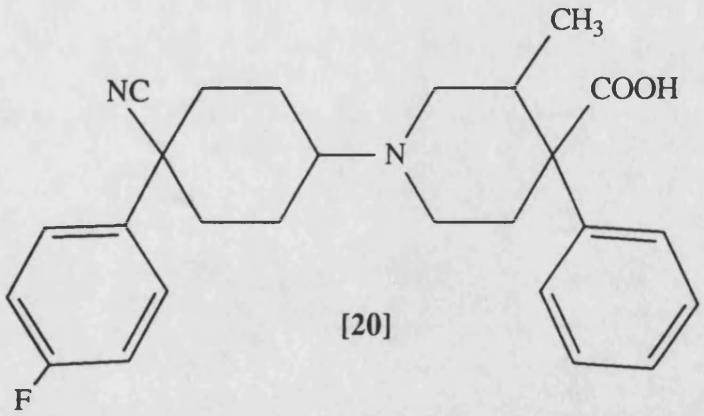
Astemizole **[19]**, is potent antihistaminic drug with a short onset and a long duration of action. It was discovered by Janssens *et al.*,[113,114,115] while looking for a neuroleptic drug, hence it is structurally different from known H_1-receptor antagonists.

[19]



Astemizole has moderate $5HT_2$ activity, and has a high affinity for the α-adrenergic receptor. Astemizole does not cross the blood-brain barrier and hence has no noticable CNS and sedative properties[116]. Astemizole is commercially available and is used in allergic disorders[117].

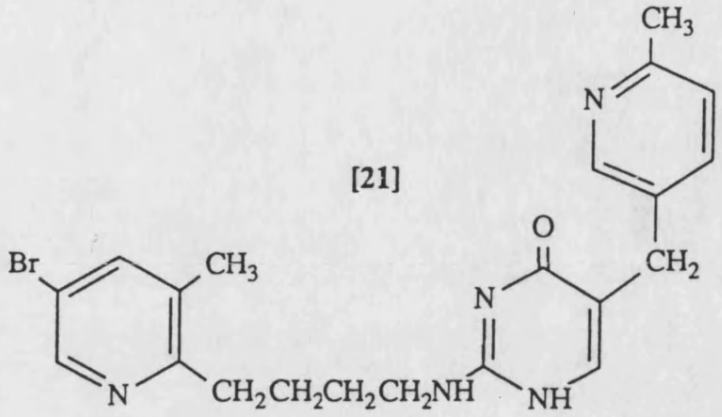
Cabastine **[20]**, one of a series of the 4-phenylcyclohexylamines, is a chiral compound with the levocabastine the more potent enantiomer. It has no noticable anticholinergic or antisaratonergic activity[118]. Cabastine is approximately 100 times more potent than astemizole.



[20]

Levocabastine has already been evaluated in several clinical trials; low doses resulted in a significant reduction of symptoms of allergic conjunctivitis and rhinitis with no adverse side-effects.

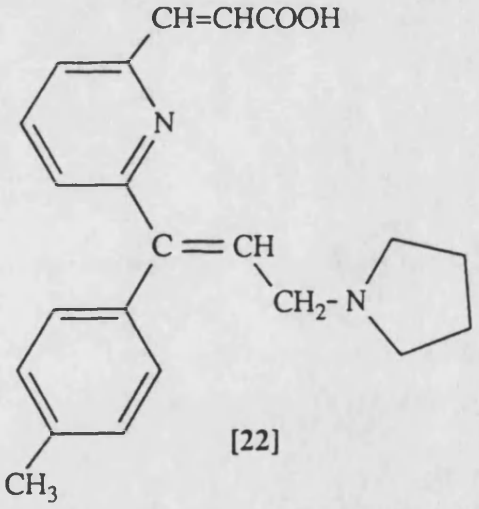
Durant and colleagues[119], synthesised a unique potent H_1-antagonist in temelastine



[21]

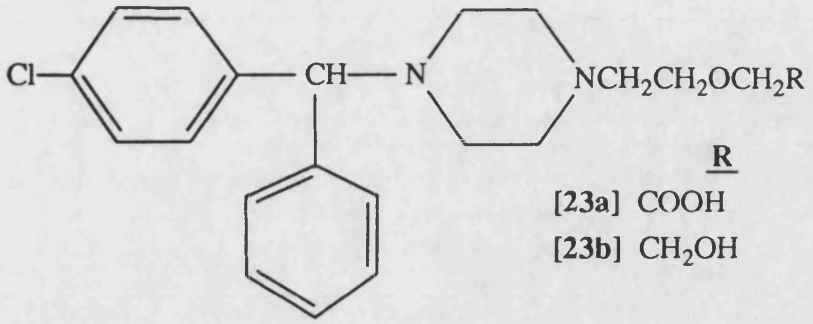
In a clinical trial, temelastine showed significant antihistaminic activity and produced no sedation[121]. Its efficacy in allergic conditions has yet to be shown.

The antihistaminics, acrivastine [22], a triprolidine analogue, was designed specifically as drugs that will not cross the blood-brain barrier. In doing so, the major side-effects may be avoided, as interaction with the CNS is lost[122].



[22]

Cetirizine [23a],a metabolite of hydroxyzine [23b], a H_1- blocker based on the classical H_1-receptor antagonists, does not cross the blood-brain barrier. It is a potent antagonist with little affinity for adrenergic, dopaminergic and seratonergic receptors[123].



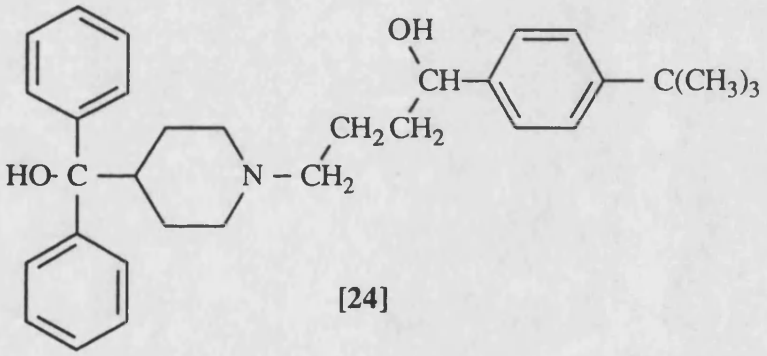
R

[23a] COOH

[23b] CH_2OH

Cetirizine has long lasting activity, with no sedative side-effects[124]. It is effective in blocking the histamine receptors in the skin and lungs[125,126].

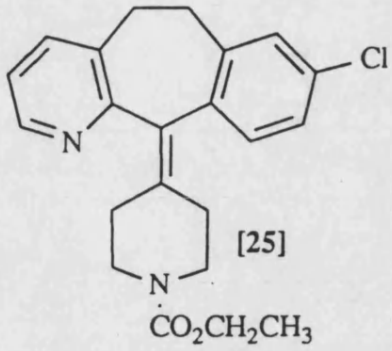
The clinically useful terfenadine **[24]**, is a selective H_1-receptor antagonist with no significant activity on other receptor systems. It shows reduced passage through the blood-brain barrier[127].



[24]

Therapeutically, terfenadine is employed in the treatment of allergic rhinitis, bronchial asthma and skin diseases.

Based on the azatidine series, loratidine **[25]** is devoid of any anticholinergic and CNS-depressant activity[128]. Pharmacological evaluation of loratidine by Ahn and Barnett[129] has produced interesting results, in the sense that they showed selectivity of the drug in tissues that contain H_1-receptors.



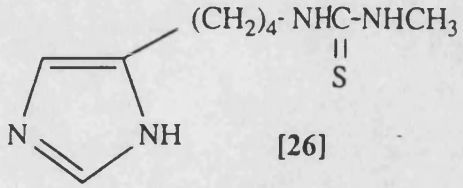
[25]

Due to the reduced basicity of the piperidine nitrogen, loratidine is rapidly absorbed after oral administration and therefore shows a rapid onset of action. Since the major metabolite of loratidine, descarboxyethoxyloratidine, is also a potent H_1-receptor antagonist, the *in vivo* activity is long-lasting[128]. As a consequence of the favourable pharmacokinetic profile, loratidine can be administered once a day for effectiveness in allergic conditions.

1.23 Histamine H_2-Receptor Antagonists.

It has long been recognised that the actions of histamine on intestinal smooth muscle and on gastric acid secretion are distinctly different, the former being antagonised by H_1-blockers which do not affect the secretion of gastric acid in response to histamine. This subject has been reviewed by Daly and Price[130] and by Leurs and colleagues[105].

Black and his colleagues[14] showed that buramimide [26], the first selective H_2-histamine antagonist, blocked the H_2-receptor-stimulated action of gastric acid secretion.

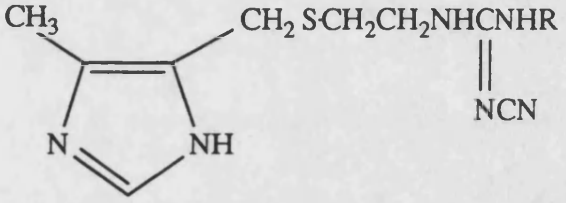


[26]

Cimetidine [27a], was later marketed as the first H_2-antagonist and is used clinically

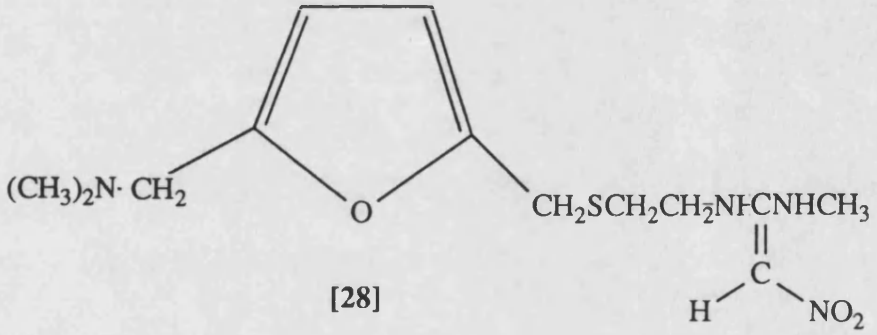
for the treatment of stomach ulcerations. Cimetidine is a competitive antagonist which inhibits the contraction of isolated uterus and the secretion of gastric acid as well as increasing the constriction of guinea pig isolated atrium[14].

Etinidine **[27b]**, an analogue of cimetidine, was found to be twice as active as cimetidine[131,132]. Other cimetidine analogues have been synthesised with selective antagonism at the H_2-site.



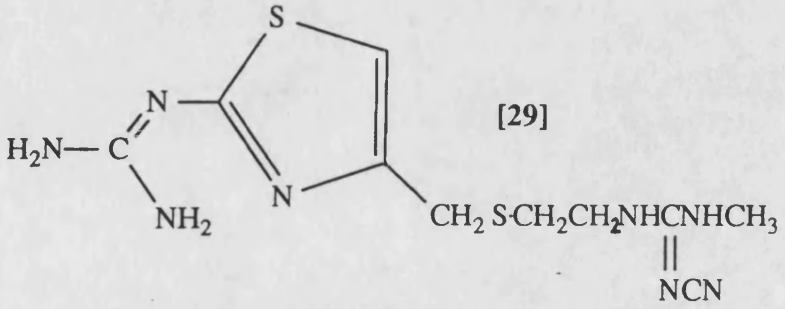
	R
[27a]	CH_3
[27b]	$CH_2C{\equiv}CH$

Improvement of the H_2-antagonist activity was achieved by Bradshaw *et al.*,[133] in ranitidine **[28]**, whereby the imidazole ring was replaced by a furyl system. Analogues of ranitidine were also synthesised[134,135].



[28]

Changing the heterocyclic moiety of cimetidine produced a potent H_2-antagonist in tiotidine **[29]** (derived from the 1,3-thiazole heterocycle)[136].

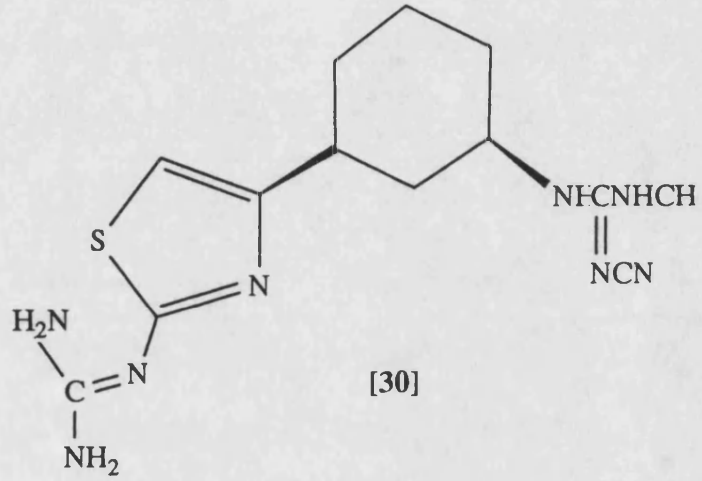


[29]

Tiotidine failed its clinical test due to damaging side-effects. Tiotidine, however, is

being used as a radioligand in histamine H_2-receptor binding studies[137]. In contrast to what has been found in cimetidine, the replacement of the sulphur atom in the side chain of tiotidine does not lead to a reduction in H_2-antagonist activity[138].

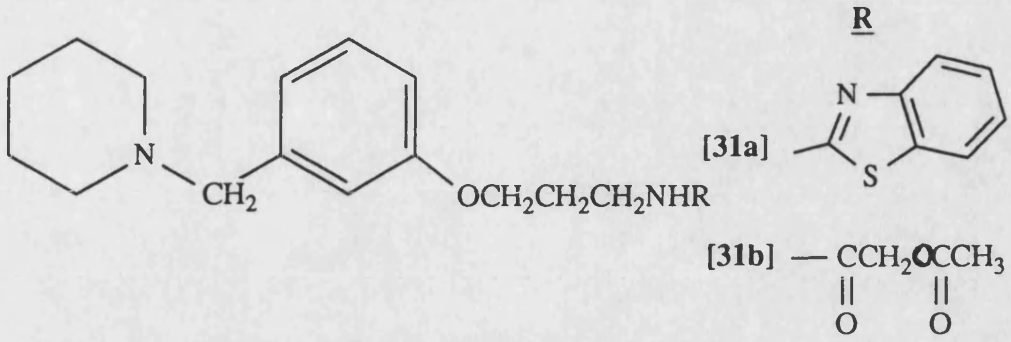
A particularly interesting modification of the structure of tiotidine can be found in which the flexible alkyl chain is incorporated into a cyclohexane ring system **[30]**, rendering the whole structure fairly rigid. The H_2-antagonistic activity of compound **[30]** is higher than that of tiotidine[138].



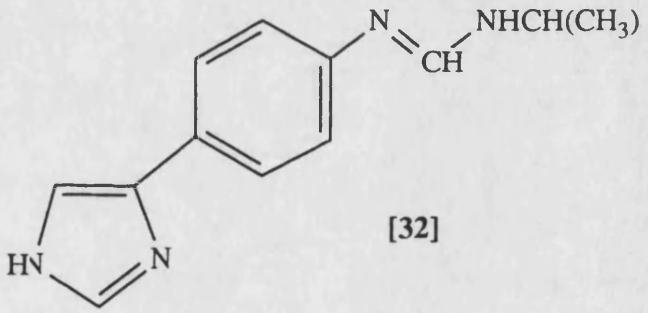
[30]

A further development of the H_2-receptor antagonists was achieved by the synthesis of pifatidine **[31a]** a potent H_2-antagonistic activity. In *in vivo* studies pifatidine was shown to be six times more active than cimetidine[139]. Pifatidine has been introduced into the market. It is applied on a once-daily dose for providing fast pain relief when compared with cimetidine and ranitidine[140].

The benzothiazole analogue of this series, zolatidine **[31b]** is also a potent antagonist at the H_2-receptors. Zolatidine is a brain penetrating H_2-receptor antagonist, which could make it a valuable tool for investigating the pharmacological and pathological roles of histamine in the CNS[141].



Mifentidine **[32]** has an altogether different structure to the known potent H_2-antagonists whereby the flexible alkyl chain connecting the aromatic substituent to the polar group is substituted with another aryl group[142]. Mifentidine is currently undergoing clinical trials, and has so far been found to be devoid of negative inotropic effects and non-specific effects on the human atrium and motility of the gastro-intestinal tract in various animal species[143].



[32]

Therapeutically, the H_2-histamine antagonists play a major role in the treatment of gastric ulcers. With regard to potency and duration of action, however, research for new H_2-antagonists has been redirected because complete inhibition of gastric acid secretion has been found to result in severe gastric damage.

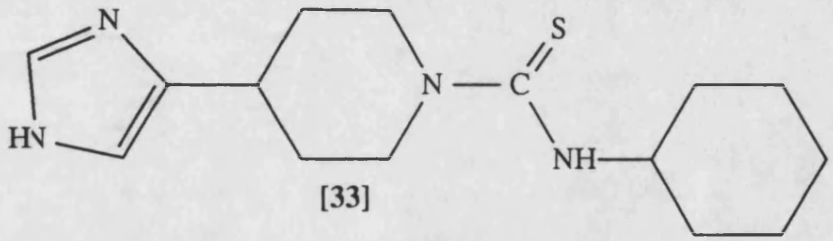
1.3 HISTAMINE H_3 RECEPTORS.

Histamine H_3-receptors were originally identified as inhibitory autoreceptors on histamine-containing nerve terminals in rat cerebral cortex[143], but have since been shown to inhibit the release of a variety of neurotransmitters in both central and

peripheral tissues[144,145].

1.31 Histamine H_3-receptor Antagonists.

The original definition of a novel H_3-receptor controlling histamine release in rat cerebral cortical slices was based on the finding that several existing H_1- and H_2-receptor agonists and antagonists were effective H_3-receptor antagonists[15,146]. Thus, the weak H_2-antagonist burimamide is approximately two orders of magnitude more potent as an inhibitor of H_3-receptor-mediated responses. The H_2-agonist impromidine and the H_1-agonist betahistamine also posses H_3-receptor antagonist properties.



[33]

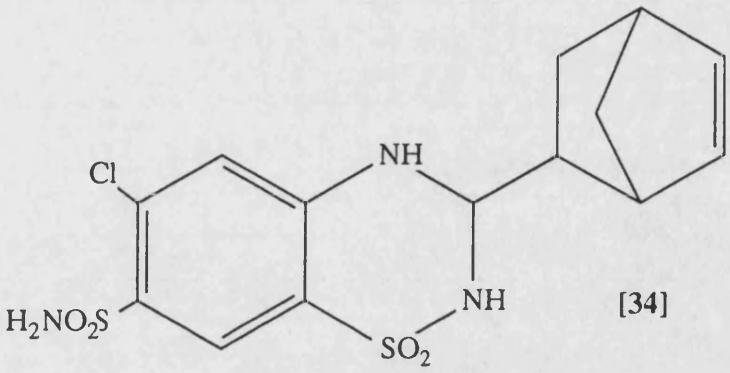
Thioperamide **[33]** is,however, now recognised as the primary H_3-antagonist for receptor classification studies because of its high affinity and good receptor selectivity[144]. This compound also appears to cross the blood-brain barrier and should be of utility in unravelling the behavioural role of H_3-receptors in the CNS.

1.4 CHIRALITY.

This section is presented because it is relevant to the work done in this thesis. Many of the compounds synthesised in this work contain one or more chiral centres (See chapter **2** and **3**). Structural isomerisation and conformational studies are also discussed, and are relevant (See chapter **2** and **3**).

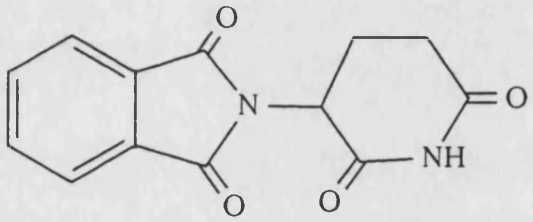
One of the major driving forces at present for the increasing awareness of the consequence of stereochemistry and biological activity is the increasing interest the drug regulatory authorities are taking in the subject. Indeed in FDA guidelines[147] it is stated that, even in racemates, enantiomers may be considered as impurities and that safety and efficacy data need to be produced for each stereoisomer including physical and chemical information. This means that an "inactive" stereoisomer may be treated as a 50% impurity unless a lot of supporting work is available. Thus the importance of developing single enantiomers is vital.

In terms of regulation comes the question as to what to do about drugs marketed at present. Many older drugs were introduced without adequate information on their stereochemical identity or composition. For example, the antihypertensive agent cyclothiazide **[34]** is marketed as a mixture of two racemates and small but significant differences in batches of the marketed drug have been observed[148]. Whether this is of therapeutic consequence is unclear, and may never be resolved, but it serves to highlight the lack of concern in the past on this issue.



[34]

A more positive consequence of the re-examination of older drugs may be the marketing of a single enantiomer, where a racemate has been marketed previously, thus avoiding undesirable side-effects giving an older drug new life. This has happened with thalidomide **[35]**[149], where the (+) enantiomer provides the desired hypnotic effects and the (-) isomer is responsible for the adverse teratogenic effects[150]. This particular example highlights the need for chiral resolution of drug compounds.

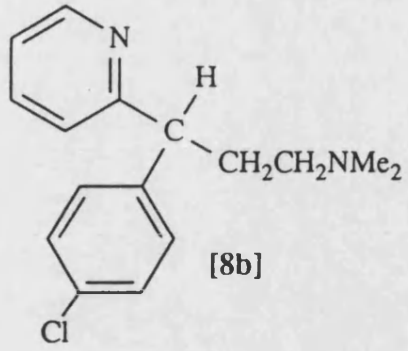


[35]

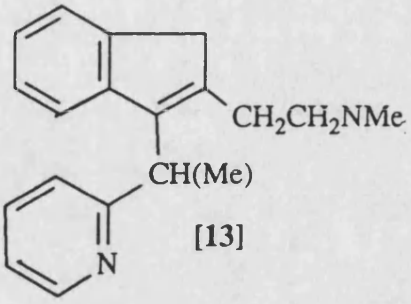
Many drugs with chiral centres have been resolved in order to increase the potency of the drug and/or reduce the unwanted side-effects[151]. For instance, an *in vitro* study of the antihistaminic drug chlorpheniramine **[8b]** showed that the *dextro* isomer was twice as potent as the racemate, and 200 times more active than the *levo* isomer[152].

Recently, Casy *et al.*,[153] described the resolution of the chiral H_1-histamine antagonists chlorpheniramine **[8b]**, dimethindene **[13]**, carbinoxamine **[36]**, and mebrophenhydramine **[37]**. The optical purities of the antipodal products were investigated by chiral HPLC systems, which utilised α-acid glycoprotein and β-cyclodextrin columns.

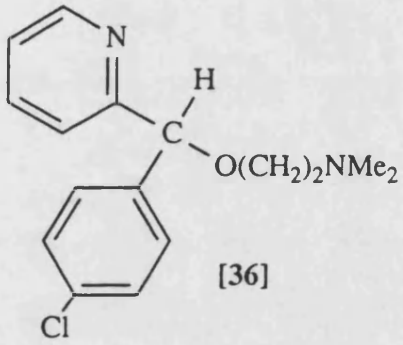
FIGURE 2.



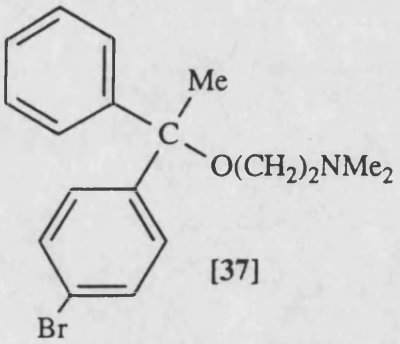
[8b]



[13]



[36]

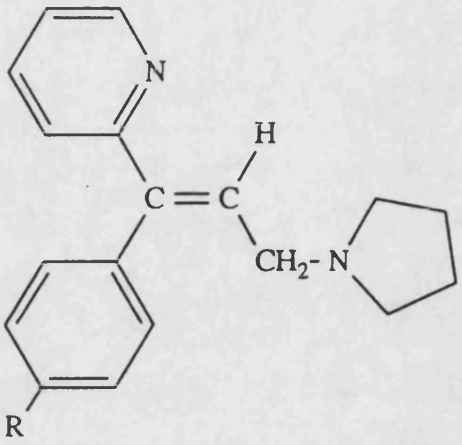


[37]

The same authors tested the antipodal pairs of chlorpheniramine **[8b]** and dimethindene **[13]** in biological systems for antihistaminic activity. They found that the *levo* isomer of dimethindene was 70 times more potent than its antipode in guinea pig ileum preparations.

Geometric isomers of triprolidine analogues have also been resolved and tested[154]. It was found that tripolidine **[7]** is the most active, whilst E-isomers of triprolidine analogues were generally more active in *in vivo* studies than the Z-isomers. The active isomers are shown below.

FIGURE 3.



R

[7] CH_3

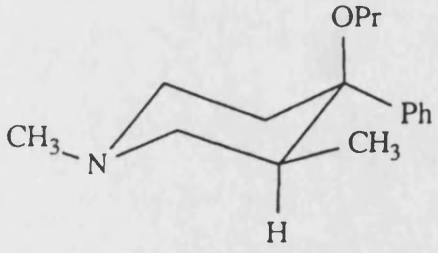
[38] CH_2CH_3

[39] Cl

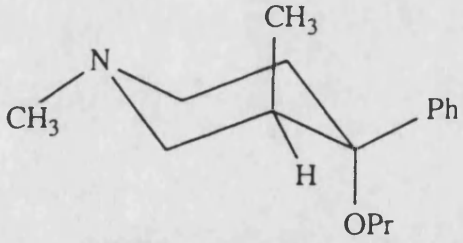
[40] Br

Conformational diastereomers can also lead to unexpected pharmacological results. A good example is that of the 3-methyl reversed esters of pethidine (meperidine), where the configuration of alphaprodine and betaprodine have been established unequivocally by X-ray crystallography as *trans*-isomer **[41]** (*t*-3-Me r-4-Ph) and the *cis*-isomer **[42]** (*c*-3-Me r-4-Ph) respectively[155] with the two isomers in the following conformations in the solid state (Figure **4**, below).

FIGURE 4.



[41] Alphaprodine

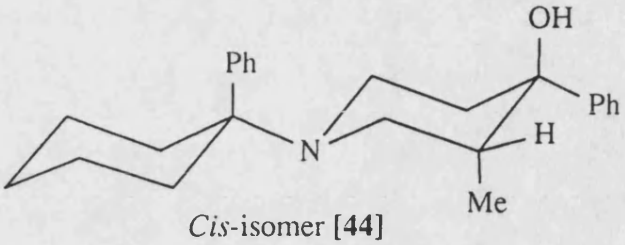


[42] Betaprodine

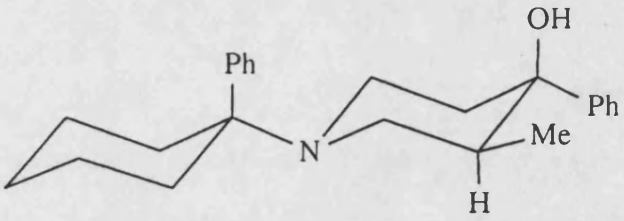
Biologically, it has been shown that betaprodine is five times more active than alphaprodine as an analgesic agent.

Recent examples of conformational isomers are seen in some of the phencyclidine derivitives[156], as analgesics. The *trans*-isomer **[43]** (*t*-3-Me r-4-Ph) was found to be three times more potent than morphine, whilst the *cis*-isomer **[44]** (*c*-3-Me r-4-Ph) was inactive.

FIGURE 5.



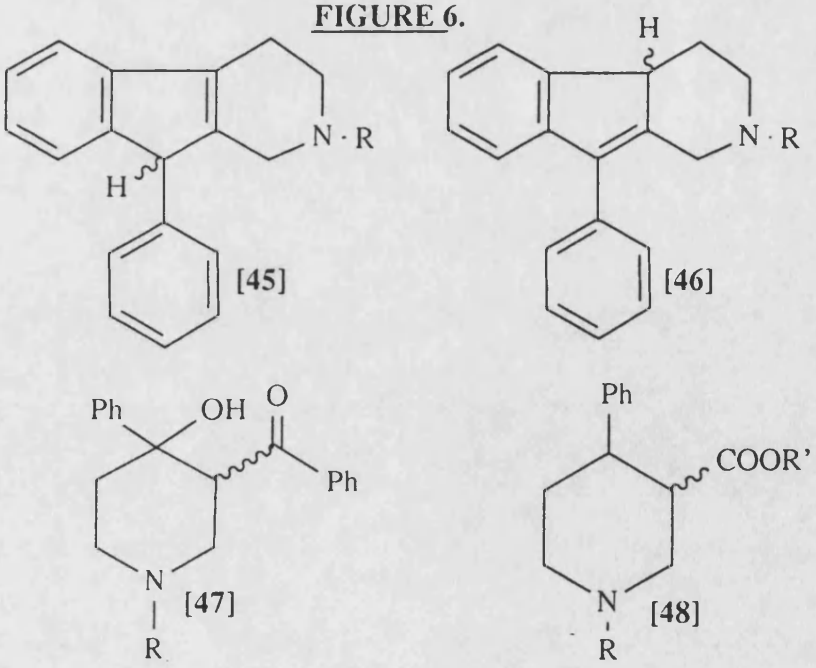
Cis-isomer **[44]**



Trans-isomer **[43]**

The next chapter in this thesis deals with the geometric isomers of phenindamine analogues, which possess chiral centres. Some of the precursors synthesised are diastereomeric (Figure **6**). These types of compounds were submitted for pharmacological analysis.

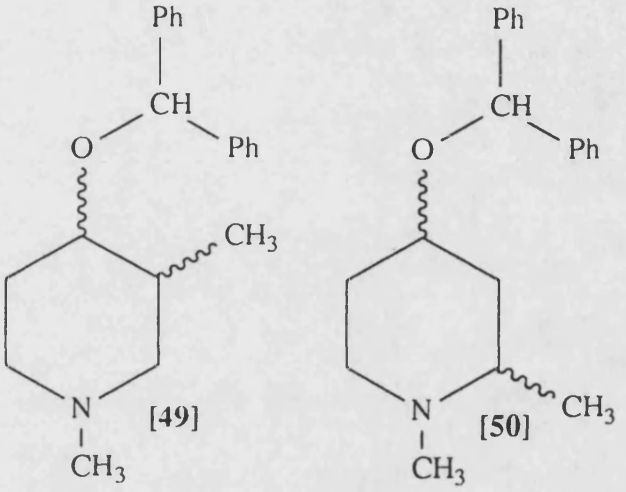
FIGURE 6.



Chapter **3**, deals with the synthesis and conformational analysis of histryl and some of

its diastereomers (Figure 7, below).

FIGURE 7.



CHAPTER 2.

THE PHENINDAMINE WORK.

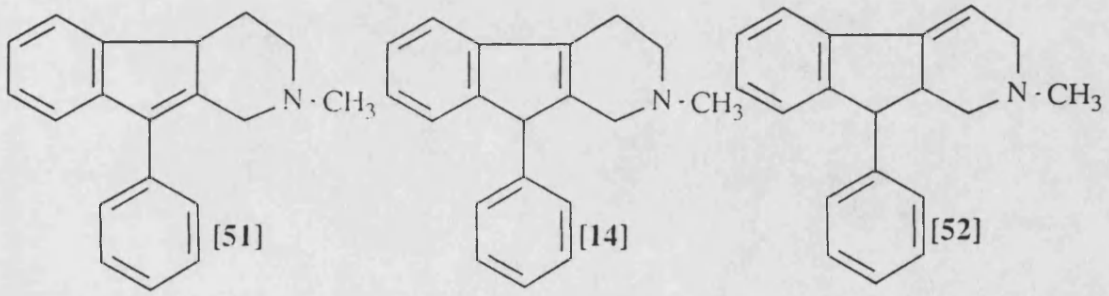
2.1 INTRODUCTION.

This chapter deals with the synthesis and stereochemical evaluations of the precursors and corresponding phenindamine analogues as potential H_1- and/or H_2-histamine receptor antagonists. An investigation into the chiral separation of the phenindamine analogues synthesised was also undertaken.

In 1950, Plati and Wenner[157,158] synthesised a structurally unrelated antihistaminic compound. This compound, more commonly known as phenindamine tartrate **[14]** (Thephorin, 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene tartrate, 2-methyl-2,3,4,9-tetrahydro-9- phenyl-1*H*-indeno[2,1-c]pyridine tartrate), was a rigid compound although still contained the CH_2CH_2N substituent thought to be required for antihistaminic activity.

The synthetic pathway by which phenindamine was obtained is outlined in Scheme **1**. Plati and Wenner[157] predicted that phenindamine can exist as two out of the possible three structural isomers with respect to the indene alkenic double bond (Figure **9**), based on ultra violet studies of the hydrobromide salt of **[51]** and the tartrate salt of **[14]**. Structure **[52]** was never isolated.

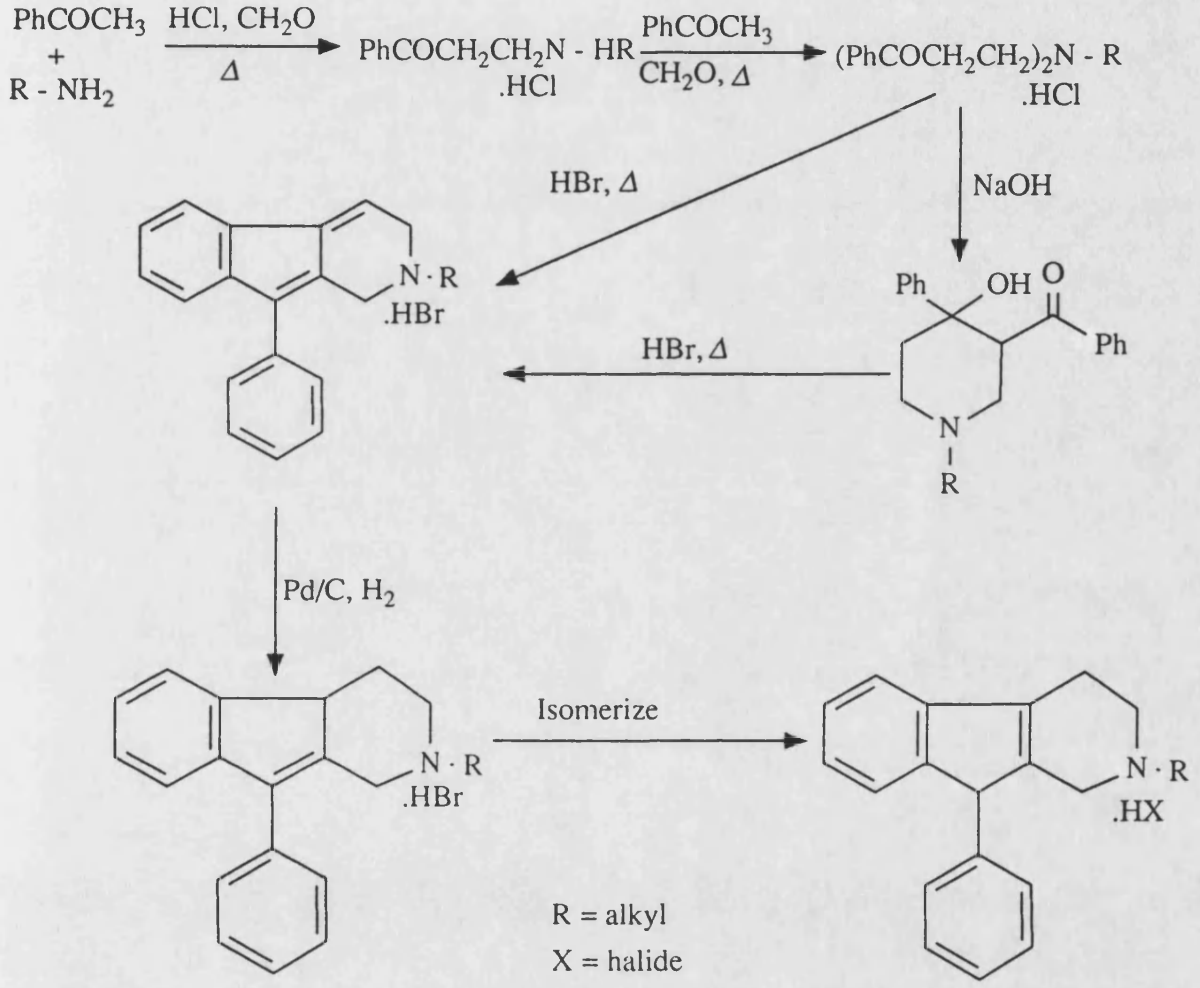
FIGURE 9.



[51] [14] [52]

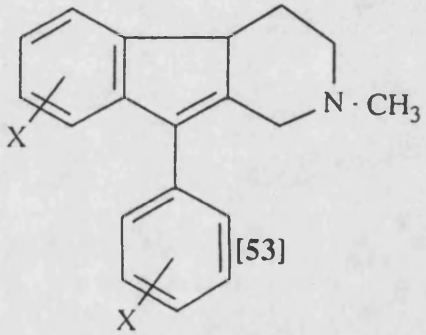
In a short communication, Branch *et al.*,[159] provided ^1H NMR and ^{13}C NMR evidence to show that Plati and Wenner were right to predict the structure of phenindamine

SCHEME 1.


PhCOCH3
+
R - NH2
HCl, CH2O
Δ
PhCOCH2CH2N - HR
.HCl
PhCOCH3
CH2O, Δ
(PhCOCH2CH2)2N - R
.HCl
HBr, Δ
NaOH
N · R
.HBr
Ph
OH
O
Ph
HBr, Δ
N
R
Pd/C, H2
Isomerize
N · R
.HBr
N · R
.HX
R = alkyl
X = halide

tartrate [**14**] and phenindamine hydrobromide [**51**]. The same authors also isolated phenindamine as its free base and showed, using ^{13}C NMR that it contained a mixture of structural isomers [**14**] and [**51**].

In 1992, Casy and colleagues[160] published results of some of the aryl-substituted analogues of phenindamine of the type [**53**] based on the synthetic pathway outlined in Scheme **1**. The ^{13}C NMR and ^{1}H NMR data of the salts of these analogues showed that the indene alkenic double bond was situated in the 9,9a position. No salts of these analogues were isolated in which the position of the double bond was situated at the 4a,9a position.

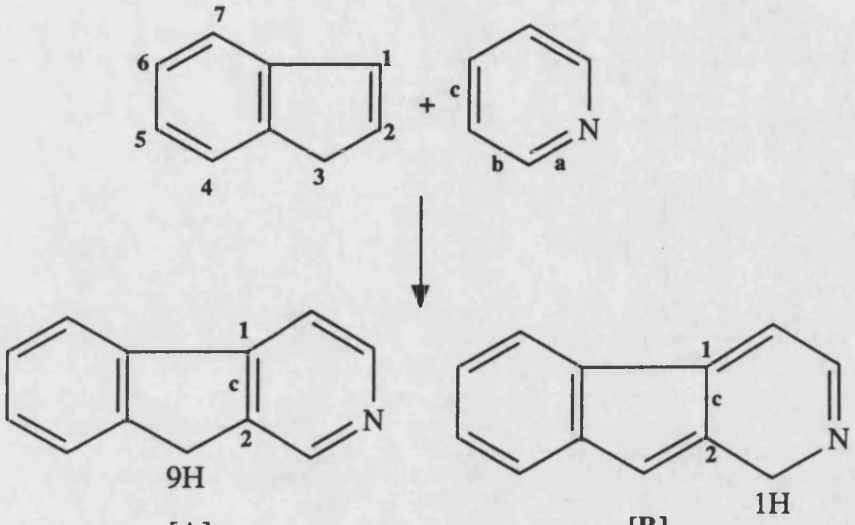


[53]

2.1.1 Nomenclature.

The nomenclature of the phenindamine molecule is based on the fusion of an indene fragment to a pyridine ring. Indene and pyridine rings can be fused in several ways leading to different structural isomers, all of which may be classified as indenopyridines.

FIGURE 10.



Two structural isomers may be considered in naming phenindamine and its analogues. The official IUPAC name of **[A]** is 9*H*-indeno[2,1-c]pyridine and structure **[B]** is described as the 1*H*-indeno[2,1-c]pyridine[161]. The letters and numbers within the brackets refer to the point of fusion of the indene and the pyridine as shown in Figure **10** above. Thus, the two structural isomers of phenindamine are officially named (under the IUPAC nomenclature rules) as

2-methyl-9-phenyl-2,3,4,9-tetrahydro-1*H*-indeno[2,1-c] pyridine for structure **[14]** and

2-methyl-9-phenyl-2,3,4,4a- tetrahydro-1*H*-indeno[2,1-c]pyridine for structure **[51]**.

2.12 Pharmacology.

Lehmann demonstrated that phenindamine tartrate was a potent antagonist of histamine at H_1-histamine receptors. Phenindamine tartrate **[14]** was found to be a considerably more potent antagonist of histamine than phenindamine hydrobromide **[51]** on isolated guinea pig's ileum, in the spray test, against intracardial histamine and against anaphylactic shock[162]. Recently, Casy *et al.*,[160] demonstrated that the 4a,9a isomer of phenindamine was more active than the 9,9a isomer in *in vivo* studies. Phenindamine

tartrate **[14]** was shown to be a very potent antagonist of histamine induced hypotension in anaesthetised cats. Phenindamine tartrate **[14]** effectively protected unanaesthetised rabbits against lethal doses of histamine[163].

Phenindamine tartrate **[14]** was shown to reduce histamine induced gastric acid secretion in unanaesthetised dogs by a factor of about 30%. Phenindamine tartrate **[14]** was also shown to be a effective as an anti-ulcer drug in rats[163]. These tests indicate that phenindamine tartrate **[14]** is a moderate H_2-histamine antagonist.

The aryl-substituted 9,9a-ene analogues of phenindamine showed little or no antihistaminic activity when compared to phenindamine tartrate **[14]** in compound 48/80 lethality tests[160].

2.13 Toxicology.

Acute toxicity of Thephorin **[14]** was determined in mice , rats, and guinea pigs. Thephorin was about as toxic as benadryl. Fatal doses of Thephorin caused severe convulsions followed by paralysis and cessation of respiration.

Chronic toxicity studies on oral administration were carried out in rats and dogs up to eight months without encountering severe symptoms. Blood analyses were normal and histological tissue examination did not show any pathological changes.

2.14 Clinical Uses.

Thephorin **[14]** has the properties and uses of the antihistaminic drugs considered to act primarily on H_1-histamine receptors. It is less potent than promethazine hydrochloride,

but it does not produce drowsiness as encountered by many other antihistamines. It also has a moderate anticholinergic action.

Thephorin **[14]** is given orally in doses of 25-50mg once or twice a day, indicating that it is a long-acting drug. It may be applied locally for the relief of pruritic allergic dermatoses and insect bites/stings.

Thephorin **[14]** is used therapeutically for pallitative treatment in allergic reactions. It may be administered to seasonal hay fever sufferers. It has also been used for the prevention and treatment of motion sickness.

2.15 Aims and Objectives.

So far, it has been demonstrated that the position of the indene double bond of the phenindamine structure is a major determinant of antihistaminic activity[160,162], and as yet, no analogues of phenindamine salts have been isolated where the double bond is situated in the 4a,9a position. As a consequence of this, a major aim of this work is to synthesise analogues of phenindamine in which the indene double bond is situated in the more pharmacologically active 4a,9a position. The use of ^{1}H NMR and ^{13}C NMR techniques is of valuable use for determining the position of the alkenic double bond of the phenindamine analogues synthesised.

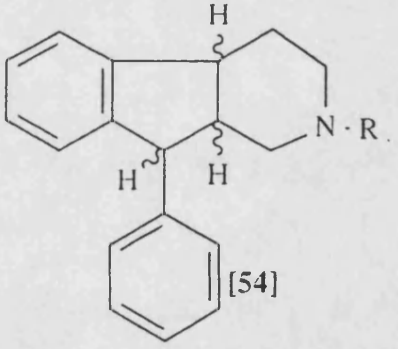
Before the discovery of the H_2-receptor[14], Lehmann and Stefko[163] realised that phenindamine tartrate , although a potent antagonist at the H_1-histamine receptor, was also a moderate antagonist at the H_2-histamine receptor. With the evidence that very potent H_2-histamine receptor antagonists such as cimetidine and ranitidine may cause stomach cancer in the long term, due to their ability to block completely the acid

secretion, it was anticipated that the synthesis of phenindamine analogues in which the N-2 position or at the aryl rings may produce a shift from H_1- to H_2-antihistamine activity.

Due to the rigidity of the phenindamine framework, analogues synthesised may be of use as probes for histamine receptor recognition.

Due to the increasing understanding of the importance of chirality in biological activity, this work also aims to separate the racemic mixture of the marketed phenindamine tartrate **[14]** and some of its analogues using chromatographic techniques, for pharmacological evaluations (See section **2.44**).

Some studies of the fully reduced phenindamine analogues of structure type **[54]** will be described with a view to obtain evidence of relative stereochemical structure-activity relationships.



[54]

Syntheses of phenindamine analogues where the fused rings are "broken" to form non-rigid compounds were also investigated. The emphasis of such a study was to try and retain the double bond in the right position for antihistaminic activity.

The detailed aims and objectives of the first part of this work thus entail:-

1) Synthesis and stereochemical studies of piperidine intermediates.

2) Synthesis and stereochemical studies of the diene compounds derived from the piperidines.

3) Synthesis and stereochemical studies of N-2 and aryl-substituted phenindamine analogues.

4) Synthesis and stereochemical studies of fully-reduced phenindamine analogues.

5) Synthesis of N-dealkylated products of phenindamine and precursor piperidines and dienes, and subsequent realkylation with a variety of substituents.

6) Synthesis and stereochemistry of other analogues of phenindamine.

7) Pharmacological evaluation of the phenindamine analogues and some of their precursors.

One pathway by which phenindamine analogues may be synthesised is by varying the substituent on the N-2 position (Scheme 1). This route, considered to be the Mannich Route, was to some extent researched by Plati and Wenner[165], however, apart from the microanalytical data, the compounds synthesised were not characterized fully, and only phenindamine was synthesised as the pharmacologically active compound.

2.2 THE MANNICH REACTION.

The synthesis of precursors to phenindamine and its analogues involves the application of the Mannich reaction. The first observation of the Mannich reaction was made by

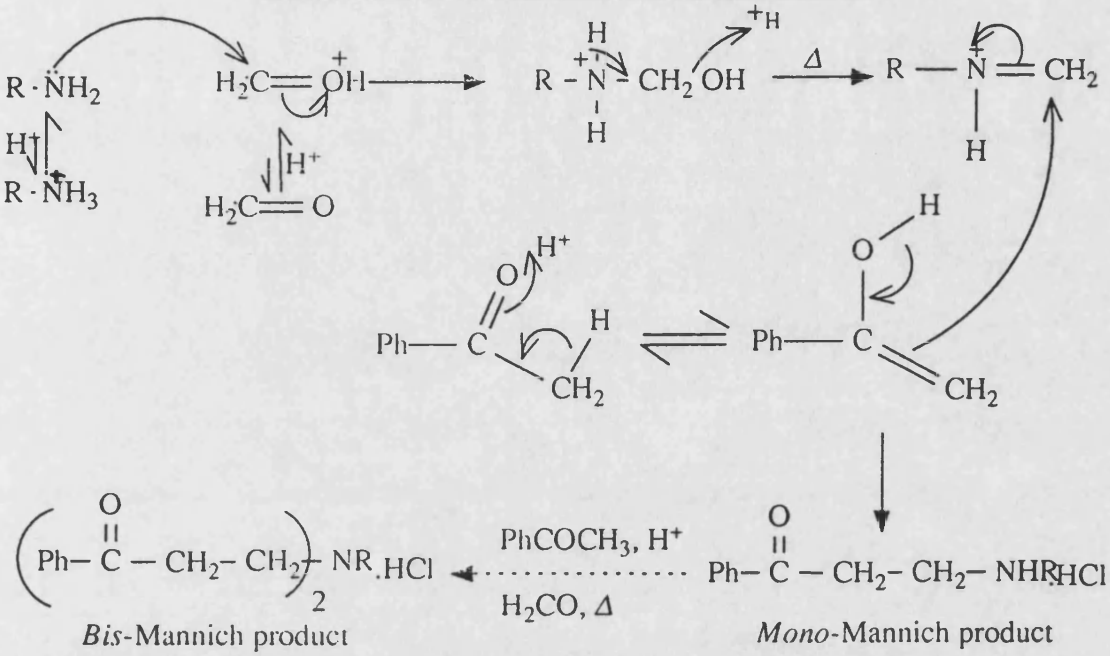
$$3\ PhCOCH_3 + 3\ HCOH + NH_4Cl \longrightarrow (PhCOCH_2CH_2)_3N\ .HCl + 3\ H_2O$$

[55]

For the purpose of the present work, the Mannich reaction involved the condensation of formaldehyde and acetophenone with a primary amine. The reaction was catalysed by aqueous acid.

The present view of the reaction mechanism (Scheme 2) involves the nucleophilic attack by the lone pair electrons of nitrogen (of the primary amine) on the carbonyl carbon atom of the formaldehyde. This is followed by the elimination of water to yield a resonance-stabilized carbocation. Attack by the enol form of acetophenone on the carbon atom of the carbanion gives the *mono*-Mannich product. (Repetition of this process leads to the formation of the *bis*-Mannich product as the hydrochloride salt). The carbonyl addition reaction is powerfully catalysed by the aqueous acid, since protonation of the carbonyl oxygen renders the carbonyl carbon considerably more electrophilic which in turn makes it more readily attacked by a nucleophile.

SCHEME 2: THE MANNICH REACTION.



R	
[56]	CH_2Ph
[57]	$C(CH_3)_3$
[58]	Cyclohexyl

When the Mannich reaction was first carried out using two moles of acetophenone, one mole of the amine hydrochloride, excess formaldehyde, in the presence of 10% w/v of hydrochloric acid for a 0.75 h reflux, the *mono*-Mannich base hydrochloride was isolated in compounds **[56]**, **[57]** and **[58]**. Under similar conditions, but with 30% w/v dilute acid used, and a two hour reflux, ^1H NMR, ^{13}C NMR and infra red data showed that the piperidine hydrochloride was formed in compounds **[59]**-**[67]** and **[69]** (See section **2.22**). This was unexpected as it was thought that the *bis*-Mannich product would be formed[168]. The next section involves the synthetic aspects in forming the piperidines and their stereochemical evaluations.

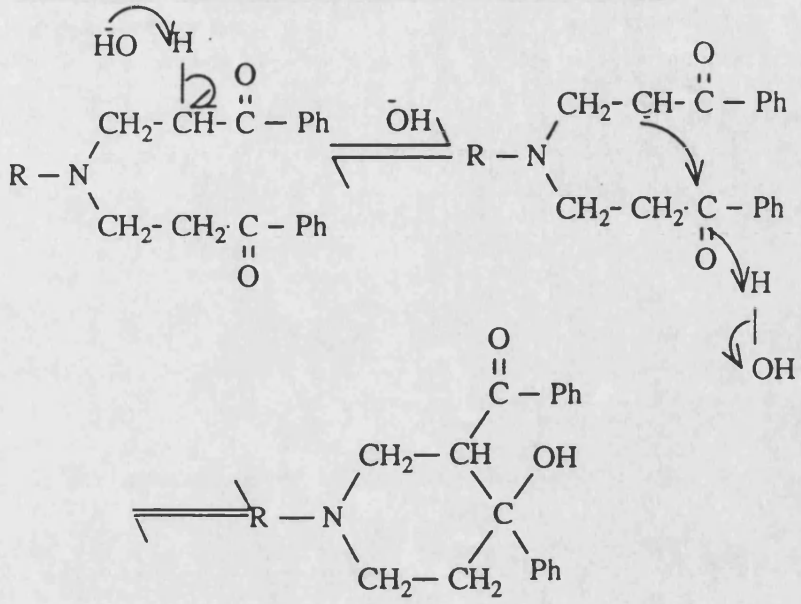
2.21 The Piperidines.

Plati and Wenner[165,167] synthesized a series of the 1-alkyl-3-benzoyl-4-hydroxy-4-phenylpiperidines by the addition of base to the *bis*-Mannich products. As discussed earlier, the piperidines were obtained from the Mannich reaction. This result may be explained *via* aldol condensation mechanisms, which are discussed next.

Under the influence of dilute base or dilute acid, two molecules of an aldehyde or ketone may combine to form a β-hydroxyaldehyde or β-hydroxyketone. This reaction is called the aldol condensation. If the aldehyde or ketone does not have an α-hydrogen, the aldol condensation cannot take place.

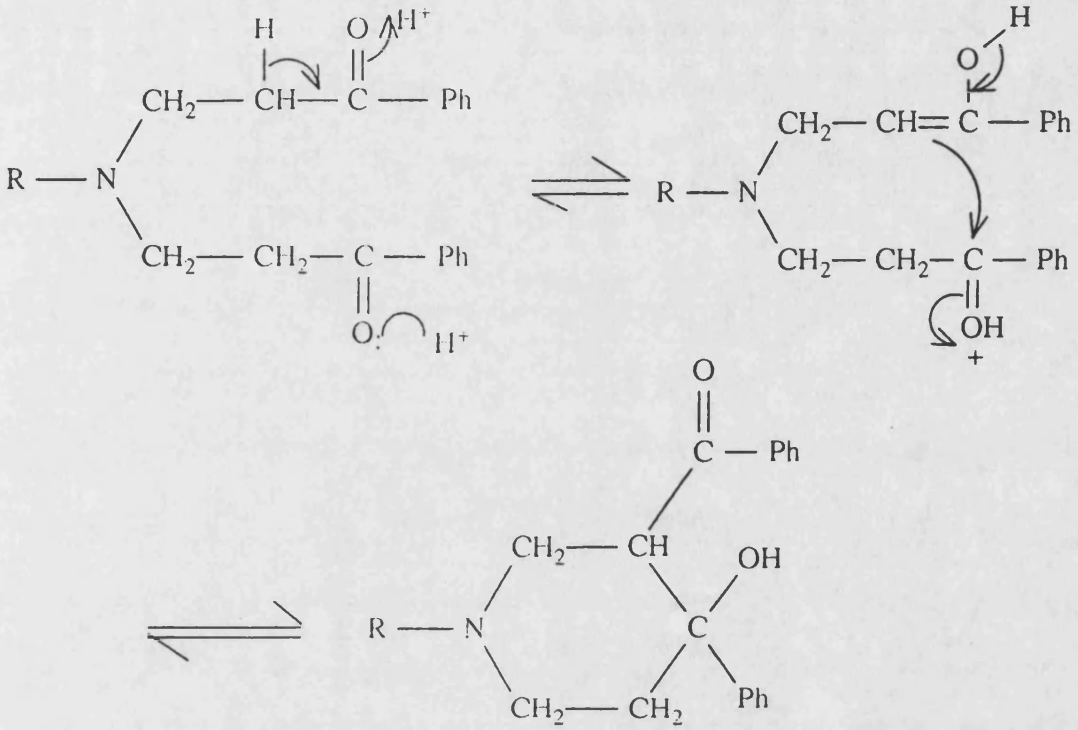
Plati and Wenner[165,167] synthesised the piperidines from the *bis*-Mannich product. This type of reaction undergoes *via* a base-catalysed aldol condensation. As depicted in Scheme 3, the base catalysed intramolecular aldol condensation may be achieved by the addition of a solution of sodium hydroxide to a suspension of the *bis*-Mannich product. The mechanism of this type of reaction depends upon the base abstracting the acidic α-hydrogen of the ketone, which in turn attacks the electropositive carbon of the other carbonyl group forming the cyclized tertiary alcohol.

SCHEME 3: Base-Catalysed Aldol Condensation.



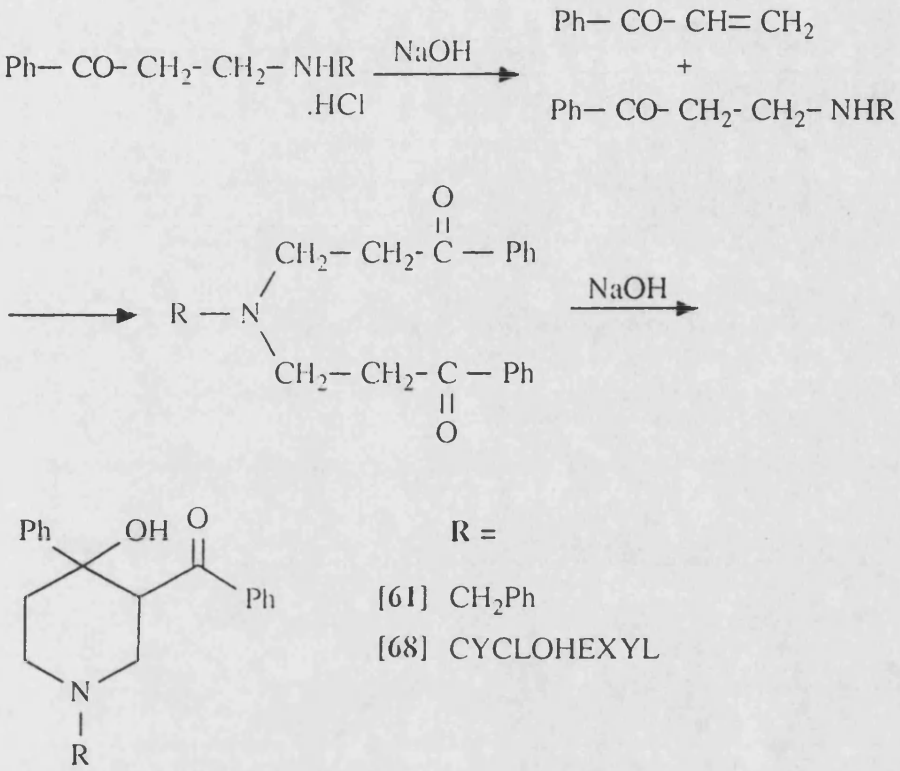
As depicted in Scheme 4, the acid promotes the formation of an ambient concentration of the enol form of the ketone, and this undergoes attack by the protonated form of the second molecule of the carbonyl compound, a carbocation. The fact that the "one pot" Mannich reaction gave the piperidine hydrochloride was a result of the formation of the *bis*-Mannich product (not isolated) followed by an acid catalysed aldol condensation.

SCHEME 4: Acid-Catalysed Aldol condensation.



For this work, the addition of aqueous base to the *mono*-Mannich products gave the corresponding piperidines [61] and [68] (Scheme 5). The route by which this reaction proceeds differs from the one explained above.

Scheme 5.



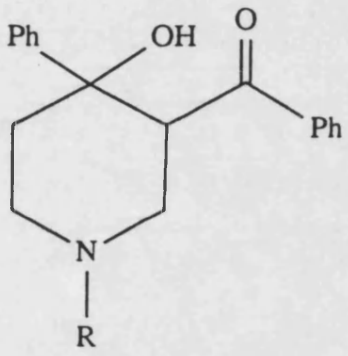
When the *mono*-Mannich base hydrochloride is added to a solutuion of sodium hydroxide (30% w/v) with stirring, the molecule can form two intermediates; the mono-Mannich base, and the vinylic ketone (*via* a Hoffmann degredation). These two compounds then combine to form the *bis*-Mannich base. The *bis*-Mannich base readily cyclizes to the piperidine *via* the base catalysed intramolecular aldol condensation (see earlier).

The next section of the work deals with the stereochemical studies using ^{1}H NMR and ^{13}C NMR, tools which were unavailable for the original authors[145,167] of the 2-alkyl-3-benzoyl-4-hydroxy-4- phenylpiperidines.

2.22 Structural Evidence of the Piperidines.

Little evidence apart from combustion analysis was published in the original work[165,167]. It was deemed important to investigate the structural evidence of the piperidines using NMR techniques. The piperidines are chemically versatile intermediates[168] and have been reported to exert biological activity[169]. The analogues synthesised in this work are presented in Figure **11** below;

FIGURE 11.



COMPD. No.	R
[59]	CH_3
[60]	CH_2CH_3
[61]	CH_2Ph
[62]	CH_2CH_2Ph
[63]	Cyclopropyl
[64]	$CH(CH_3)_2$
[65]	Butyl
[66]	$CH(CH_2CH_3)_2$
[67]	Hexyl
[68]	Cyclohexyl
[69]	Cyclohexylmethyl

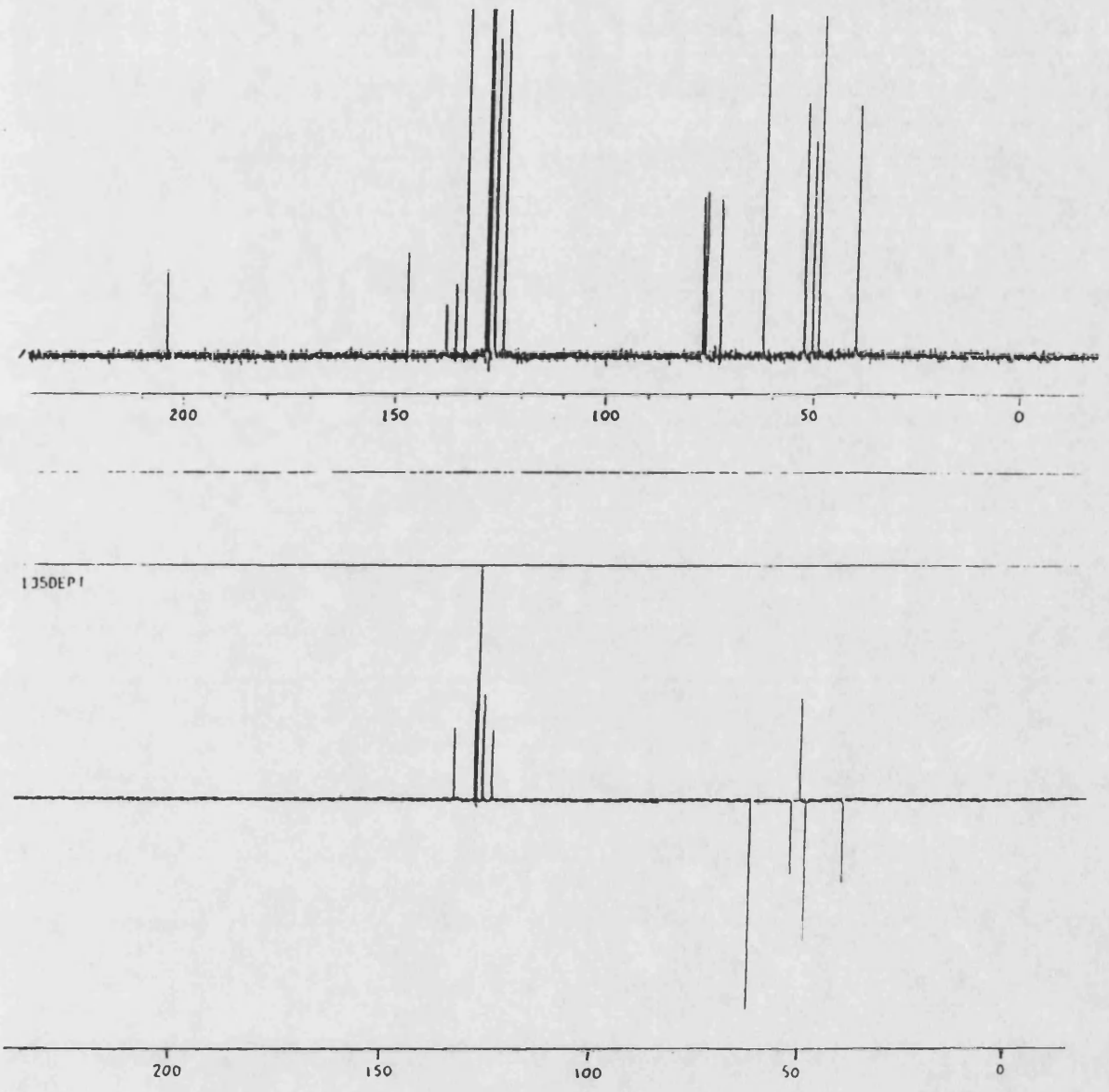
The infra red spectra of the piperidines synthesised showed the presence of the C=O stretch at around 1690 cm^{-1} and a small broad peak at 3400 cm^{-1} corresponding a to tertiary hydroxy substituent, which was absent in the mono-Mannich products.

2.22.1 ^{13}C NMR Analysis of the Piperidines.

The ^{13}C NMR spectrum (Spectrum **1**) of 3-benzoyl-1-benzyl-4-hydroxy-4-phenylpiperidine **[61]** is used as an example to illustrate the structural

SPECTRUM 1: 67.8 MHz ^{13}C NMR ($CDCl_3$) OF

3-BENZOYL-1-BENZYL-4-HYDROXY-4-PHENYLPIPERIDINE HCl [61]



evidence of the piperidines.

Difficulty was experienced in assigning the aromatic carbons, as some of the signals were very close to each other. Overlapping of two of the signals was experienced. Out of the nine possible aromatic CH signals (equivalent CH signals were expected due to symmetry of the compound), only eight were observed in the spectrum.

The aliphatic carbon atoms of the methine, methylene and methyl were identified using DEPT experiments. Assignments of the methylene carbons was based on their chemical shift. The highest field CH_2 at δ35.42 was assigned to the C-5, since nitrogen has a strong deshielding influence causing low field shift of C-2, C-6 and the N-benzyl CH_2. The lowest field methylene at δ59.39 was assigned to the N-benzyl CH_2 which is doubly deshielded by the nitrogen and the phenyl group. The C-2 carbon suffers β-deshielding effect from the 3-benzoyl group thus giving it a lower field chemical shift (δ49.75) than the C-6 carbon. The signal at δ46.41 was thus assigned to the C-6 carbon. The C-4 quaternal signal resonated at δ70.77, while the C-3 methine carbon appeared at δ45.80. The carbonyl signal (δ199.90) was within its expected range (δ162-δ214)[170].

Only one signal for each carbon was present in the ^{13}C NMR of 3-benzoyl-1-benzyl-4-hydroxy-4-phenylpiperidine **[61]**, implying that only one diastereomer, out of the possible two was formed (See section **2.22.3**). The ^{13}C NMR analyses of the remaining N-substituted piperidines (figure **11**) were assigned in a similar fashion to the example given above. Similarly, all the ^{13}C NMR spectra of the analogues showed only one signal for each carbon atom present. Table **4** (in Experimental) shows the ^{13}C NMR data for the piperidine analogues (See section **5.22**).

2.22.2 ^{1}H NMR Analysis of the Piperidines.

To illustrate the structural analysis of the piperidines synthesised, a 400 MHz ^{1}H NMR (Spectrum 2) 3-benzoyl-4-hydroxy-1-methyl-4-phenylpiperidine **[59]** is used as an example.

The aromatic protons resonated in the region of δ7.90-7.10, in which two protons were deshielded and were assigned to the two ortho hydrogens of the ring of the benzoyl substituent. The remaining eight protons were centered around δ7.5(3H), δ7.4(2H), δ7.2(2H) and δ7.1(1H).

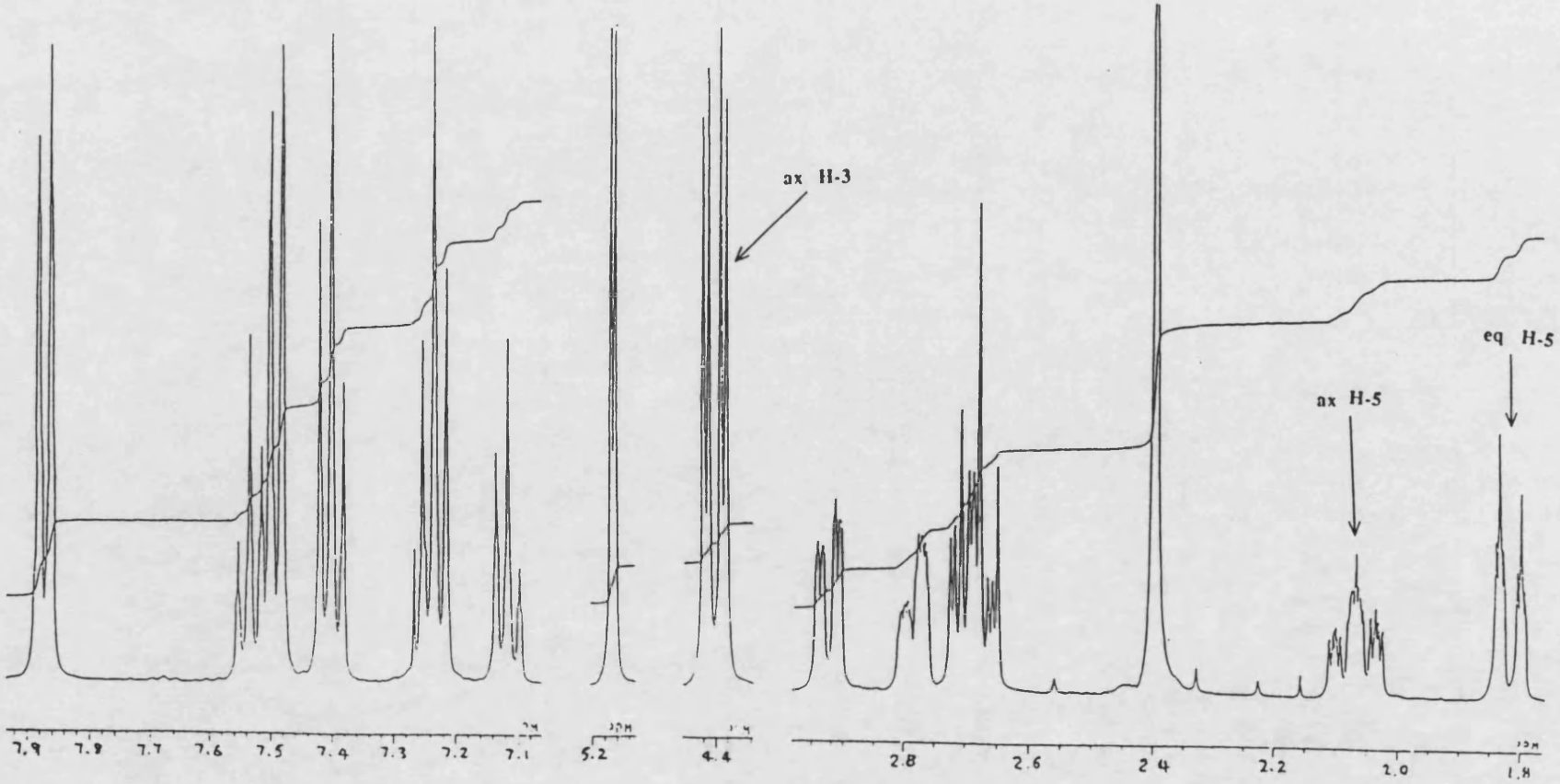
An unresolved doublet of doublets at δ2.93 was assigned to the equatorial H-2 proton. This proton was mainly assigned as such because it is in the equatorial plane and is β-deshielded by the benzoyl group. The equatorial H-6 proton was a multiplet at δ2.77. A multiplet at δ2.72-2.65 which integrated to two protons was assigned to the axial H-2 and H-6 hydrogens. The N-methyl singlet resonated at δ2.39. The position of this signal is comparable to the literature value (δ2.3)[171].

The two most shielded signals were assigned to the H-5 protons. The multiplet centred around δ2.07 was assigned to the axial H-5 proton, whilst the doublet of triplets at δ1.84 was given to the equatorial H-5 proton. The multiplicity of the former signal is due to one di-axial coupling with the axial H-6 proton, one axial-equatorial coupling with the equatorial H-6 and one geminal coupling with H-5 protons.

The doublet of doublets at δ4.40 was assigned to the H-3 proton, as it is the most deshielded proton of the piperidine ring due to the presence of the electron withdrawing alpha carbonyl. The multiplicity of this signal can be justified by the coupling of one

SPECTRUM 2: 400 MHz ^{1}H NMR ($CDCl_3$) OF

3-BENZOYL-4-HYDROXY-1-METHYL-4-PHENYLPIPERIDINE [59].



axial-axial (11.28 Hz) and one axial-equatorial (3.22 Hz) interaction with the H-2 protons. On the basis of these coupling constants the H-3 proton must be situated in the axial position. Consequently, the benzoyl group must lie in the more spacious equatorial plane. Lastly, the hydroxy proton (δ5.16) showed a doublet of magnitude 2.56 Hz. This signal disappeared with the deuterium oxide shake (See section **2.22.3**).

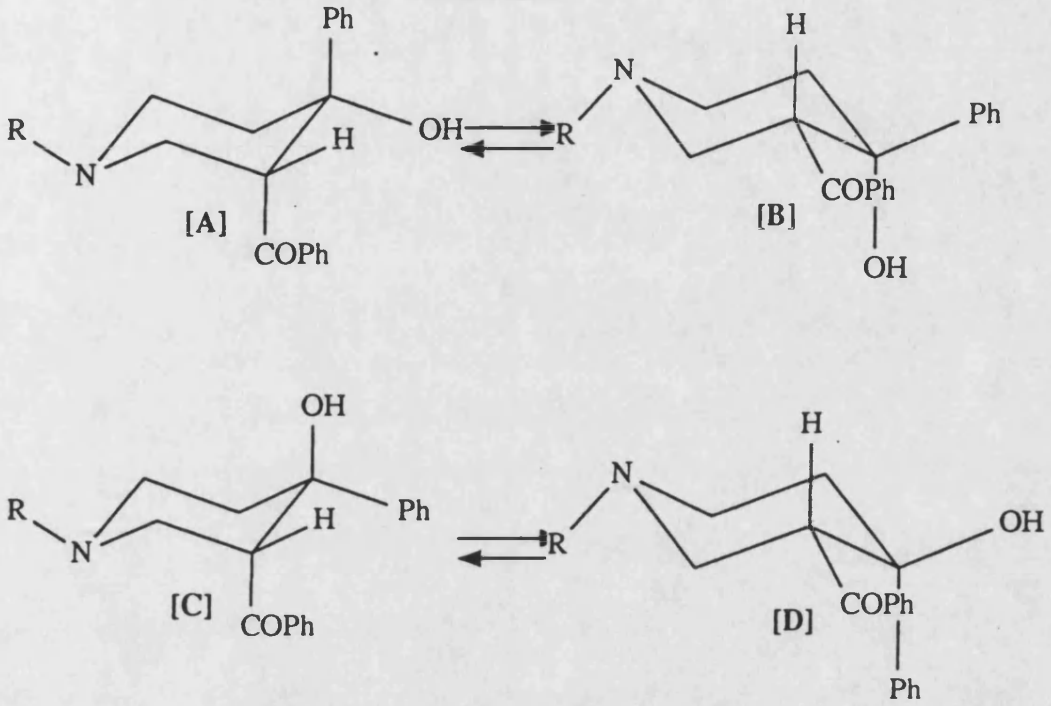
The piperidines synthesised have asymmetric centres in the ring, namely at the 3- and 4-positions. This can gives rise to four possible conformers (Figure **12**). The ^{1}H and ^{13}C NMR data for all the piperidines synthesised, confirmed that only one diastereomer was produced for each analogue. In all of the piperidines analogues, all of the H-3 proton signals of the NMR were doublet of doublets with one large coupling (10.99-12.09 Hz) and one small coupling (4.43-4.03 Hz), indicating that it lies in the axial plane.

Out of the eleven piperidine synthesised, seven showed the hydroxy proton as a doublet (Table **5** in Experimental), the remaining four gave singlets (Table **6** in Experimental). The doublet from the hydroxy signal, and the axial position of the H-3 proton play a significant part in determining the conformation of the piperidines, which is discussed next.

2.22.3 Conformation of the Piperidines.

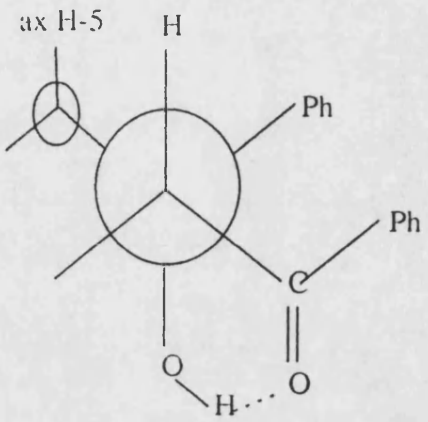
This section deals with the conformational analyses of the diastereomeric piperidines. Out of the possible four conformers illustrated in Figure **12**, it is clear that conformer [C] will not exhibit intramolecular covalent hydrogen bonding between the 3-benzoyl and 4-hydroxy groups as both groups are axial to one another and hence too far apart for any interaction.

Figure 12.



Conformers **[A]** and **[C]** show that the 3-methine proton of the ring is situated in the equatorial plane, and as stated earlier (See Section **2.22.2**), the piperidines formed had the 3-methine proton in the axial position. On this assumption, it would seem unlikely that such a structure would be formed from the aldol condensation, and thus ruled out. Out of the remaining two possible stereomers, conformer **[B]** exhibits a W-pathway from the hydroxy proton to the axial H-5 proton (see Newman Diagram, Figure **13**). A W-pathway of this nature only exists if the molecule concerned is of a fixed orientation, as is the case in this example (due to conformational restriction caused by the intramolecular H-bonding of the carbonyl of the 3-benzoyl substituent of the ring to the 4-hydroxy group).

FIGURE 13.



Newman Diagram for Structure [B]

If a W-pathway exists between the 4-hydroxy proton to the axial H-5 proton, a doublet of magnitude 1-3 Hz of the proton NMR signal of the hydroxy proton would be observed. Thus, the seven piperidine analogues that showed such a doublet, must therefore have structure [B]. Structure [D] thus corresponds to the remaining four piperidine analogues as the H-3 proton is axial and no W-pathway exists; the hydroxy does not show up as a doublet. The apperarence of the doublet signal of the 4-hydroxy proton was also reported by Casy and Co-workers[160].

2.22.4 Mass Spectral Analyses of the Piperidines.

Analyses of the mass spectra of the piperidines showed the molecular ion ($M^{\cdot+}$). Common major signals were detected indicating a similar molecular "backbone" exists. A similar breakdown pattern was also seen (Table 1, Scheme 6).

SCHEME 6.

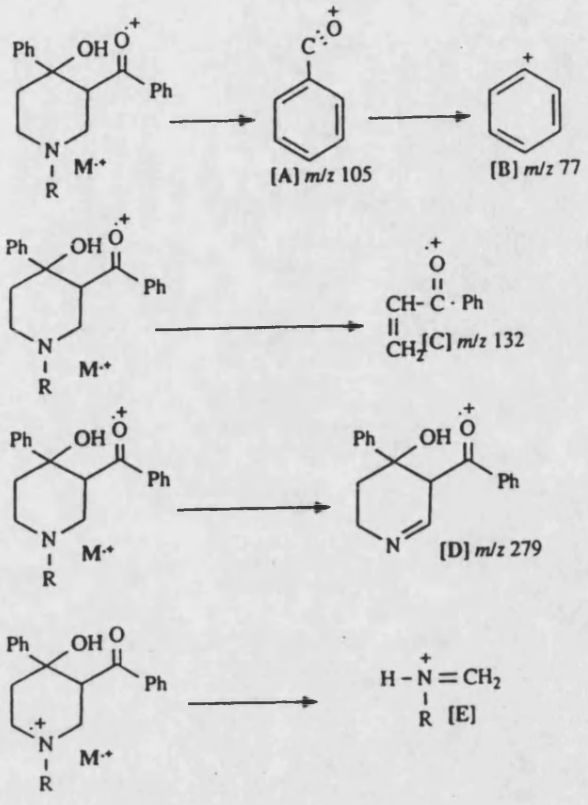


TABLE 1: Percentage Abundance of Fragment Ions of the Piperidine Analogues,

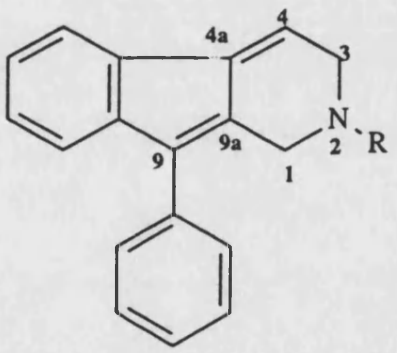
COMP. No.	ION TYPE					
	M^+	A	B	C	D	E
[59]	8	82	57	21	26	-
[60]	57	100	69	25	8	-
[61]	1	100	89	30	26	23
[62]	13	100	69	30	-	43
[63]	7	100	80	19	1	14
[64]	1	47	37	9	1	1
[65]	1	100	81	31	1	15
[67]	1	100	79	36	1	9
[69]	1	81	61	24	1	6

2.3 THE 2,3-DIHYDRO-1*H*-INDENO[2,1-c]PYRIDINES.

2.31 Synthesis of Cyclic Dienes.

The synthesis of the diene compounds 2,3-dihydro-1*H*- indeno[2,1-c]pyridines can be carried out in two ways[171]. Firstly, they can be prepared directly from the *bis*-Mannich hydrochloride using hydrobromic acid (40-48%) or concentrated sulphuric acid at elevated temperatures. Alternatively, they may be synthesised from the corresponding piperidine with the same dehydrating reagents. For this work, all the dienes (Figure 14) were synthesised from the corresponding piperidines. The analogues synthesised are presented below;

FIGURE 14.

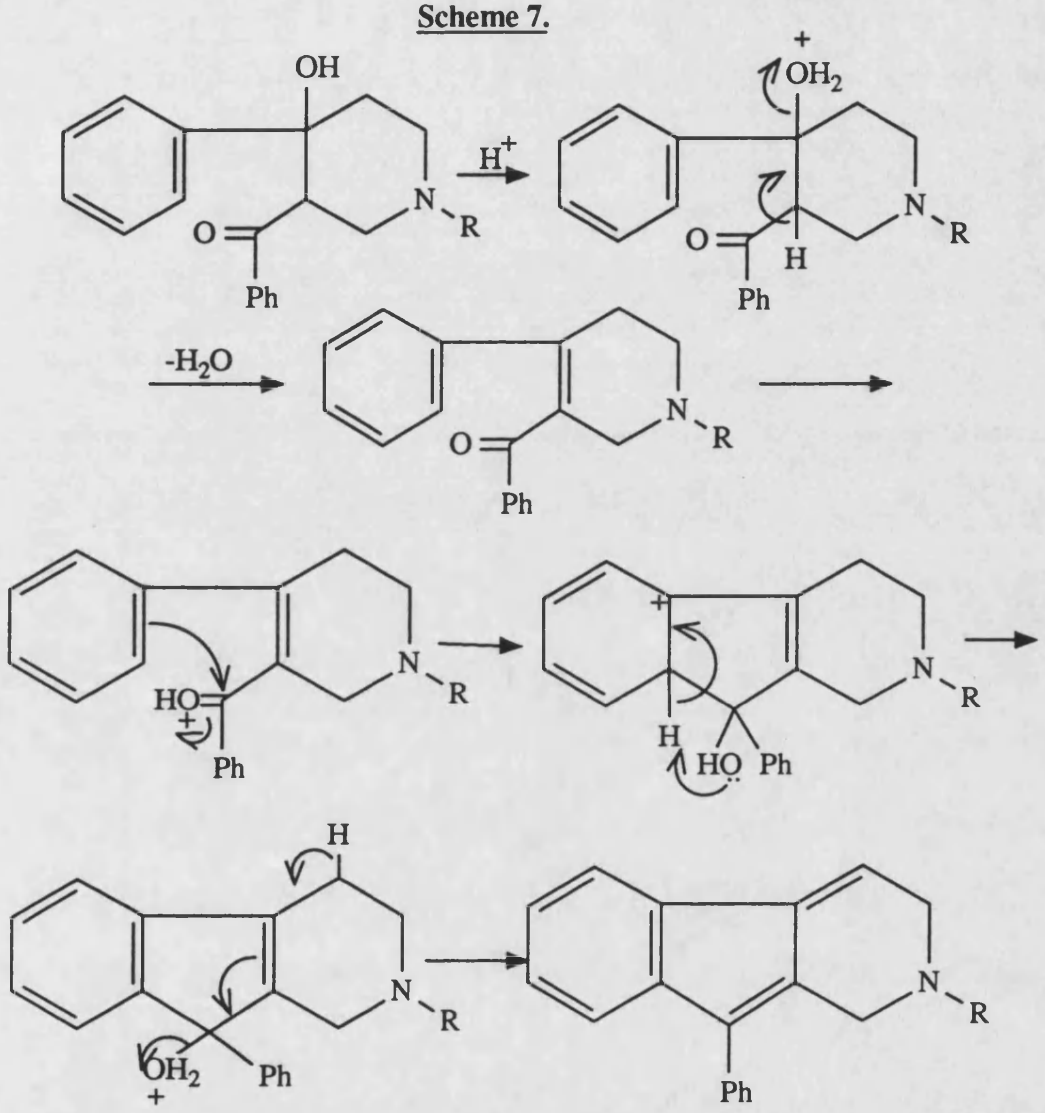


COMPD No.	R
[70]	CH_3
[71]	CH_2CH_3
[72]	CH_2Ph
[73]	CH_2CH_2Ph
[74]	Butyl
[75]	$CH(CH_2CH_3)_2$
[76]	Hexyl
[77]	Cyclohexyl
[78]	Cyclohexylmethyl

The reaction mechanisms involved in the synthesis of the diene compounds from their corresponding piperidines are ring closure and dehydration. As depicted in Scheme 7, the initial process involves protonation of the 4-hydroxyl substituent to form the carbocation with the consequent loss of water. The alkene formed then cyclizes to give the tricyclic ring system *via* a second dehydration process, in which the double bond from the aromatic species attacks the carbonyl carbocation. The aromaticity is then regenerated by the abstraction of the proton of the ring by the negatively charged

carbonyl intermediate. Once the tricyclic compound is formed, the tertiary alcohol is readily dehydrated in the presence of acid to give the diene compound.

Scheme 7.



2.32 Evidence of Structure of the Dienes.

The infra-red spectra of the dienes synthesised showed the absence of the carbonyl stretch (1690 cm^{-1}), and the hydroxyl stretch at around 3400 cm^{-1} present in the precursor piperidines.

2.32.1 ^{1}H NMR Analysis of the Dienes.

For the purpose of discussing the structural evidence of the dienes, the ^{1}H NMR spectrum of 2-ethyl-9-phenyl- 2,3-dihydro-1*H*-indeno[2,1-c]pyridine **[71]** (Spectrum 3)is used as an example.

The aromatic signals were observed as a multiplet centred at δ7.63. The lowest field aliphatic signal (δ6.63) was assigned to the vinylic H-4 proton. This is because it is fully conjugated to the aryl groups giving it a lower field resonance than the other non-aromatic protons. The H-4 proton resonance appeared as a triplet due to the equal coupling of the two H-3 protons. The signal up-field from the H-4 resonance (δ4.45), which integrated to two hydrogens can be assigned to the H-1 protons because it appears as a singlet as vicinal protons are absent. The signal centred around δ4.16, is due to the H-3 protons, which appears as a broad singlet. Ideally, this signal should be a doublet due to the coupling with the vinylic proton.

Since the geminal protons at C-1 (δ4.45) have the same resonance position, their magnetic environment cannot differ. Similarly, geminal protons at C-3 (δ4.16) are equivalent. This situation is probably brought about by a rapid (NMR-fast) interconversion between the two chair conformations of the nitrogen-containing ring (Figure **15**, below).

SPECTRUM 3: 270 MHz ^{1}H NMR ($CDCl_3$) OF

2-ETHYL-9-PHENYL-2,3-DIHYDRO-1*H*-INDENO[2,1-c]PYRIDINE HBr [71].

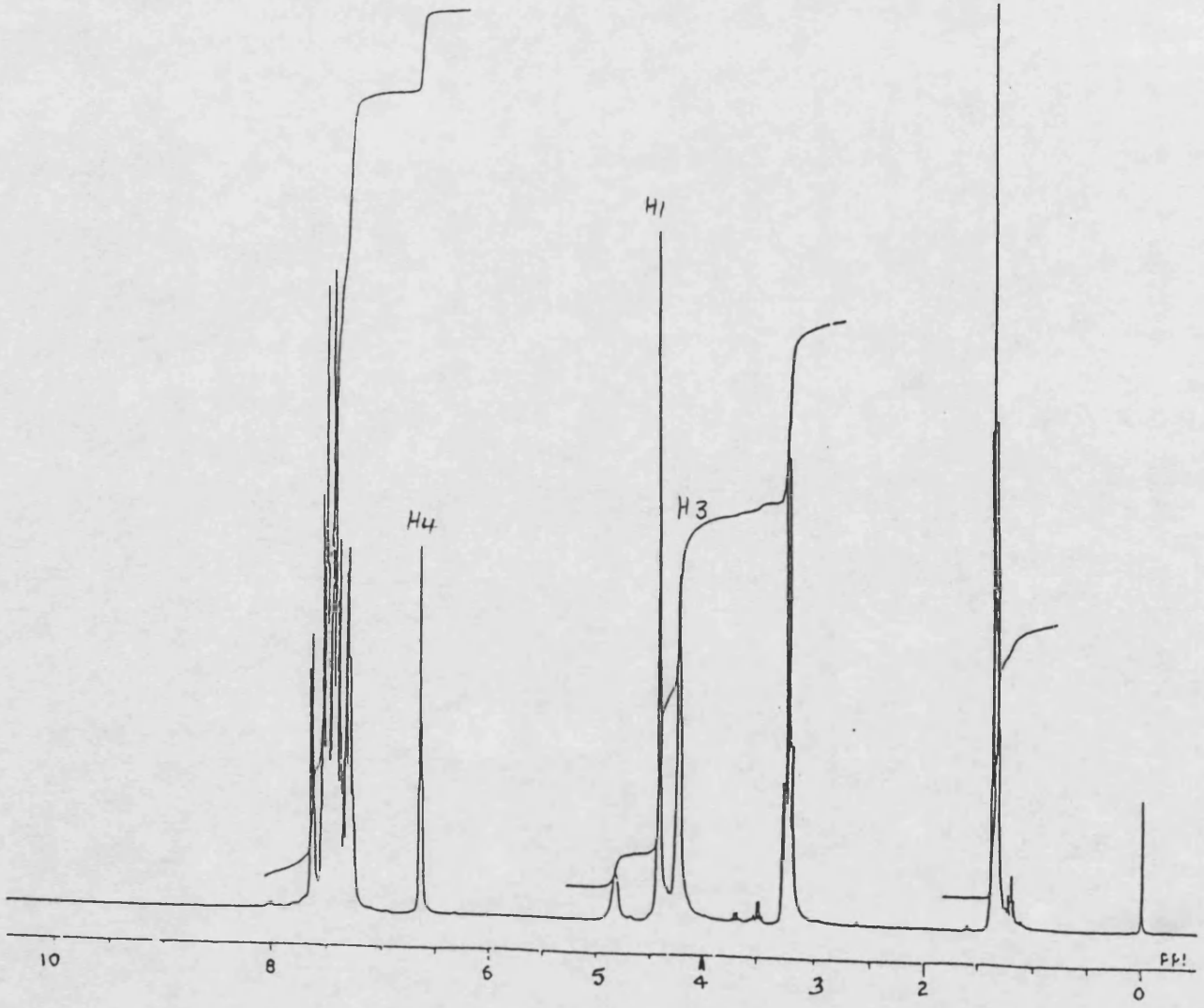
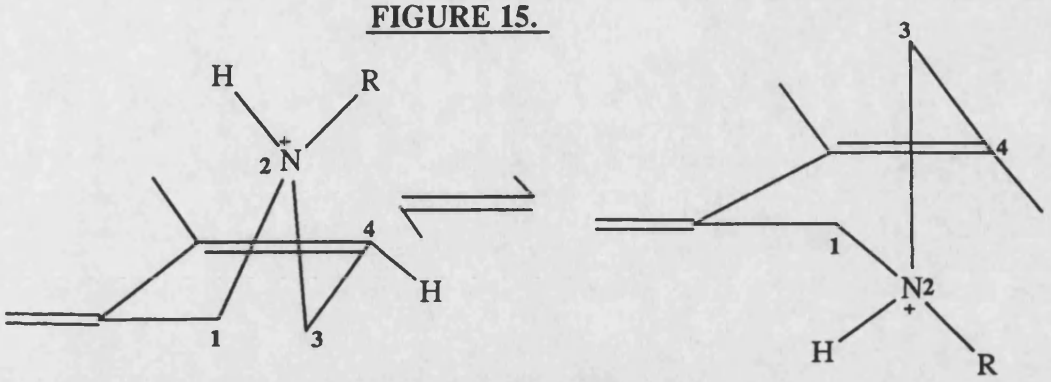


FIGURE 15.



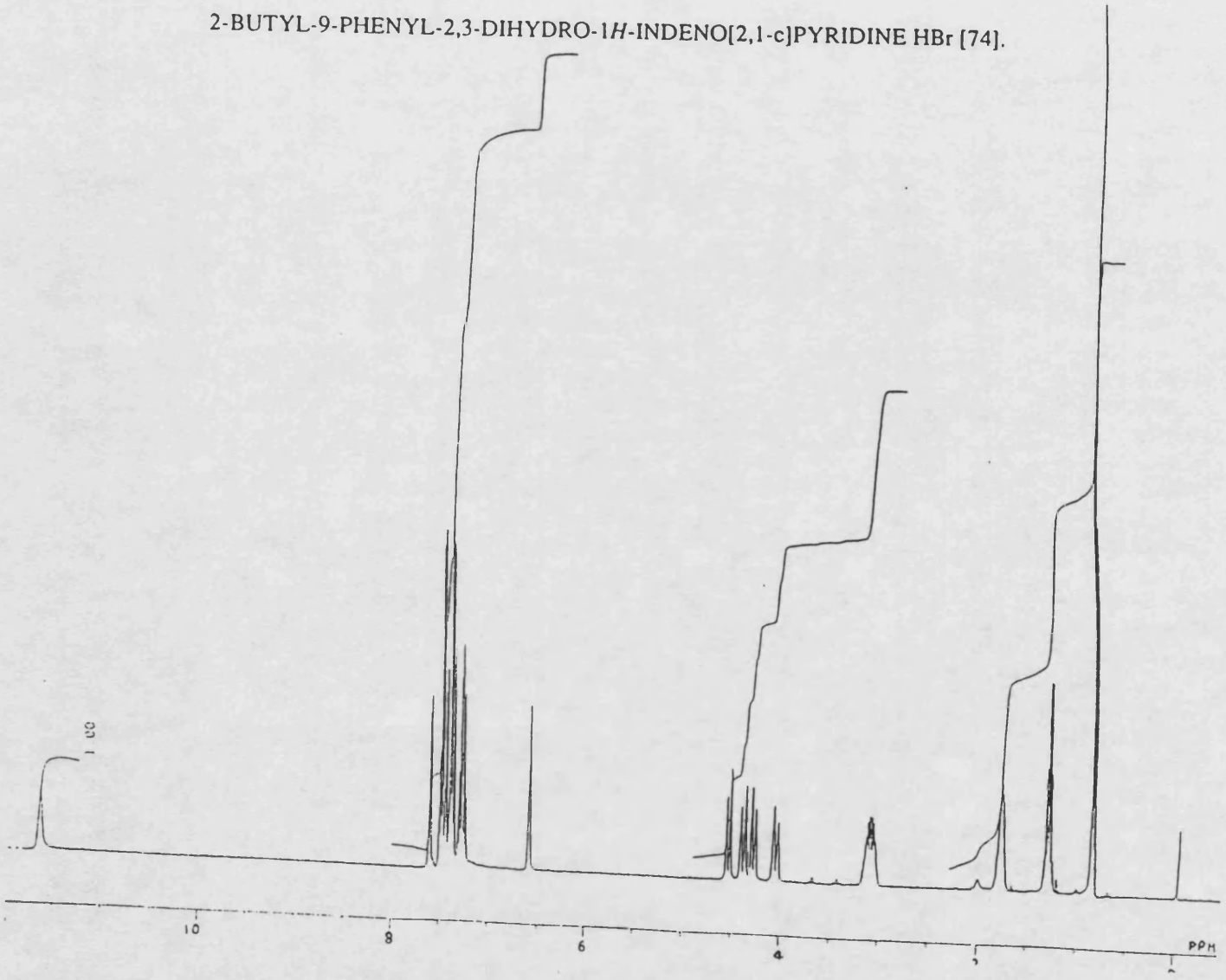
If the conformational interconversion is slow (NMR-slow), then the geminal pairs of protons at C-1 and C-3 become non-equivalent, and their chemical shifts would differ. Such protons may produce multiplet resonance signals.

The ^{1}H NMR spectra of compounds **[72]**(R=CH_2Ph), **[74]**(R=butyl), **[75]**(R=CH{CH_2CH_3}$_2$), **[76]**(R=hexyl), **[77]**(R=cyclohexyl) and **[78]**(R=cyclohexylmethyl) were far more complex than the original one described above. It must be assumed that the complexity of these spectra must be due to the NMR-slow interconversion rate. To illustrate this, the spectrum of 2-butyl-2,3-dihydro-1*H*-indeno[2,1-c] pyridine **[74]** is analysed below (Spectrum **4**).

Firstly, the geminal pair of protons at C-1(ax H-1: 4.30ppm, eq H-1: 4.54ppm) and C-3(ax H-3: 4.06ppm, eq H-3: 4.36ppm) are magnetically non-equivalent. In consequence, each geminal pair gave rise to an NMR signal of an AB type (doublet pair of separation 13-16 Hz., typical of geminal coupling) further complicated by vicinal coupling to $^+$N-H and H-4. Thus the C-1 protons produced a net doublet of doublets, whilst the C-3 pair formed a doublet of triplets because these protons are vicinally coupled to the vinylic H-4 proton as well as the $^+$N-H. Assignments of signals in the region 4-5ppm could be made with confidence on this basis even though the two AB pairs overlapped.

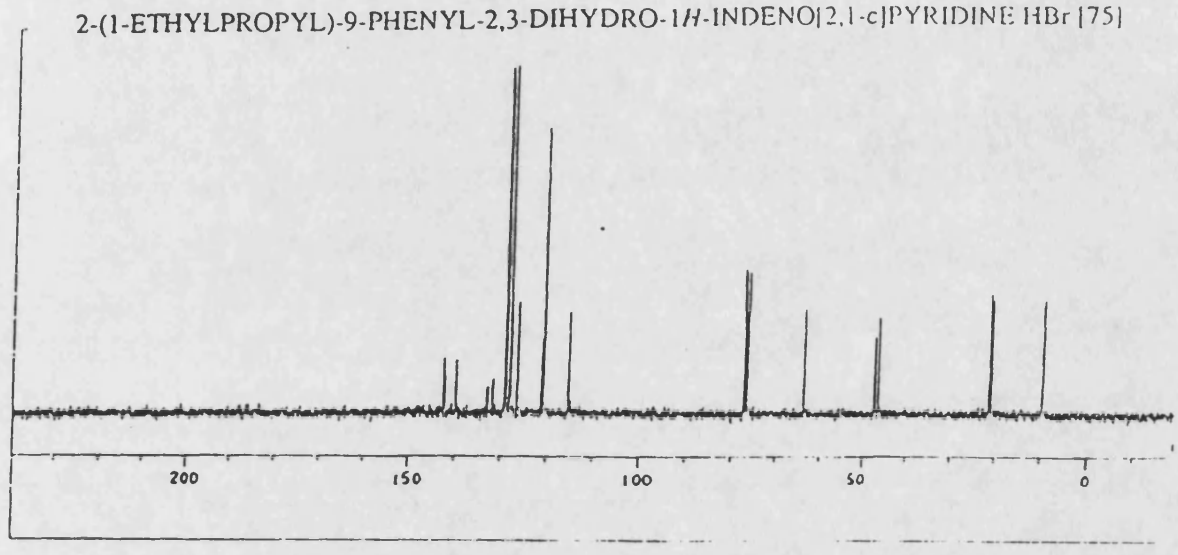
SPECTRUM 4: 270 MHz ^{1}H NMR ($CDCl_3$) OF

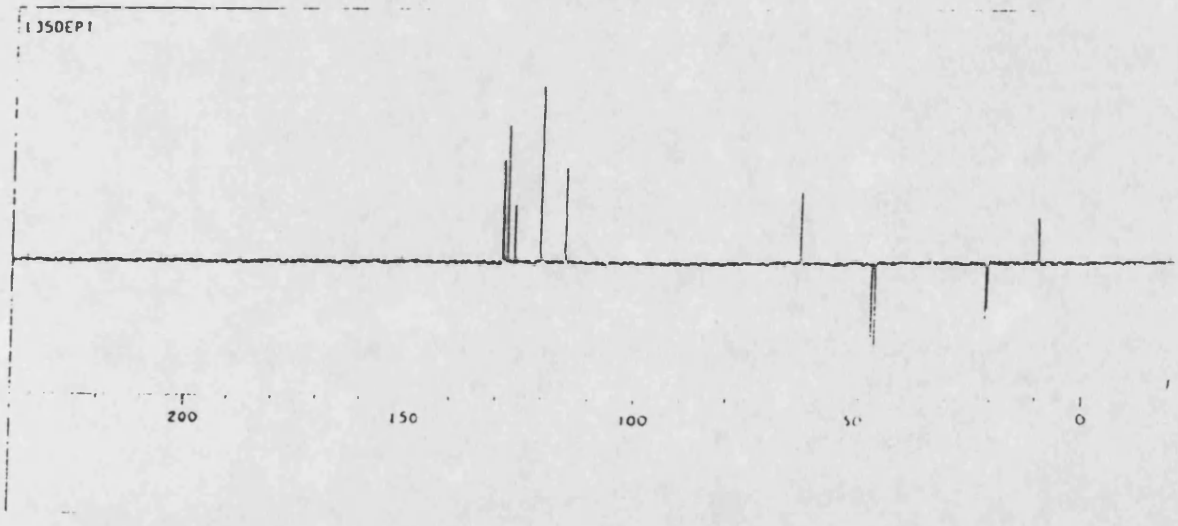
2-BUTYL-9-PHENYL-2,3-DIHYDRO-1*H*-INDENO[2,1-c]PYRIDINE HBr [74].



SPECTRUM 5: 67.8 MHz ^{13}C NMR ($CDCl_3$) OF

2-(1-ETHYLPROPYL)-9-PHENYL-2,3-DIHYDRO-1*H*-INDENO[2,1-c]PYRIDINE HBr [75]





2.32.2 ^{13}C NMR Evidence of the Dienes.

As an example, the ^{13}C NMR spectrum (Spectrum 5) of 2-(1-ethylpropyl)-9-phenyl-2,3-dihydro-1*H*-indeno[2,1-c] pyridine hydrobromide [75] is analysed. The assignments of the carbons were based on DEPT experiments and chemical shifts. Seven signals were observed for the aromatic C-H (δ115.44-129.06). It was accepted that overlapping had occurred as there should have been nine. Three signals were detected for the aromatic C_q(δ131.85-142.49).

The methylene carbons were assigned on chemical shift grounds; the highest field signals at δ21.57 and δ21.05 was assigned to the N-CH($\underline{C}H_2CH_3)_2$, whilst the lowest field methylenes were assigned to C-1 (δ46.67) and C-3 (δ47.52) respectively. The high field methine signal at δ63.96 was assigned to N-$\underline{C}$H($CH_2CH_3)_2$, and two signals at δ9.99 and δ9.86 were assigned to the methyl signals (N-CH[$CH_2\underline{C}H_3]_2$). The aliphatic quaternal signals at δ121.21, δ131.85, and δ133.02 were assigned to the C-4a, C-9a, and C-9.

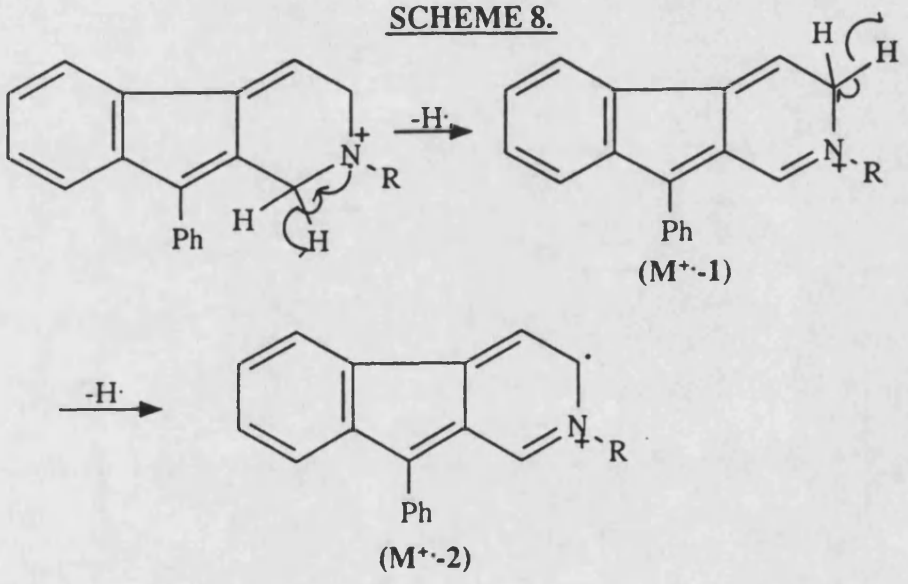
2.32.3 Mass Spectral Analysis of the Dienes.

The mass spectra of the diene analogues did not show many fragment ions under low eV. E.I., probably due to the stability of the ring system. The results are presented in Table 2, and the fragmentation is outlined in Scheme 8 below.

TABLE 2.

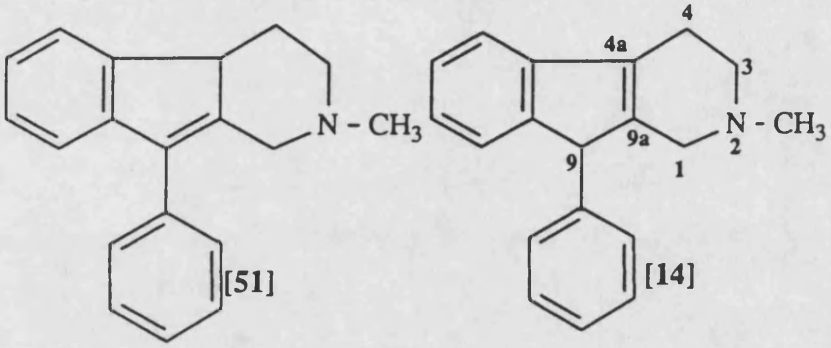
COMPD. No.	$M^{\cdot+}$	$M^{\cdot+}$-1	$M^{\cdot+}$-2
[70]	100	55	33
[71]	96	29	16
[72]	100	27	6
[73]	66	22	31
[74]	100	80	23
[75]	96	100	13
[76]	100	45	67

SCHEME 8.



2.4 N-2 SUBSTITUTED PHENINDAMINE ANALOGUES.

As stated earlier (Section **2.1**), phenindamine was first synthesised by Plati and Wenner[157,158] *via* the Mannich route. Two geometric isomers were isolated, one as the tartrate salt **[14]**, and the other as the hydrobromide salt **[51]**.



[51] **[14]**

In 1992, Casy and colleagues[160] published some results of some of the aryl-substituted analogues of phenindamine. These compounds, all 9,9a-enes, however showed little or no activity at the H_1-histamine receptor. They confirmed that the position of the indene double bond was a major factor for antihistaminic activity. For the purpose of this work, it was hoped that varying the substituent at the N-2 site may affect the position of the indene double bond to shift from the 9,9a position to the more active 4a,9a site.

2.41 Synthesis of Phenindamine Analogues.

Plati and Wenner[157] reduced 2-methyl-9-phenyl-2,3- dihydro-1*H*-indeno[2,1-c]pyridine hydrobromide **[70]** with Raney nickel at room temperature for 4 h to give phenindamine hydrobromide **[51]**. The hydrobromide **[51]** was basified and treated with D-tartaric acid to give the pharmacologically active phenindamine tartrate **[14]**.

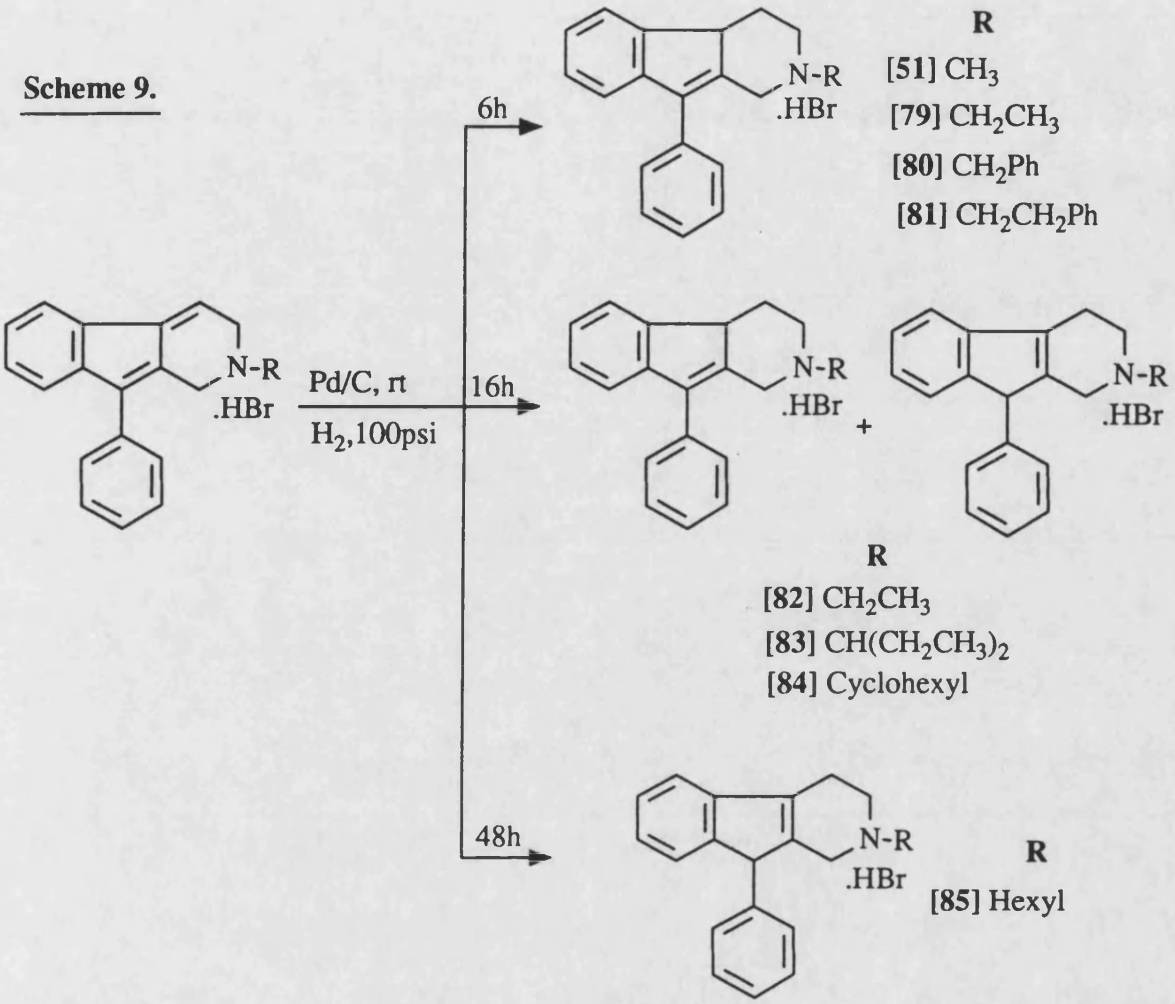
Casy *et al.*,[160] successfully synthesised aryl-substituted phenindamine analogues (where the indene double bond was situated in the 9,9a position) from their precursor

diene analogues using palladium catalyst at room temperature but under pressure. The reduction process used in this work was similar to the one used by Casy and co-workers[160] but an examination of the reaction time was also included as part of this work. The longer reaction time afforded a cleaner product. It was also found that the reaction time was a major factor involved in the isomerization of the mono-enes (See section **2.42**).

A selection of the N-substituted dienes synthesised in this work (See below) were reduced under mild catalytic conditions to give their corresponding mono-enes (phenindamine analogues). For some of these analogues, the anionic components were changed to try to isomerise the indene double bond from the 9,9a to the 4a,9a position. For some of the analogues, this was achieved, and is discussed next.

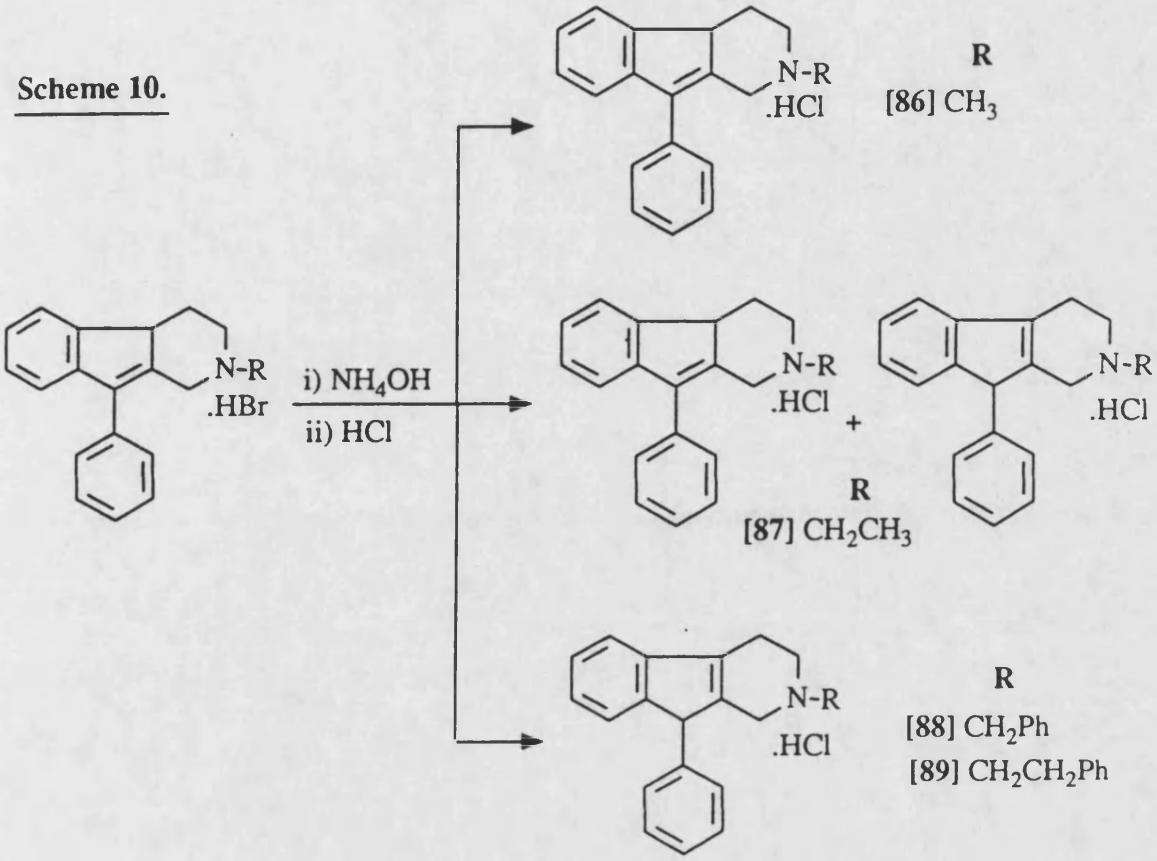
Scheme **9** illustrates the catalytic reductions of a selection of the dienes. In all cases where the diene hydrobromides were catalytically reduced for a period of 6 h, the double bond in the products were found to be situated in the 9,9a position. However, when some of the analogues were reduced with a longer reaction time (16 h), isomeric mixtures were observed in the NMR spectra of the recrystallized products. When diene **[76]**(R=hexyl, X=Br) was reduced for 48 h, only the 4a,9a isomer **[85]** was isolated (78% yield).

Scheme 9.



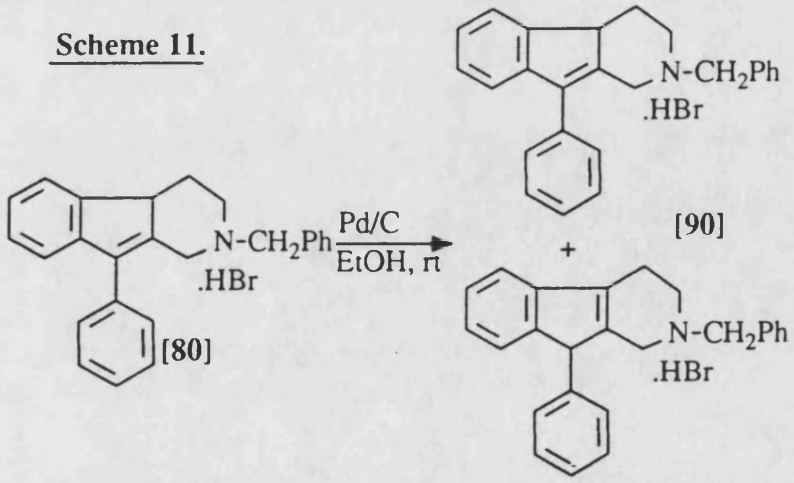
When the 9,9a-enes of compounds **[80]**(R=CH_2Ph, X=Br) and **[81]**(R= CH_2CH_2Ph, X=Br) were basified and then converted to their corresponding hydrochloride salts, the indene double bond shifted to the 4a,9a position (compounds **[88]** and **[89]** respectively). When compound **[51]**(R=Me, X=Br, 9,9a-ene) was converted to its corresponding HCl salts the alkenic bond did not shift (compound **[86]**). However, when compound **[79]**(R=Et, X=Br, 9,9a-ene) was converted to its HCl salt, a mixture of the structural isomers of the 9,9a- and 4a,9a-enes resulted (compound **[87]**) (Scheme **10**).

Scheme 10.



When compound **[80]**(R=CH_2Ph, 9,9a-ene) was dissolved in ethanol and stirred with palladium at room temperature for three weeks, an isomeric mixture of the 9,9a and 4a,9a alkenes resulted (compound **[90]**) (Scheme **11**).

Scheme 11.



The results obtained from the analogues synthesised show that the position of the indene double bond may be dependent on the anion present and/or the substituent at the

N-2 position. A detailed examination of these results indicate that a more logical solution may exist.

Although both double bonds of the diene molecule are conjugated to the phenyl substituents, the 4,4a alkenic bond is less hindered (as the 9,9a alkenic bond is flanked by the 9-phenyl substituent) and hence more accessible for reduction. Thus, no analogues of phenindamine are formed with the double bond in the 4,4a position (See section **2.1**). Consequently, phenindamine analogues with the double bond situated in the 9,9a position are afforded.

This, however, does not explain the formation of the 4a,9a-enes, which have been detected following reduction. It is apparent that a more complex process might be taking place to produce the 4a,9a-enes. Due to the mild conditions required for the reduction of only one of the two possible alkenic bonds in the diene derivatives, the remaining double bond, if left long enough with the catalyst may undergo co-ordination and subsequent isomerization.

2.42 Isomerization of Alkenic Double Bonds.

Isomerization is the process by which chemical bonds or groups are redistributed within a given molecule. Alkene isomerization involves the redistribution of the C=C double bond within a molecule. Many *d*-block elements are capable of co-ordinating to an alkene, and thus affect isomerisation[172]. During metal catalysed isomerization, an alkene undergoes two activation processes; activation by co-ordination and activation by addition.

It is the activation by addition process which is responsible for moving the hydrogen

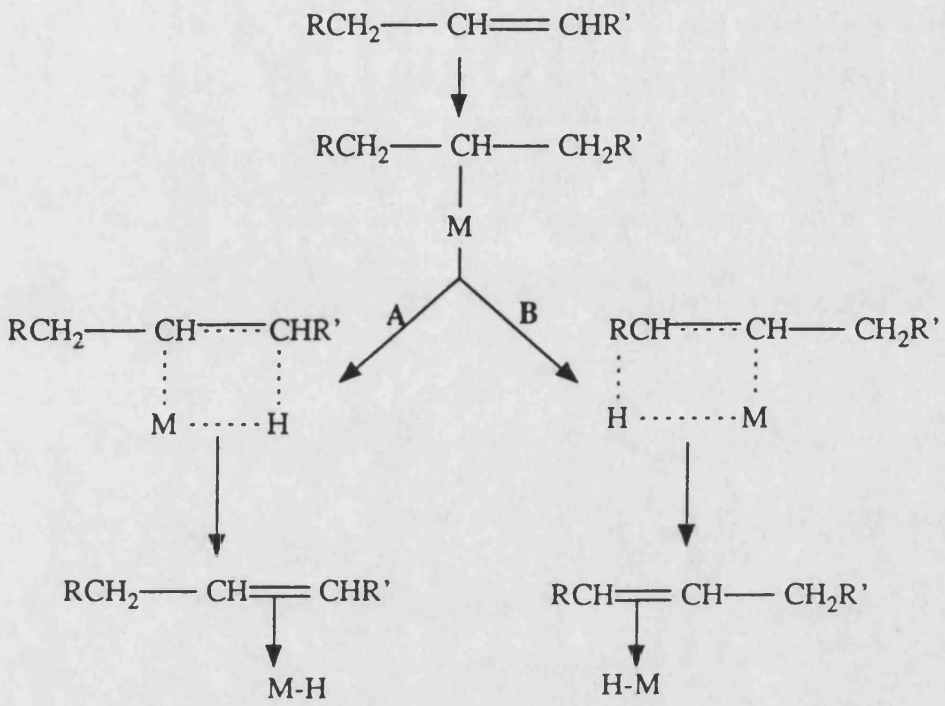
atom around. Double bond migration essentially involves movement of the hydrogen, from the allylic position to the α-carbon atom of the double bond;

It is this process which the metal complex catalyses. Mechanistically, two main types of isomerization have emerged. Those involving metal-alkyl and those involving metal-allyl intermediates.

2.42.1 Isomerization *via* Metal-Alkyl Intermediates.

The essential species in this sequence is a metal-hydride complex. Co-ordination of the alkene gives a hydrido-alkene-metal complex which rapidly undergoes a hydride ligand migration reaction to form a metal-alkyl species (Scheme **12**). The migration probably occurs *via* a four-centre transition state and is extremely rapid for almost all transition-metal hydrido-alkene complexes. Once formed, the metal-alkyl species can undergo a β-elimination proximity interaction *via* either Path **A** or Path **B**.

SCHEME 12.



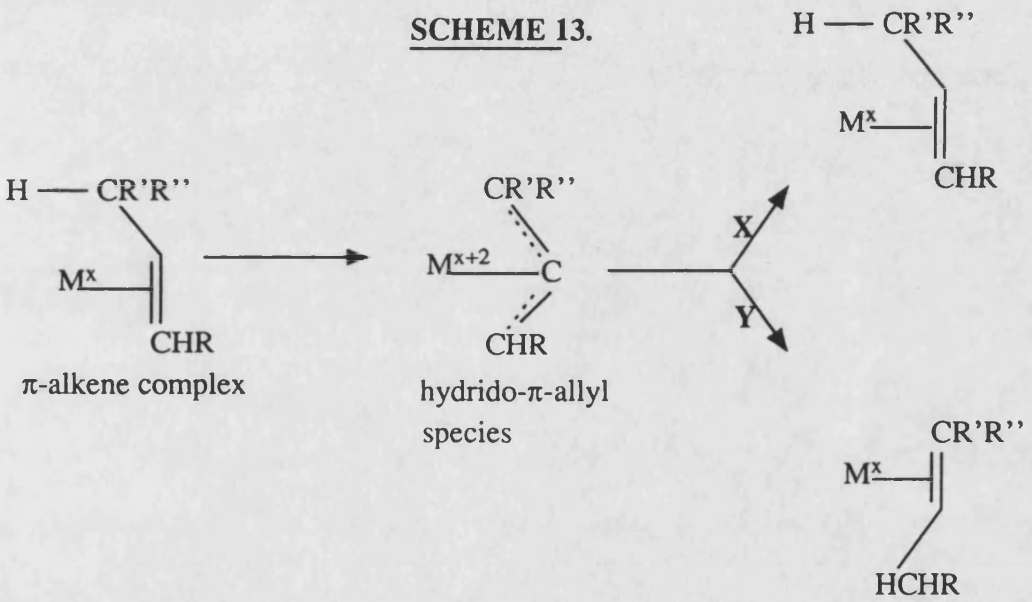
Path **A** results in no net migration of the double bond. Path **B**, in which the hydrogen abstraction occurs at the sites other than at which the initial H addition occurred, results in a net migration of the double bond one position along the "chain". Providing the alkene co-ordinated to the metal can exchange with alkene present in the reaction medium, the above sequence of reaction constitutes a catalytic isomerization cycle.

In the above isomerization system, the active metal-hydride species was either added as such or generated *in situ* from a suitable hydrogen source. In the second mechanistic class of metal-catalysed isomerization reactions, the metal hydride species is generated from the suitable alkene.

2.42.2 Isomerization *via* Metal-Allyl Intermediates.

An alternative pathway leading to alkene isomerization (Scheme **13**) is *via* the formation of a metal-allyl complex. In this sequence initial alkene co-ordination is followed by hydrogen abstraction from a sp^3 hybridized carbon centre adjacent to the double bond to give the hydrido-metal-allyl species. In such a species, generally referred to as an allyl complex, the C_3 unit is then π bonded to the metal, all three carbon atoms are within bonding distance of the metal centre and the unit effectively occupies two co-ordination sites in the complex.

SCHEME 13.



Whether or not double bond migration occurs depends on how the hydride is re-inserted back to the allyl unit. Path **X** results in no net movement of the double bond. Path **Y** moves the double bond one step along the carbon skeleton.

In going from the π-alkene complex to the hydrido-π-allyl species there is an increase of the two units in both the formal oxidation state and co-ordination number of the metal centre. Unlike metal-alkyl isomerization systems previously discussed, the isomerization catalysis cycle involves the π-allyl-metal species involves a redox sequence. Such a sequence can be adapted to the palladium catalyst;

$$Pd^0 \longrightarrow Pd^2 \longrightarrow Pd^0$$

This mechanism is only available to metal complexes in a low oxidation state, for which x+2 is readily attainable, as is the case for palladium[173].

The common feature of the two alkene isomerizations outlined above is the presence at some stage in the catalysis cycle of the metal-hydrido species. Palladium has been researched in the isomerization of several types of alkenic molecules, in some organometallic reactions[173,174,175] As a catalyst, palladium, may be implicated in such isomerization processes.

2.42.3 Isomerization of Phenindamine Analogues.

Both explanations are supported by the fact that when **[79]**(R=Et, X=Br) was reduced for a period of 6h, only the 9,9a ene was produced, however, when the same starting material was reduced for 18 h, a mixture of the 9-9a ene and 4a-9a ene products were afforded. Also, when the diene **[76]**(R=hexyl) was reduced for a period of 48 h, only the 4a-9a ene isomer was afforded in high yield (78%). Furthermore, when compound **[80]**(R=CH_2Ph, 9,9a-ene), was stirred with palladium in ethanol for a long period of time, in the absence of hydrogen, a mixture of isomers resulted. This experiment showed clearly that the palladium is involved in isomerization of alkenic bonds.

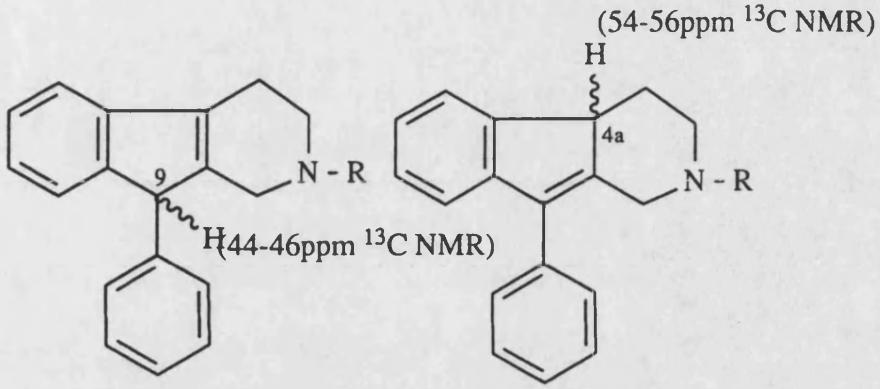
Thus, the reduction products are susceptible to isomerization by the palladium catalyst if time permits. The hydrogens required for the isomerization process can either be abstracted from the compound concerned, or from the H_2 in the hydrogenation vessel. However, it is more likely that the hydrogens are abstracted from the compound; isomerization of **[80]**(R=CH_2Ph, X=Br, 9,9a-ene) in the absence of H_2 did afford a mixture of isomers **[90]**(R=CH_2Ph, X=Br).

In principle, all reactions are reversible; an equilibrium distribution of products will result from any reaction if proper experimental conditions are found. In practice, however, it is often difficult or impossible to reach equilibrium, and nonequilibrium product distribution results. Thus, for the purpose of this work, the hydrogenation of the dienes, the 9,9a-ene isomers are formed faster than the 4a,9a enes as the 4,4a alkenic bond is less sterically hindered and more accessible for reduction. Such a process is thermodynamically controlled (a reversible reaction) and hence affords the thermodynamic products. However, when the reaction conditions are altered (by time or other parameters), whereby irreversible conditions are imposed, the reaction is governed kinetically. Thus, it would be true to say that the 4a,9a enes are the kinetic products.

2.43 Structural Evidence of the Phenindamine Analogues.

2.43.1 ^{13}C NMR Evidence of Phenindamine Analogues.

The assignments of the non-aromatic CH signals were based on the chemical shift data already published[160]. It was realised that a CH signal observed around 55ppm may be assigned to the 9-carbon atom, whilst a CH signal situated at approximately 45ppm may be assigned to the 4a-carbon atom.



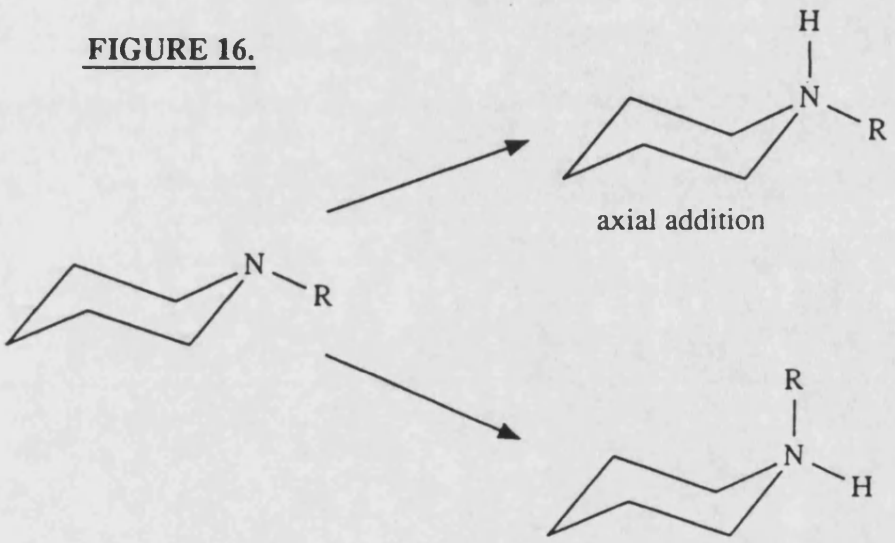
The ^{13}C NMR spectra of the phenindamine analogues synthesised provided evidence of the presence of either one single structure, epimerization (with respect to the nitrogen atom) or isomeric mixtures. These observations are discussed in more detail below.

The ^{13}C NMR spectra of compounds **[51]**(R=CH_3, X=Br), **[80]**(R=CH_2Ph, X=Br) and **[81]**(R=CH_2CH_2Ph, X=Br) showed doubling up of some of the signals. Compound **[51]**(R=CH_3, X=Br) had two high field aliphatic CH signals at δ45.28 and δ45.93 clearly indicating the presence of two epimers of the 9,9a-ene isomer. The ^{13}C NMR spectra of compounds **[80]**(R=CH_2Ph) and **[81]**(R=CH_2CH_2Ph) showed the presence of only one high field CH signal (δ45.90 for **[80]** and δ45.82 for **[81]**), however, other signals were duplicated, indicating that epimerization had occurred. The ^{13}C NMR spectrum of compound **[79]**(R=CH_2CH_3, X=Br), showed the presence of one high field non-aromatic methine signal (δ45.67), and all other signals were not duplicated indicating that only one epimer of the 9,9a-ene salt was afforded.

The ^{13}C NMR spectra of mixtures **[82]**(R=CH_2CH_3, X=Br), **[87]**(R=CH_2CH_3, X=Cl), **[83]**(R=$CH(CH_2CH_3)_2$, X=Br) and **[84]**(R=cyclohexyl, X=Br), showed the presence of two non-aromatic CH signals, one in the region of 45ppm and the other around 55ppm. Other signals were also duplicated. This type of duplication indicates that geometric isomers (9,9a- and 4a,9a-enes) were afforded.

The ^{13}C NMR spectra of compounds **[88]**($R=CH_2Ph$, X=Cl) and **[89]**($R=CH_2CH_2Ph$, X=Cl) also showed doubling up of the signals, however, the high field methine signals allocated to the non-aromatic CH were in the region of 55-56ppm. This indicates that epimers of the 4a,9a-enes were afforded. This type of epimerization is brought about as a result of the two modes of addition of a proton to the nitrogen lone pair of electrons (Figure **16**). The addition can either be axial or equatorial.

FIGURE 16.



Usually axial addition is the preferred route as the N-R substituent adopts the less crowded equatorial conformation. However, epimers of this kind are known in derivatives where a conformational change leads to a fall in the energy of the axial N-R chair conformation. The epimeric ratio varied considerably in different N-2 substituted products depending upon the purity of the solvent and of the nature of the R group and counter ion.

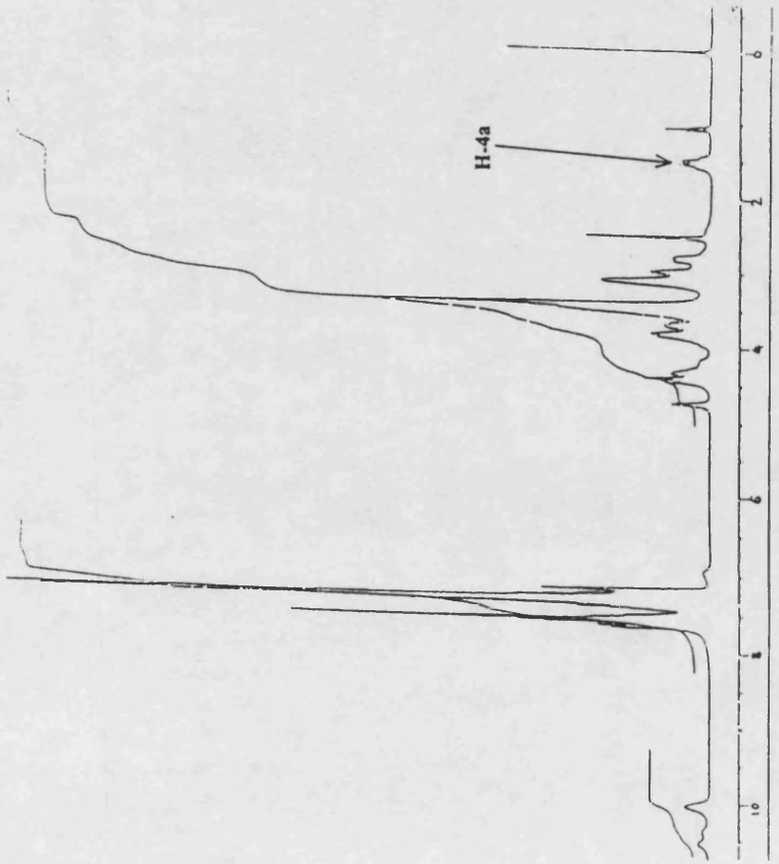
2.43.2 ^{1}H NMR Evidence of Phenindamine Analogues.

Assignments of all of the protons of the ^{1}H NMR spectra of the phenindamine analogues were difficult but resolution of the H-4a and H-9 protons were possible. Most of the aliphatic protons were seen as multiplets around the region of δ2-4.5, the aromatic signals were situated between δ7 and δ8. Using published data[159] on phenindamine hydrobromide (9,9a isomer) and phenindamine tartrate (4a,9a isomer), it was possible to assign some of the protons of the phenindamine analogues by comparative deductions. The lowest field signal (δ4-5) were assigned to the H-9 proton (observed in the 4a,9a-enes and mixtures of geometric isomers), whilst the highest field signals were assigned to the axial H-4 proton in the region 1-2ppm (only observed in the 9,9a-enes).

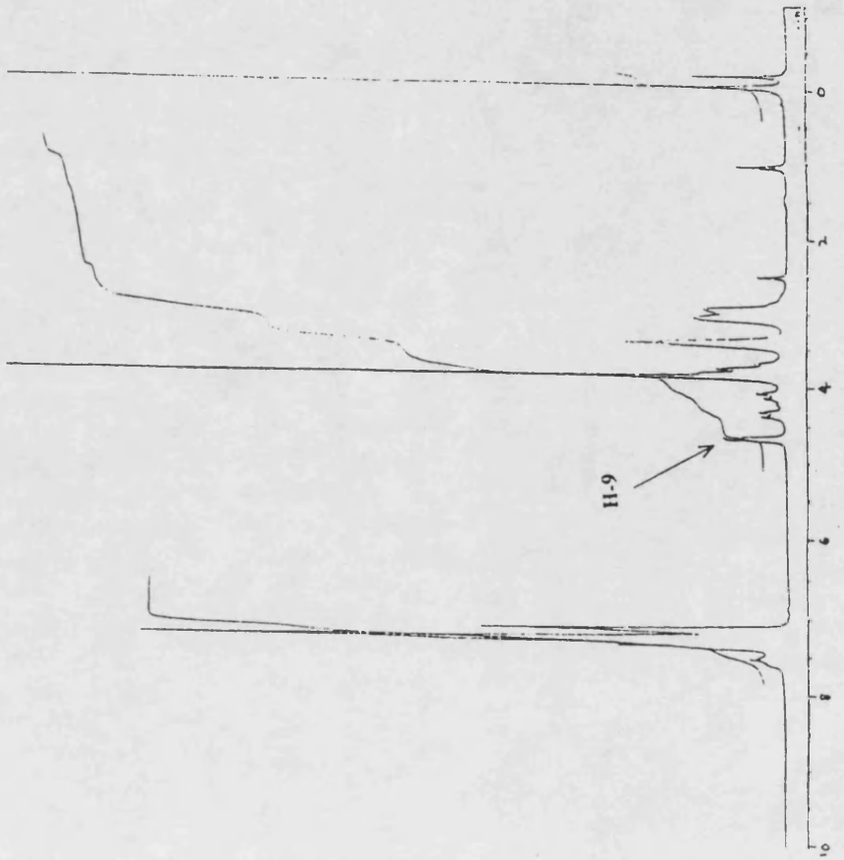
The 9,9a-ene compounds showed the presence of the axial H-4 protons as a doublet of quartets, which were absent in the 4a,9a-ene compounds. The ^{1}H NMR spectra of the 4a,9a-enes showed the presence of the H-9 proton as broad signals. The ^{1}H NMR spectra, where geometric isomers were present, the H-9 signal integrated between 0.2-0.5 of a proton, whilst the H-4a signal was part of a multiplet which included the H-1 and H-3 protons.

The ^{1}H NMR spectra of compounds **[81]**(R=CH_2CH_2Ph, X=Br) and **[89]**(R=CH_2CH_2Ph, X=Cl) are shown in spectra **6** and **7** respectively. It can be seen clearly that compound **[81]**(9,9a-ene) is lacking the H-9 proton, although a peak at δ4.74 is observed which integrated to 0.5 of a proton and is in fact part of the multiplet around δ4.41 assigned to the H-1 protons. Also, an undefined doublet of quartets at δ1.54 is assigned to the axial H-4 proton. Compound **[89]**(4a,9a-ene) lacks the axial H-4 proton, but has a broad signal at δ4.82 assigned to the H-9 proton.

SPECTRUM 6: 270 MHz ^{1}H NMR (DMSO-d_6) OF 2-PHENETHYL-9-PHENYL-2,3,4,4a-TETRAHYDRO-1*H*-INDENO[2,1-c]PYRIDINE HBr [81] (9-9a ISOMER).



SPECTRUM 7: 270 MHz ^{1}H NMR (DMSO-d_6) OF 2-PHENETHYL-9-PHENYL-2,3,4,9-TETRAHYDRO-1*H*-INDENO[2,1-c]PYRIDINE HCl [89] (4a-9a ISOMER).



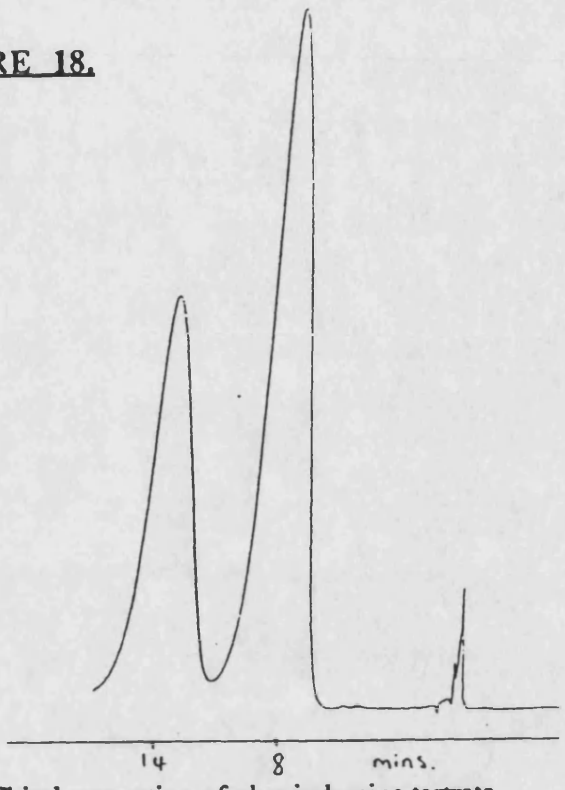
Overall, it was recognised that the ^{1}H NMR spectra of the phenindamine analogues complemented the corresponding ^{13}C NMR spectra. For instance, if epimerization was evident in the ^{13}C NMR, two exchangable singlets were observed for the +N-H proton. In conclusion, it was found easier to determine the structures of the phenindamine analogues using ^{13}C NMR data than the ^{1}H NMR data, as the main emphasis of the compounds synthesised was to determine the position of the indene double bond i.e. be it in the 4a,9a or 9,9a position.

2.44 Chiral Separation of Phenindamine Analogues.

In the last fifteen years or so, chromatographic techniques, and particularly high performance liquid chromatography (HPLC) have become predominant in pharmaceutical analysis and separations, owing to their high speed, efficiency and ease of automation. This has been particularly true in the separation and analysis of enantiomers, where selectivities are often low, and high separation efficiencies are therefore critical. Chromatographic separation of enantiomers may be effected either by derivatization and separation of the resulting diastereomers, or by incorporation of a chiral species into the stationary or mobile phase. The development of chiral chromatography has been rapid in recent years, and a range of chiral derivatizing reagents, stationary phases, and mobile phase additives are now in use.

A variety of HPLC chiral separation techniques have been developed in recent years, some of which have proved suitable for preparative applications. Many racemates of known drugs have been resolved using such procedures, including the phenothiazine antihistamine trimeprazine which was resolved into its antipodes at greater than 95% optically purity[176].

FIGURE 18.



Chiral separation of phenindamine tartrate using SGE-C8 8/5 column containing β-cyclodextrin hydrate,

Chiral separation of 2-phenethyl-9-phenyl-2,3,4,4a-tetrahydro-1*H*-indeno[2,1-c]pyridine HBr using LC-ABZ column containing β-cyclodextrin hydrate.

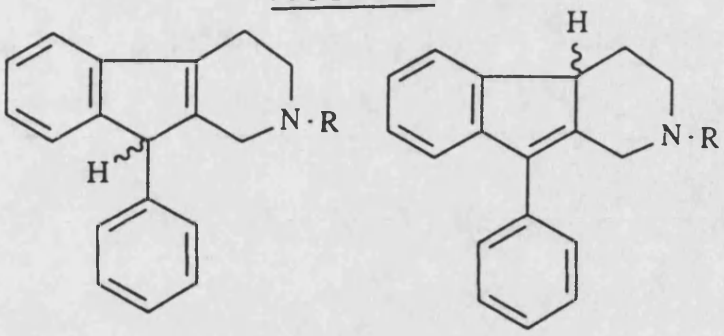
The criterion for chiral separation of compounds using HPLC techniques incorporated with a chiral complexing reagent such as β-cyclodextrins, is that the substrate should contain at least one aromatic substituent, and an electronegative atom. The chiral centre should be close (one or two bonds away) to the aromatic group, and be between three to four bonds away from the electronegative atom. Such criteria fit the phenindamine analogues synthesised.

The procedure for the separation of chiral compounds described by Cooper and Jefferies[176], which was used for semi-preparative chiral separation of trimeprazine (an antihistamine), was also utilised for the chiral separation of phenindamine tartrate. The mobile phase used was acetonitrile and aqueous triethylammonium acetate (0.8% TEA v/v, acetic acid to pH4). The column (SGE-C8 8/5) contained 20mg/ml of β-cyclodextrin hydrate. Base line separation was achieved (Figure **16**). This implies that both enantiomers may be separated.

Thephorin **[14]** and seven other derivatives synthesised in this work (Figure **17**) were examined using a LC-ABZ column and various mobile phases containing β-cyclodextrins to effect enantiomeric resolution. The derivatives used differed in the position of the indene double bond be it in the 9,9a position or the 4a,9a position. This would give rise to a chiral centre in the 4a position or 9 position respectively. The mobile phase was kept at an acidic pH (3.5) so that the analogues were always in the salt form. This is important as isomerization may result if the free bases were produced[159]. Of the derivatives used, and under these conditions only two compounds showed that chiral separation was achieved. These compounds were **[79]**(9,9a isomer R=Et) and **[81]**(9,9a isomer, R=CH_2CH_2Ph). Figure **18** shows the chiral separation of **[81]**. Other parameters such as pH and solvent were changed to try and achieve

separation of the other derivatives, but this was unsuccessful.

FIGURE 17.



[14] R = CH_3 **[51]** R = CH_3

[85] R = Hexyl **[79]** R = CH_2CH_3

[88] R = CH_2Ph **[80]** R = CH_2Ph

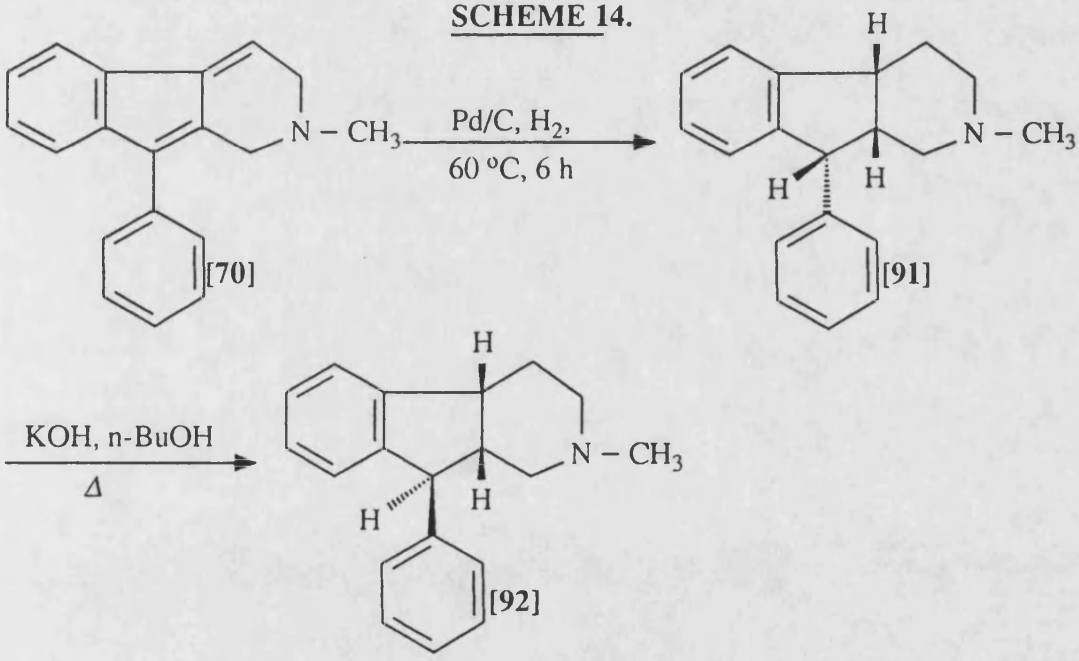
[89] R = CH_2CH_2Ph **[81]** R = CH_2CH_2Ph

As a result of these tests, it seems hopeful that within time these chiral molecules may be resolved[177], using semi-preparative techniques and hence allow evaluation of the pharmacological activity of the different enantiomers.

2.5 THE 2,3,4,4a,9,9a-HEXAHYDRO-1*H*-INDENO[2,1-c]PYRIDINES.

Plati and Wenner[157] prepared the hexahydro product from the diene **[70]** by the use of platinum oxide as the hydrogenating catalyst at 60-70°C to accelerate the absorption of two moles of hydrogen. Ham and Leeming[178] also investigated the hexahydro compound **[91]** which was considered correctly to be a single compound using a 60 MHz ^{1}H NMR spectrometer. Treatment of the base with potassium hydroxide in butan-1-ol gave a second isomer. Casy *et al.*,[160] synthesised and fully characterised the hexahydro product of phenindamine (Scheme **14**). The antihistaminic activity of the all *cis* hexahydro product **[91]** was negligible whilst the *trans*-hexahydro product **[92]** was slightly active when compared to phenindamine tartrate.

SCHEME 14.



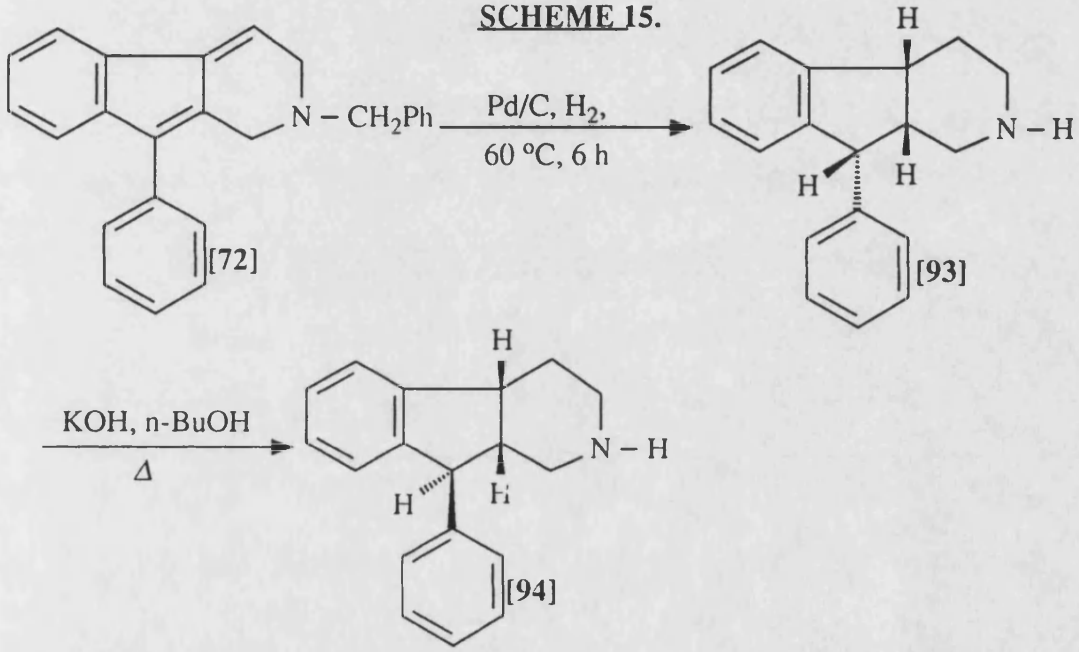
The *all cis* product is denoted as such, when the hydrogens in the 9, 9a, and 4a positions are on the same side as expected from catalytic processes. The *trans* product is termed so, by epimerisation of the *cis*-isomer at the H-9 hydrogen.

The aim of this work was to characterize fully the N-dealkylated *cis* and *trans* hexahydro products and to realkylate with a variety of substituents to try and modify

the antihistaminic potency.

Catalytic reduction of diene **[72]**(R=CH_2Ph) with palladium on charcoal at 70°C for 6 hours yielded the *all cis*-9-phenyl-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-c] pyridine **[93]** as the hydrobromide salt. Treatment of the product with a hot suspension of potassium hydroxide in butan-1-ol gave the *trans* product **[94]** (Scheme **15**).

SCHEME 15.



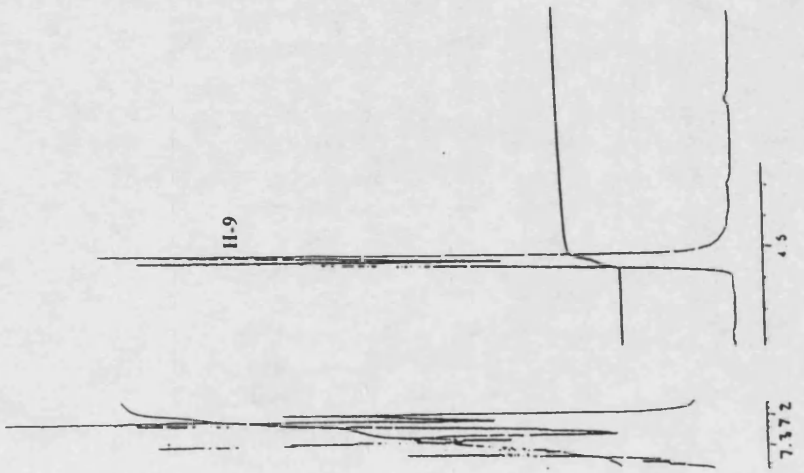
It was expected, that the catalytic product **[93]** would be of a *cis* stereochemistry and would have no benzyl group. The mechanism by which the *cis* product is converted to the *trans* is one where the base (^-OH) would abstract the most acidic proton, which in this case is the 9-methine, and re-insert it to form the *trans* product[179,180].

2.51 Structural Evidence for the *Cis*- and *Trans*-Hexahydro Products.

The ^1H NMR (Spectrum **8**) of the *cis* product **[93]** showed a doublet corresponding to one proton at δ4.56 with a coupling constant 5.86 Hz. The signal was assigned to the 9-methine proton (on chemical shift grounds as well as multiplicity). The magnitude of the coupling constant is similar to the normal signal for *cis* stereochemistry. In

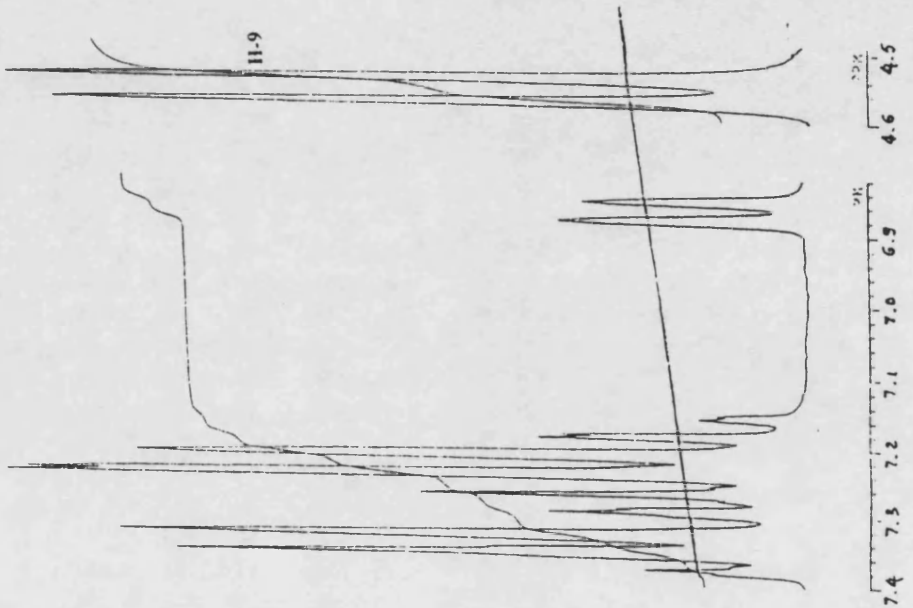
SPECTRUM 8: 270 MHz ^{1}H NMR (DMSO-d_6) OF THE ALL *CIS*

9-PHENYL-2,3,4,4a,9,9a-HEXAHYDRO-1*H*-INDENO[2,1-c]PYRIDINE HBr [93]



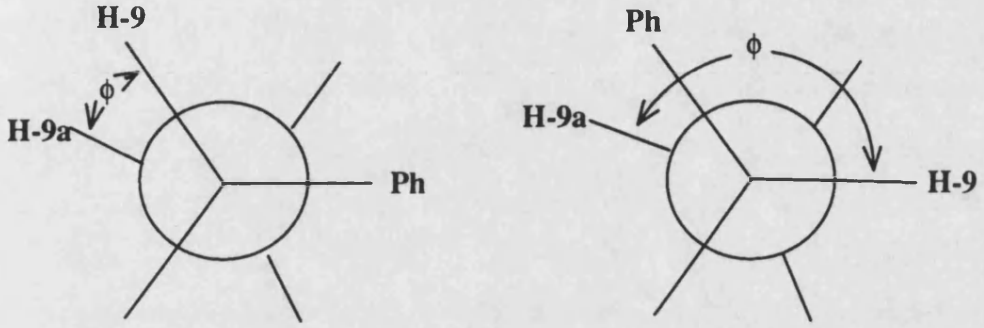
SPECTRUM 9: 270 MHz ^{1}H NMR (DMSO-d_6) OF THE *TRANS*

9-PHENYL-2,3,4,4a,9,9a-HEXAHYDRO-1*H*-INDENO[2,1-c]PYRIDINE HCl [94]



comparison, the ^{1}H NMR (Spectrum **9**) of the *trans* product **[94]** gave a doublet at δ4.55 with a coupling constant of 9.89 Hz. These values can be explained in more detail in Figure **19** below.

FIGURE 19.



cis-isomer *trans*-isomer

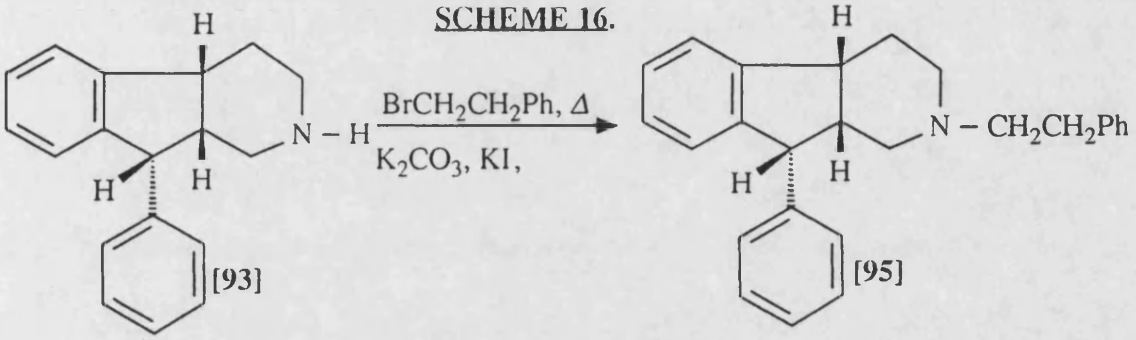
For the *cis* isomer, the dihedral angle (ϕ) between H-9 and H-9a is significantly smaller than that in the *trans* epimer (20-30° in *cis* isomer, approaching 180° in *trans* epimer). From the ^{3}J/ϕ relationship of Karplus[181], a dihedral angle approaching 180° should lead to a coupling interaction of greater magnitude than the one in the 20-30° range. Hence, the magnitude of ^{3}J of the H-9 doublet of the *trans* epimer should be greater than that of the *cis* isomer if these arguments are valid, and this was found to be the case. However, an eclipsed *cis* conformation (large J value) and a syaggered *trans* conformation (small J value) is also possible.

The ^{13}C NMR of the *cis* isomer **[93]** gave the three methine signals at δ39.76 ppm, δ42.62 ppm and δ53.03 ppm, which correspond to the C-9a, C-4a, and C-9 respectively. The allocations of these signals were based on those explained earlier for the phenindamine analogues, where it was shown that the 9-carbon signal was the most deshielded. However, in the absence of the indene double bond, the 9a-carbon signal would be further downfield than the 4a-carbon as it is β-deshielded by the N-2 nitrogen. Similarly, signals at δ39.15, δ45.93, and δ50.08 ppm were allocated to the C-9a, C-4a, C-9 carbons from the *trans* **[94]** ^{13}C NMR spectrum.

2.52 Re-alkylation of the Hexahydro Products.

In the presence of base and dry solvent, the all *cis* hexahydro product **[93]** reacted with phenethyl bromide to give the *cis*-2-phenethyl-9-phenyl-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-c]pyridine **[95]** in 82% yield (Scheme **16**).

SCHEME 16.



The ^{1}H NMR spectrum of **[95]** showed a doublet at δ4.69 of magnitude 5.9 Hz corresponding to the H-9 proton. The presence of the phenethyl side chain was also detected, which was not present in the starting material. The ^{13}C NMR of **[95]** showed the presence of the N-$\underline{C}H_2$ (δ56.66) and N-$CH_2\underline{C}H_2Ph$ (δ21.31) signals which were absent in the starting material.

To summarize, the hexahydro products **[93]** and **[94]** were fully characterized using NMR experiments. It was also realized that re-alkylation of the N-2 unsubstituted sites may be possible. Further work on this section should include the realkylation of the *cis* and *trans* isomers with varying substituents for comparative pharmacological analysis.

2.6 N-DEALKYLATION.

One of the disadvantages of the synthesis of phenindamine analogues *via* the Mannich route (See section **2.1**) is that only a certain number of primary amines can be utilised to produce N-2 substituted analogues of phenindamine. A variety of N-2 substituents that contain double bonds or other reducible groups cannot be used as the initial primary amine in the Mannich reaction as subsequent catalytic reduction to afford the phenindamine analogues may reduce the substituents. As a result, N-dealkylation of some of the phenindamine analogues and their precursors were investigated in order to prepare the dealkylated products which may then be re-alkylated with a wider range of substituents at the N-2 position.

There are several methods that are available for N-dealkylation reactions. These methods are well documented in the literature[182,183,184,185]. Apart from catalytic N-debenzylation, most N-dealkylation (including N-debenzylation) processes occur *via* a two-step synthesis. The first step involves the protection of the amine centre by substitution with another more accessible group which may be readily removed to give the desired product. This first step is usually formed under mild conditions. The second step, which forms the N-dealkylated product, usually occurs under vigorous conditions[185]. The relatively severe reaction conditions necessary for the formation of the N-dealkylated product limits the synthetic utility. However, it has been found that carbamates, derived from 2,2,2-trichloroethyl chloroformates can be cleaved using mild conditions[186].

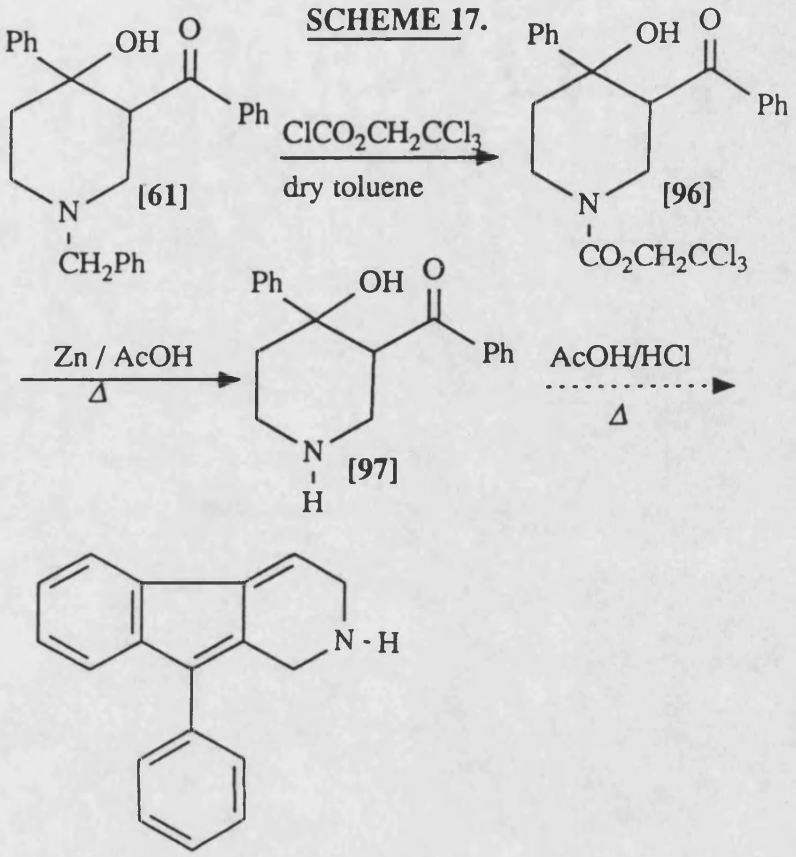
2.61 N-Dealkylation of the Piperidines.

Although interest lay in the formation of the N-dealkylated products of phenindamine analogues, it was realised that N-dealkylation of the precursors (the piperidines and the dienes) was necessary for synthetic purposes.

When 3-benzoyl-1-benzyl-4-hydroxy-4-phenyl piperidine **[61]** was treated with 2,2,2-trichloroethyl chloroformate, the carbamate **[96]** was formed which was confirmed by NMR data. The ^{13}C NMR spectrum of carbamate **[96]** showed the presence of the amide C=O at δ146.15, and a low field methylene signal at δ75.28 corresponding to N-$CO_2\underline{C}H_2CCl_3$, which were absent in the starting material. The ^{1}H NMR spectrum showed the presence of two protons in the region of δ5.09-4.66 assigned to the methylene protons of the 2,2,2-trichloroethyl substituent.

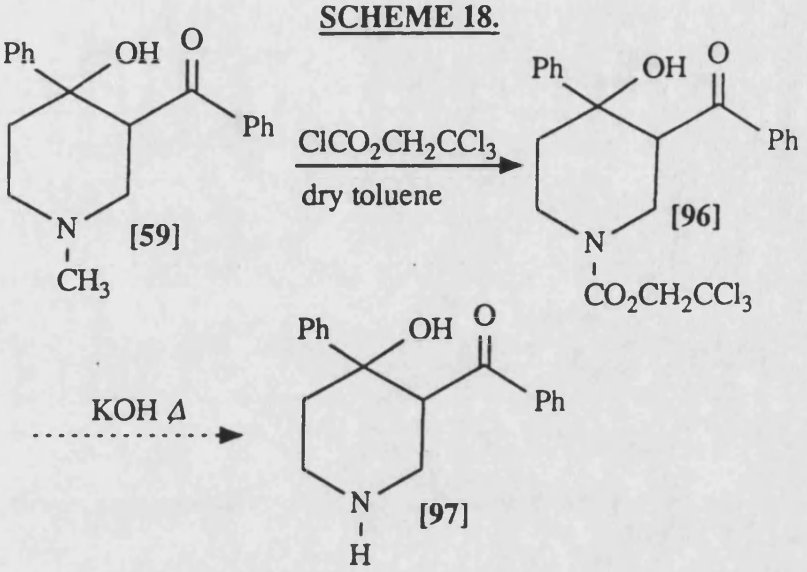
Reaction of the carbamate **[96]** with zinc and acetic acid under reflux gave 3-benzoyl-4-hydroxy-4-phenyl piperidine **[97]**, which was isolated as the hydrochloride salt (Scheme **17**), which was verified by microanalytical data. Subsequent cyclization of the product with dehydrating agents such as acetic acid and hydrochloric acid gave a crude dark oil, which was not further investigated.

SCHEME 17.



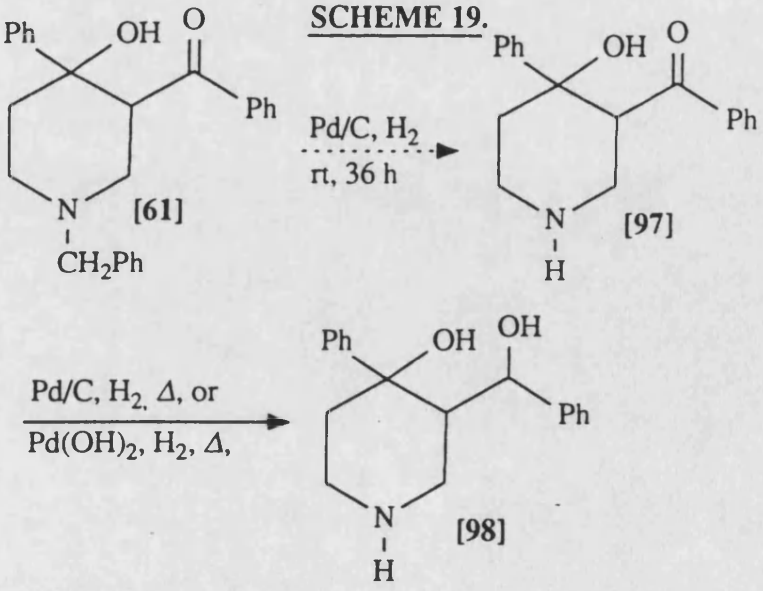
The above method was used used to demethylate 3-benzoyl-4-hydroxy-1-methyl-4-phenylpiperidine **[59]** to give the carbamate **[96]**. Reaction of the carbamate **[96]** with potassium hydroxide at elevated temperature gave a product which was black in appearance. The TLC showed a multicomponent product which was not further investigated (Scheme **18** below).

SCHEME 18.



Catalytic reduction of 3-benzoyl-1-benzyl-4-hydroxy-4- phenylpiperidine **[61]** with either palladium on charcoal at 70 °C for 6 h, or platinum hydroxide at the same temperature for 2 h gave the same product. NMR analysis of this product showed that the N-benzyl grouping was eliminated, but, the carbonyl function at the 3-position of the ring was reduced to the alcohol **[98]**. When the same catalytic conditions were repeated at room temperature, but with a longer reaction time (36 h), the starting material was recovered (Scheme **19**, below).

SCHEME 19.

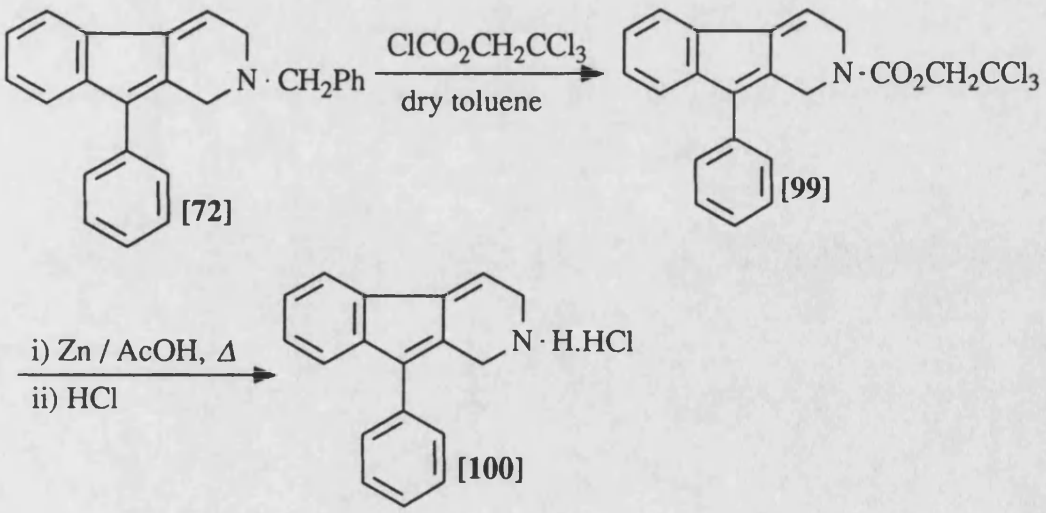


2.62 N-Dealkylation of the Diene.

Reaction of 2-benzyl-9-phenyl-2,3-dihydro-1*H*-indeno[2,1-c] pyridine **[72]** with 2,2,2-trichloroethyl chloroformate gave the desired carbamate **[99]**. The ^{13} C NMR of carbamate **[99]** showed the presence of a low field methylene $\underline{C}H_2$ at δ75.22 which was assigned to N-$CO_2\underline{C}H_2CCl_3$, which was absent in the starting material. The aromatic signals of the spectrum of carbamate **[99]** integrated to 9 protons, whilst the starting material **[72]** had 14 aromatic protons.

Reaction of the intermediate carbamate with zinc and acetic acid gave the N-dealkylated diene **[100]** which was characterised as the hydrochloride salt (Scheme **20**). The ^{1}H NMR of the N-dealkylated product **[100]** showed the absence of the 2,2,2-trichloroethyl substituent, in the sense that a singlet at δ9.92 integrated to two protons and was assigned to the N-$\underline{H}_2$ hydrogens. This signal disappeared on deuteration.

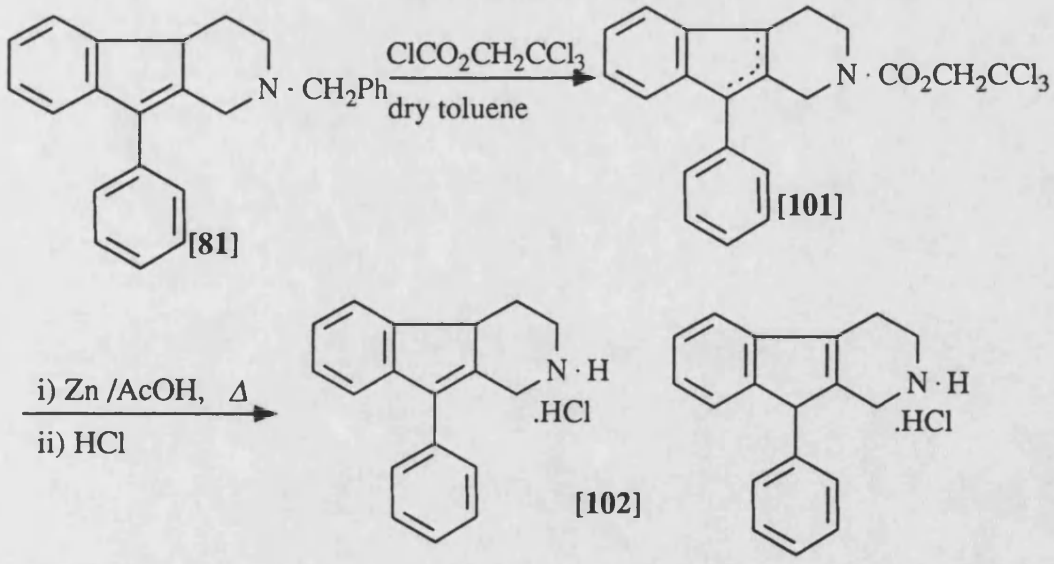
SCHEME 20.



2.63 N-Dealkylation of the Phenindamine Analogues.

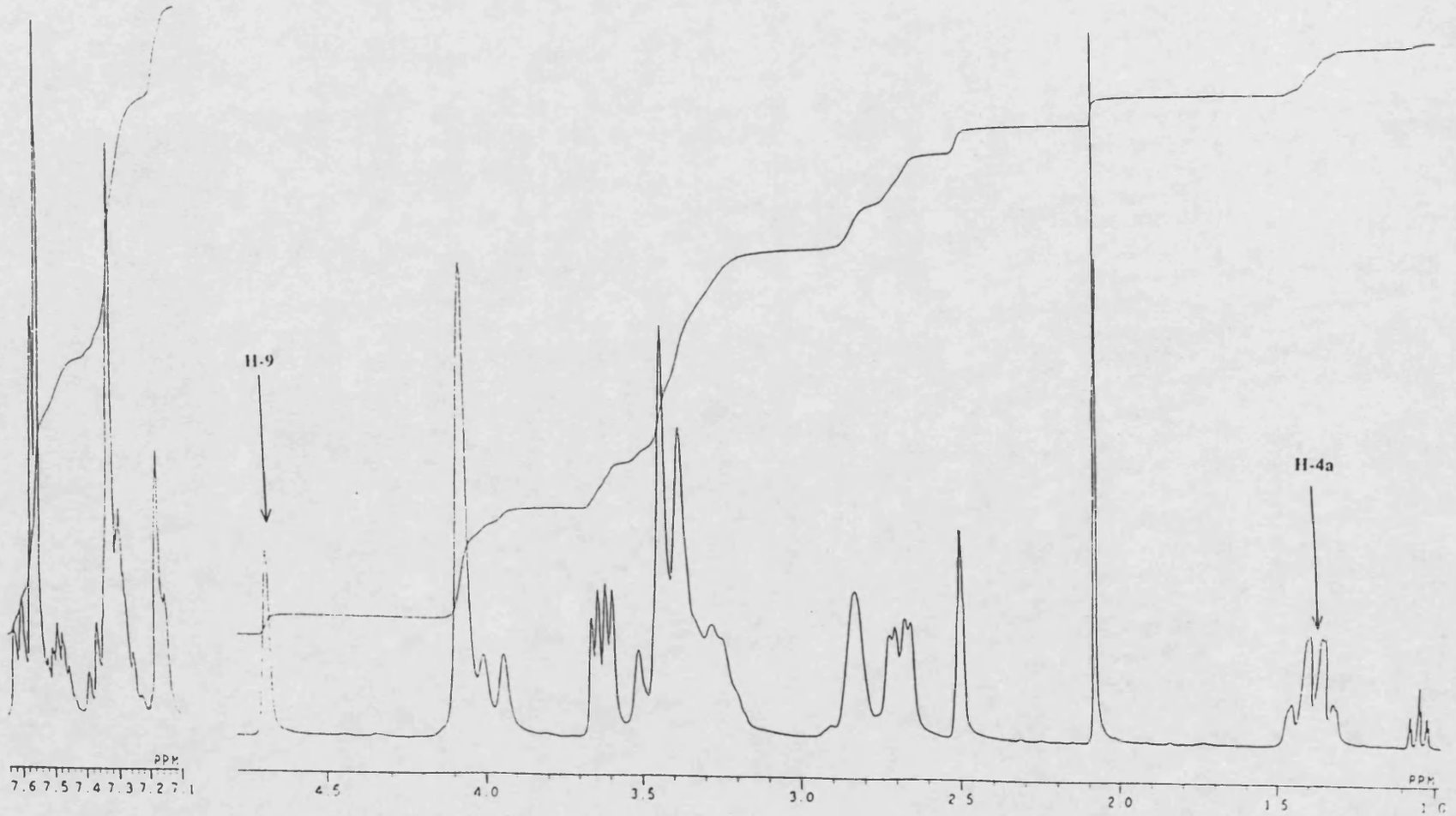
2-Benzyl-9-phenyl-2,3,4,4a-tetrahydro-1*H*-indeno[2,1-c] pyridine hydrobromide **[81]** was basified with ammonia solution extracted into toluene and treated with 2,2,2-trichloroethyl chloroformate to give a thick yellow oil **[101]** which was then treated with zinc and acetic acid under reflux to give an isomeric mixture of the 4a,9a and 9,9a-enes which was isolated as the HCl salt (Scheme **21**). This was confirmed by ^{13}C NMR data, which showed that there was two non-aromatic methine signals in which one was situated at δ45.80 and the other at δ54.91. The ^{1}H NMR spectrum (Spectrum **10**) showed a signal at δ1.42 (0.73 of a proton) assigned to the axial H-4a and another signal at δ4.68 (0.27 of a proton) assigned to the H-9 proton (See Spectrum **10**). The fact that an isomeric mixture of the N-dealkylated product **[102]** of the phenindamine analogue was formed may mean that when the N-benzyl starting material was basified, a mixture of the isomers was formed[159,160].

SCHEME 21.



In conclusion, this work was successful in the sense that non-catalytic N-debenzylation was achieved for all the precursors. Further work would be required to N-realkylate with other alkyl substituents.

SPECTRUM 10: 270 MHz ^{1}H NMR (DMSO-d_6) OF 9-PHENYL-2,3,4,4a- AND 2,3,4,9-TETRAHYDRO-1*H*-INDENO[2,1-c]PYRIDINE HCl [102] (GEOMETRIC ISOMERS).



2.7 THE ARECOLINE ROUTE TO PHENINDAMINE ANALOGUES.

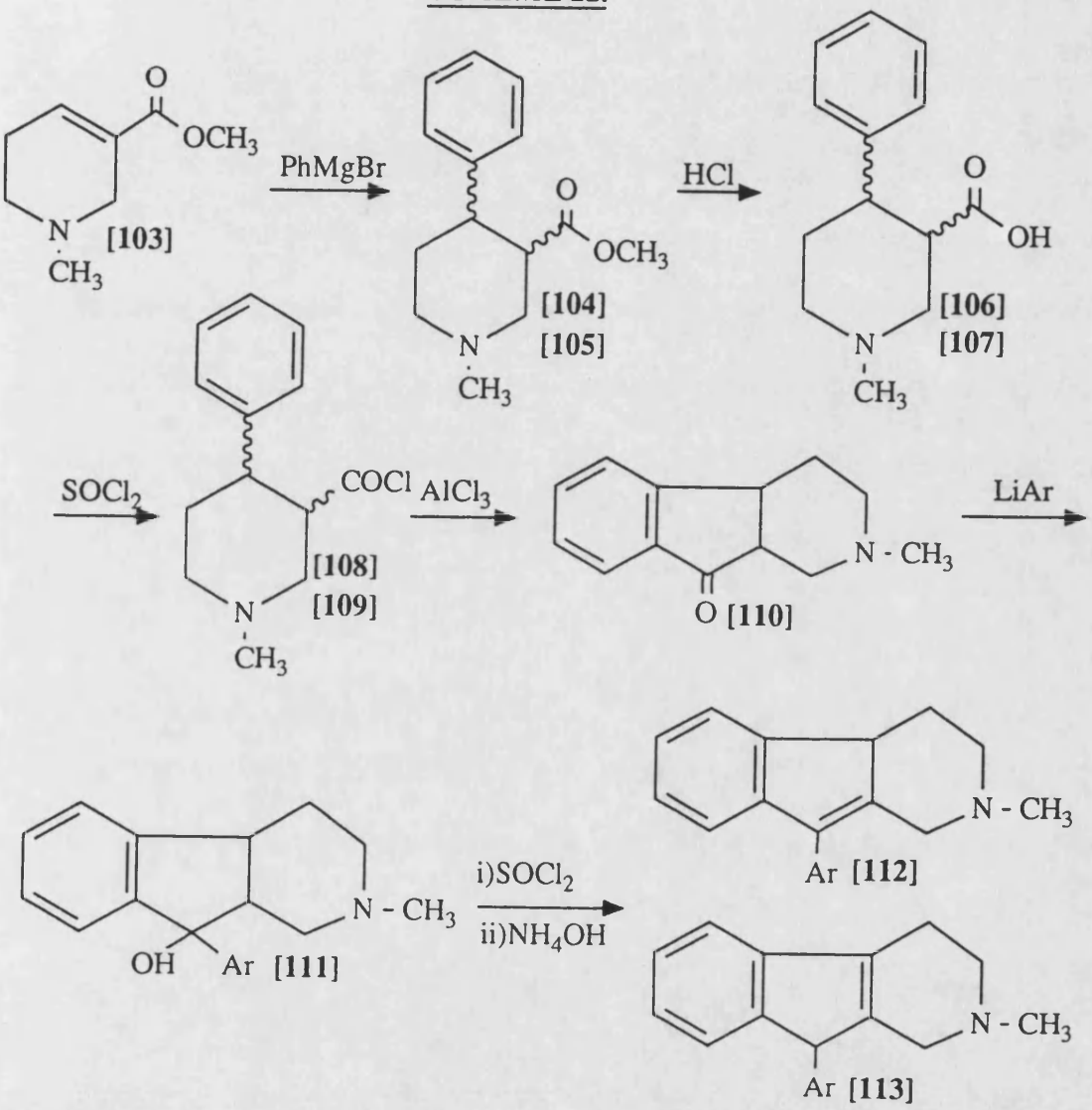
The Mannich route cannot be exploited to give access to phenindamine analogues with different substituents in the two aromatic rings, and an alternative route was sought in which the two aromatic substituents are introduced separately. To this end, arecoline was selected as the starting material.

Scheme **22** outlines the route towards the synthesis of phenindamine and its analogues. The reaction of arecoline **[103]** with phenylmagnesium bromide gives a diastereomeric product of esters **[104]** and **[105]**. Hydrolysis of the esters gives the corresponding α- and β- acids **[106]** and **[107]**. The acids are converted to their acid chlorides (**[108]** and **[109]**) and then treated with aluminum chloride to give 2-methyl-9-oxo-9-phenyl-2,3,4,4a,9,9a-hexahydro-1*H*- indeno[2,1-c]pyridine **[110]**[185]. Reaction of the 9-keto product **[110]** with aryllithium reagents afford the 9-aryl-9-hydroxy-2-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-c]pyridine **[111]** which if dehydrated should give 9-aryl-2-methyl-2,3,4,4a-tetrahydro-1*H*-indeno[2,1-c] pyridine **[112]** or 9-aryl-2-methyl-2,3,4,9-tetrahydro- 1*H*-indeno[2,1-c]pyridine **[113]**.

Plati *et al.*,[187], utilised the Arecoline route for the synthesis of phenindamine. They also separated the two diastereomers (α- and β-) of the esters by first crystallising the hydrobromide salt of the α-isomer **[104]** from the reaction mixture. The mother liquor was then neutralized, extracted, and the free base was then converted to the oxalate salts to give the β-product **[105]**. They offered no discussion on the conformational aspects of these two diastereomers.

Clarke and co-workers[188], while investigating the pharmacological activity of cocaine analogues, synthesised and derivatised the α- and β-esters **[104]** and **[105]** and their

SCHEME 22.


O
OCH3
N
CH3
[103]
PhMgBr
O
OCH3
[104]
[105]
HCl
O
OH
[106]
[107]
SOCl2
COCl
AlCl3
[108]
[109]
O [110]
N - CH3
LiAr
OH
Ar [111]
i)SOCl2
ii)NH4OH
Ar [112]
Ar [113]

corresponding alcohols. They stipulated that the β-alcohol showed intramolecular hydrogen bonding at high dilution, and as a consequence, assigned it as the *cis*-isomer (*c*-3-OH r-4-Ph). The α- and β-esters were evaluated for biological activity. No NMR data were published to support their findings. These are reported in section **2.71.2.**

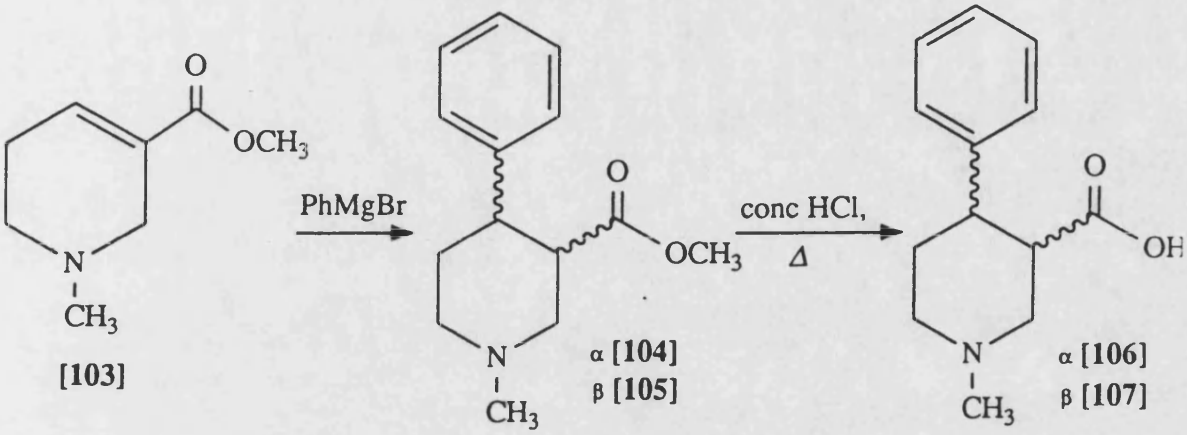
The present work was undertaken to investigate the synthesis of analogues of phenindamine with various aromatic substituents at the 9-position. Particular interest was also taken to try and determine the stereochemical aspects of the precursor synthesised, using NMR experiments.

2.71 Methyl 1-Methyl-4-Phenylpiperidine-3-Carboxylates and 1-Methyl-4-Phenylpiperidine-3-Carboxylic Acids.

The reaction of arecoline **[103]** with phenylmagnesium bromide gave a diastereoisomeric mixture of methyl 1-methyl-4-phenylpiperidine-3-carboxylates **[104]** and **[105]**. Addition of hydrogen chloride gas to the crude product in ether yielded the hydrochloride salt. Recrystallization from ethanol gave the α-isomer **[104]**. The mother liquor was evaporated and recrystallized from acetone to give the β-isomer of methyl 1-methyl-4-phenylpiperidine-3- carboxylate **[105]**.

Hydrolysis of the esters **[104]** and **[105]** with concentrated hydrochloric acid and consequent removal of the formed methanol by distillation gave the corresponding α- and β-acids **[106]** and **[107]** (Scheme **23**). The melting points of the two isolated isomeric acids were different.

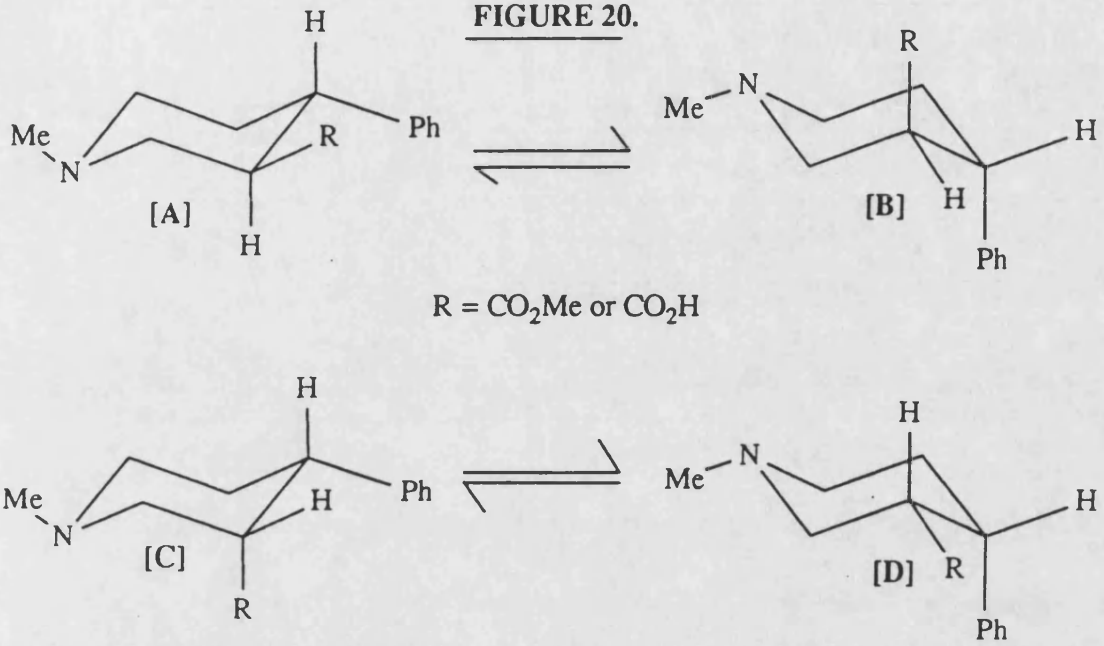
SCHEME 23.



2.7.1.1 Conformational Analysis of the Isomers of Methyl 1-Methyl-4-Phenylpiperidine-3-Carboxylates and their Corresponding Acids.

Due to the presence of two asymmetric carbon atoms at the 3- and 4-positions of the ring, four different conformers can be proposed for the diastereoisomers of methyl 1-methyl-4-phenylpiperidine-3-carboxylates and their corresponding acids (Figure 20).

FIGURE 20.



Conformers **[B]** and **[D]** are unlikely to be the more stable *trans* and *cis* arrangements as they show the 4-phenyl substituents in the axial plane, and subject to 1,3-diaxial interactions. The remaining conformers **[A]** and **[C]** are proposed for α- and β-isomers which have been isolated as their hydrochloride salts in this work.

2.7.1.2 Spectroscopic Analysis of Methyl 1-Methyl-4- Phenylpiperidine-3-Carboxylates and 1-Methyl-4- Phenylpiperidine-3-Carboxylic Acids.

The ^{1}H NMR spectra of the diastereomeric esters **[104]** and **[105]**, gave little conformational information: the H-4 (expected to be the most deshielded aliphatic proton) was not resolved sufficiently to allow measurements of axial and equatorial couplings. As a consequence, ^{1}H NMR data of the two separated ester products were not used to provide any stereochemical conformation discussed by Clarke *et al.*,[188]. The mass spectra of the different isomers were obtained, there were some common peaks in both spectra, but a few fragmentation ions detected in the β-isomer were not present in the spectrum of the α-isomer (See Experimental).

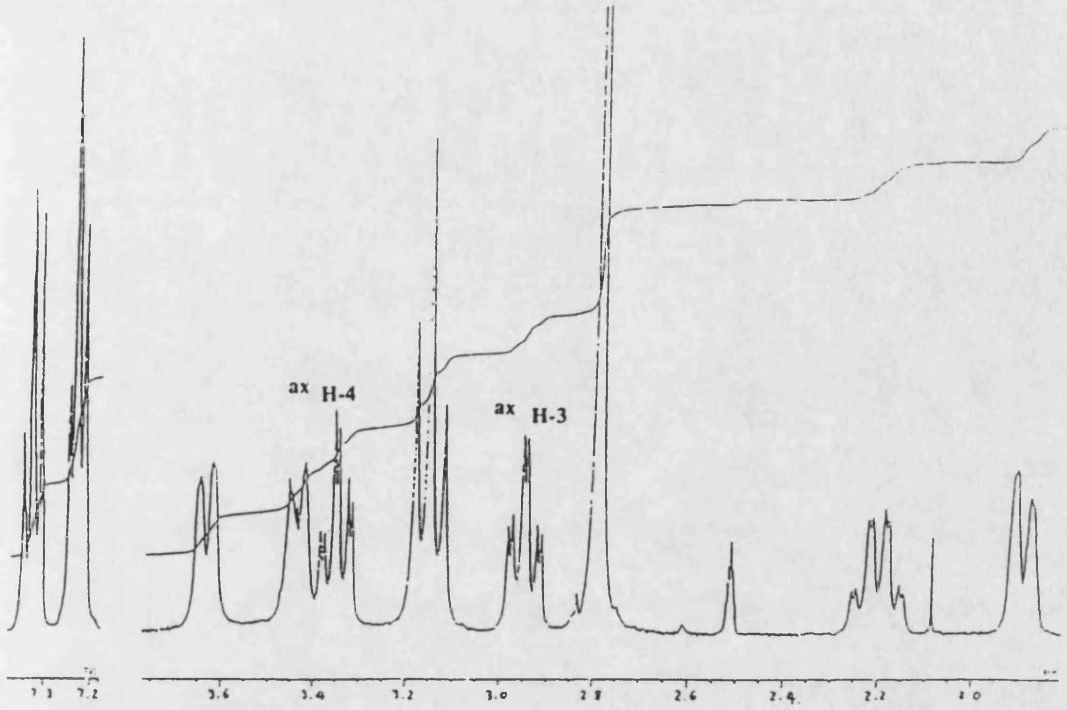
The ^{1}H NMR of the two 1-methyl-4-phenylpiperidine-3- carboxylic acids **[106]** and **[107]** showed marked differences (See spectra **11** and **12**). The ^{1}H NMR of the α-acid showed a spectrum in which individual signals were resolved sufficiently for the assignment of individual protons. Using literature references[170], it was calculated that the most deshielded protons (δ3.65-3.45) of the piperidine ring are the protons situated in the 2-position. These protons would be more deshielded than the H-6 protons due to the β-deshielding effect of the 3-carboxyl substituents.

A triplet of doublets at δ3.39 was assigned to the axH-4 proton. Coupling constants of 3.5Hz. and 8.2Hz were measured. Another triplet of doublets at δ2.97 with similar coupling constants was assigned to the axH-3 proton.

The triplet at δ3.18 (which integrated to two protons) was assigned to the axial H-2 and axial H-6 protons. The multiplet centered at δ3.65 was assigned to the equatorial H-2. The multiplet centered around δ3.45 was assigned to the equatorial H-6. The most shielded protons were assigned to the H-5protons, in which the axial H-5 (δ2.21) was further downfield than the equatorial H-5 (δ1.91).

If the α-isomer has *trans* (*t*-3-COOH r-4-Ph) stereochemistry, then the H-3 proton would be axial to the H-4 proton. This was the case, as a triplet of doublets was encountered for the H-4 proton which coupled to two axial protons (axH-3 and axH-5), and one ax/eq interaction with the eqH-5 proton. The same type of splitting was observed for the H-3 signal (two ax/ax couplings with axH-4 and axH-2; one ax/eq coupling with eqH-2) (see Figure **21**).

SPECTRUM 11: 400 MHz ^{1}H NMR (DMSO-d_6) OF α-*TRANS*-(t 3-COOH-r-4-Ph) -1-METHYL-4-PHENYLPIPERIDINE-3-CARBOXYLIC ACID HCl [106].



SPECTRUM 12: 400 MHz ^{1}H NMR (DMSO-d_6) OF β-*CIS*-(c 3-COOH-r-4-Ph) -1-METHYL-4-PHENYLPIPERIDINE-3-CARBOXYLIC ACID HCl [107].

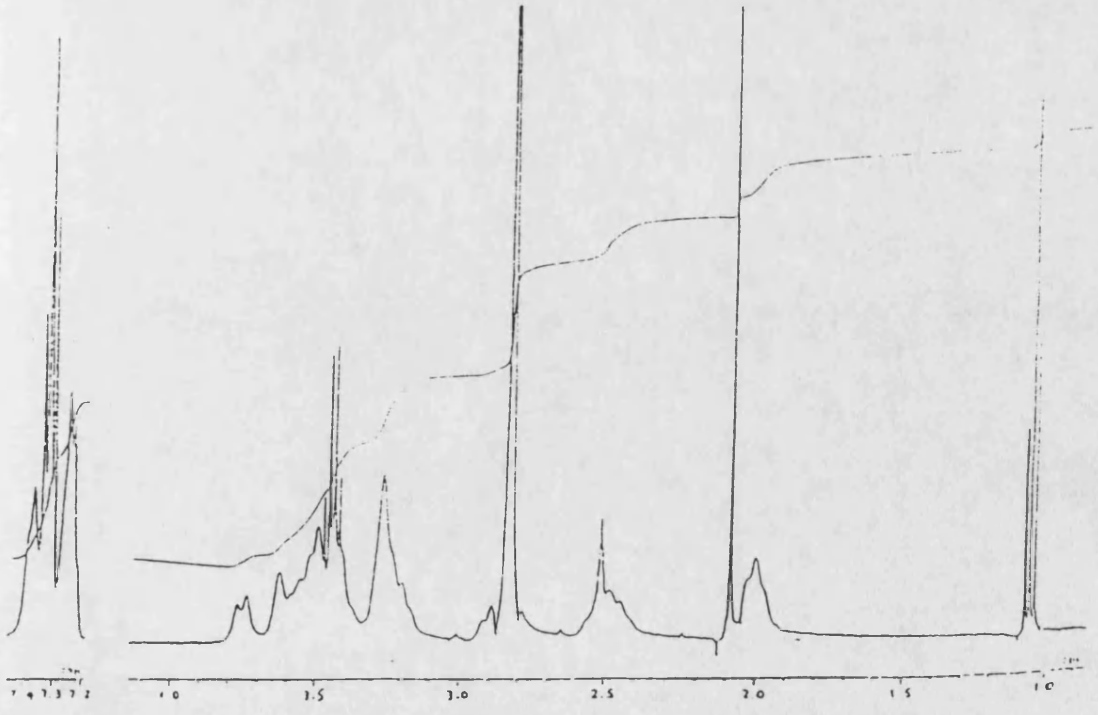
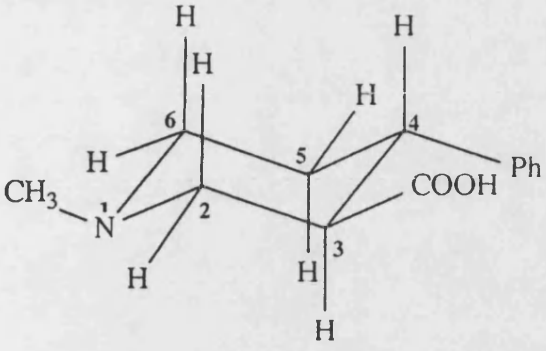


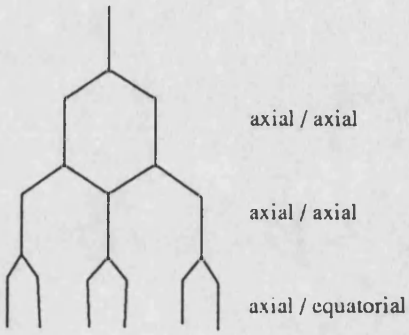
FIGURE 21.



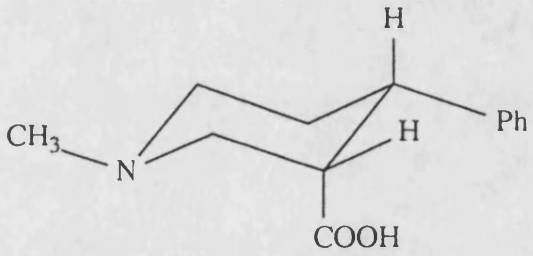
trans-isomer [**95**]

(*t*-3-COOH r-4-Ph)

Splitting Pattern For H-3 and H-4 Protons.



Thus the ^{1}H NMR analysis of the α-isomer of the acid [**106**] clearly indicates that it is the *trans* (*t*-3-COOH r-4-Ph) isomer where the 3- and 4-methine protons of the ring are situated in the axial plane. It was assumed that the β-isomer [**107**] (below) was the *cis* product where the 3-methine proton is equatorial with respect to the 4-methine proton.



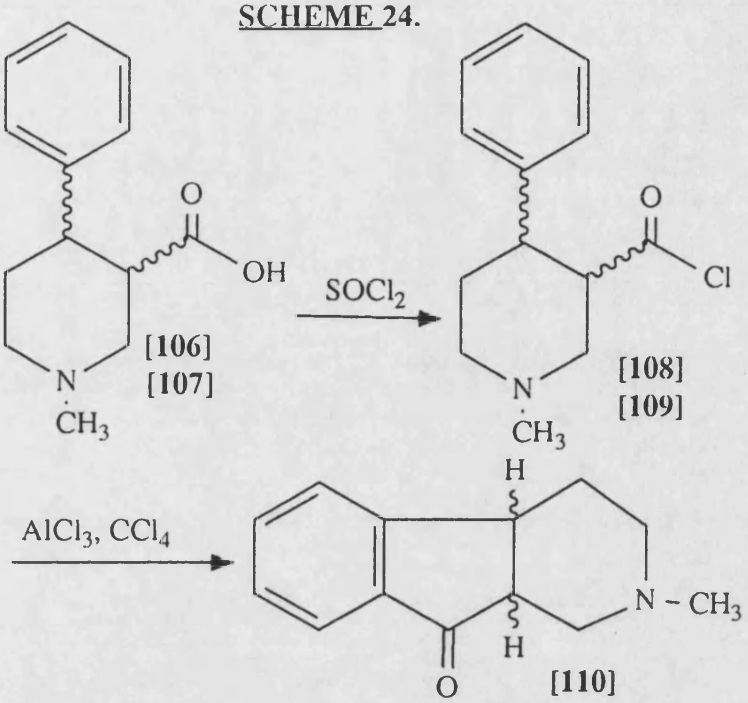
β-acid [**96**]

(*c*-3-COOH r-4-Ph)

2.7.2 Phenindamine Analogues.

The acids were treated with thionyl chloride to yield their corresponding acid chlorides, which were isolated. Friedel-Crafts acylation of the α- or β-acids with aluminium chloride gave the same product of 2-methyl-9-oxo-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-c] pyridine [**110**] in reasonable yields (40%) (Scheme **24**, below).

SCHEME 24.

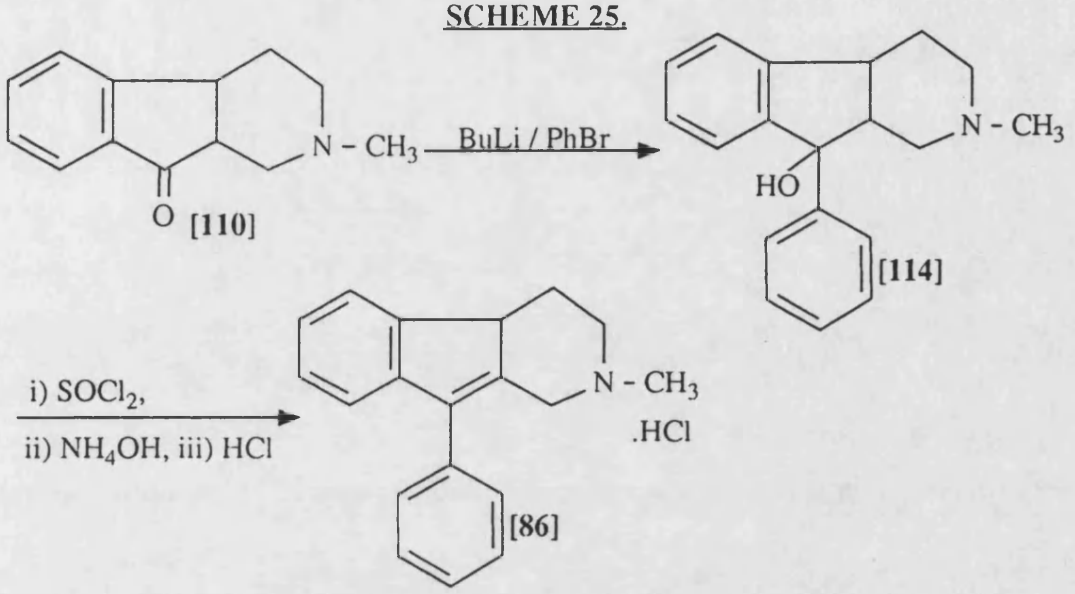


The ^{1}H and ^{13}C NMR of compound **[110]** isolated from the two separate reactions where the starting material was either the α- or the β-acids were identical. The melting point of the 9-keto product was very sharp indeed (190.5-191^{0}C). This indicated that the product can only be the one isomer. The infra red spectrum showed the presence of the C=O stretch at 1710 cm^{-1}. The ^{1}H NMR spectrum did not, however, give any information about the conformation of the ketone **[110]**. The ^{13}C NMR showed the presence of the C=O (δ201.81), and one signal each for the C-9a(δ45.24) and C-4a(δ33.92), all other carbon signals were detected and were not duplicated indicating that only one isomer was present.

Reaction of the ketone **[110]** with phenyllithium gave 9-hydroxy-2-methyl-9-phenyl-2,3,4,4a,9,9a-hexahydro-1*H*- indeno[2,1-c]pyridine **[114]** which was dehydrated to give phenindamine. The free base was converted to its hydrochloride salt and then recrystallized to give the 9,9a ene product **[86]** (Scheme **25**). The ^{1}H and ^{13}C NMR analysis of this product was identical to the one synthesised

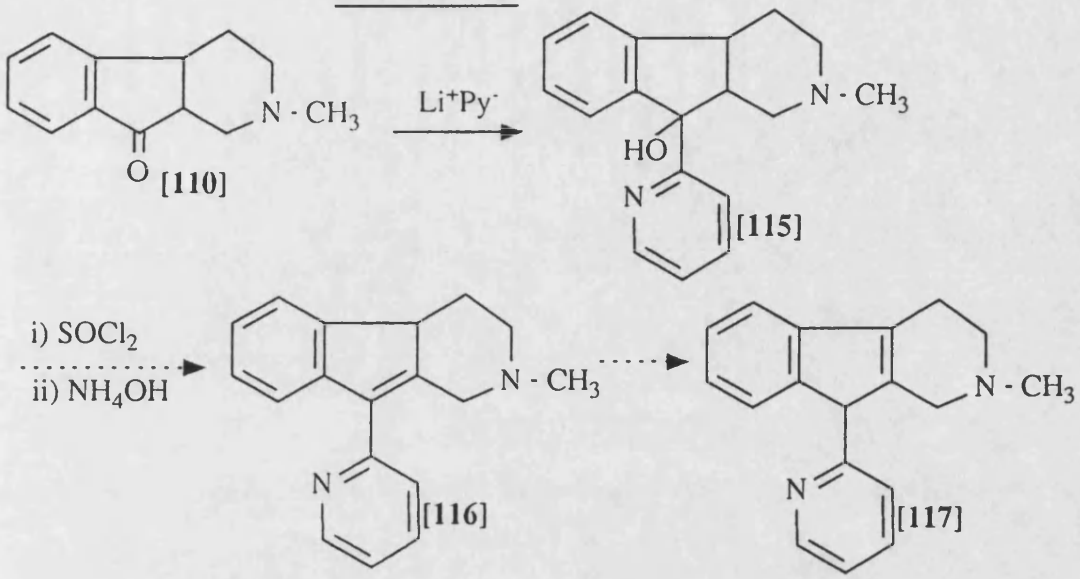
via the Mannich Route, and so was the melting point.

SCHEME 25.



Reaction of the same ketone **[110]** with 2-bromopyridine in the presence of butyllithium, afforded 9-hydroxy-2-methyl-9-(2-pyridyl)-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-c] pyridine **[115]** (Scheme **26**), in low yield. Mass spectral data showed the presence of the molecular ion ($M^{\cdot+}$ 280), as well as a fragment ion of magnitude 262, which could be attributed to the loss of water. Work was stopped at this stage. The eventual synthesis of compounds **[116]** and **[117]** would be desirable, as 2-pyridyl substituents have been implicated in antihistaminic activity (eg. Pheniramines).

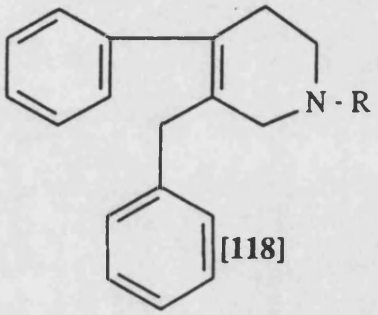
SCHEME 26.



Overall, this work did demonstrate that this synthetic route is feasible for the synthesis of aryl substituted analogues of phenindamine, especially if halogenated groups are required to be inserted in the aryl fractions.

2.8 OTHER PHENINDAMINE ANALOGUES.

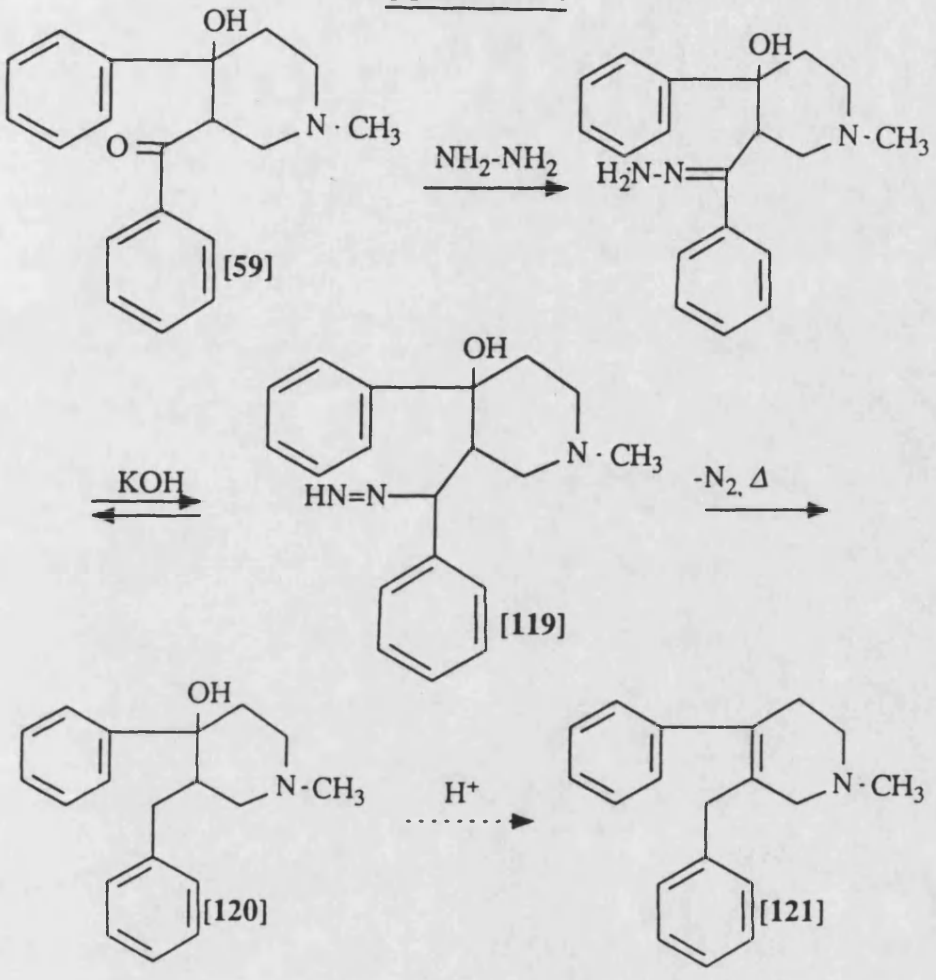
In *in vitro* studies, it was shown that 3-benzoyl-4-benzyl- 1-ethyl-4-phenylpiperidine **[60]** was a potent antagonist of histamine at the H_1-receptor (See Chapter 4). As a result, an investigation into the synthesis of analogues of phenindamine of type **[118]** below, whereby the rigidity of the phenindamine skeleton is "broken" at the 9,9a bond, was carried out.



[118]

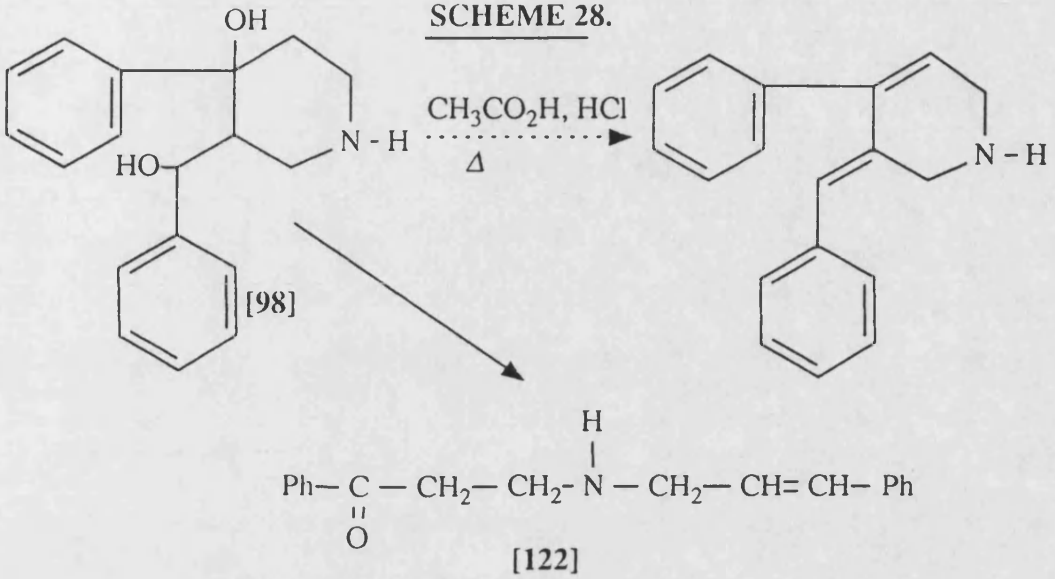
As shown in Scheme **27**, a Wolff-Kishner reaction of 3-benzoyl-4-hydroxy-1-methyl-4-phenylpiperidine **[59]** afforded the intermediate **[119]**, which when heated gave 3-benzyl-4-hydroxy-1-methyl-4-phenylpiperidine **[120]**. A number of dehydrating agents were employed to dehydrate compound **[120]** to give 3-benzyl-1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine **[121]**, but were unsuccessful. Due to this, another method was sought to try and synthesise the desired product **[121]**.

SCHEME 27.



It has already been discussed (section **2.61**) that the reduction product of 1-benzyl-3-benzoyl-4-hydroxy-4- phenylpiperidine **[72]** using palladium hydroxide and heat afforded 4-hydroxy-3-(α-hydroxybenzyl)-4-phenylpiperidine **[98]**. It was realized that dehydration of this compound would give 3-(benzylidene)-4-phenyl-1,2,5,6-tetrahydropyridine (an "open chain" analogue of the dienes). When the reaction was carried out however, NMR data showed that "ring-opening" had occurred, i.e. the desired product was not synthesised (Scheme **28**). At this stage, the reaction for the formation of "open chain" analogues of phenindamine was not further investigated.

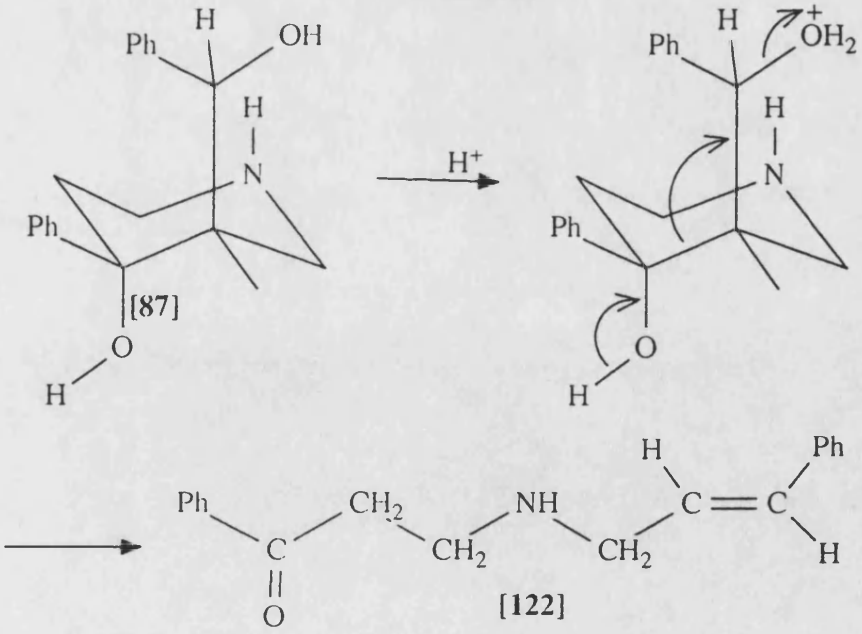
SCHEME 28.



[122]

The infra red spectrum of product **[122]** showed the presence of a carbonyl peak at 1690 cm^{-1}, which was absent from the starting material **[98]**. The ^1H NMR spectrum of compound **[122]** indicated that the product was in fact the **E**-isomer. The mechanism for this reaction is outlined below.

SCHEME 29.

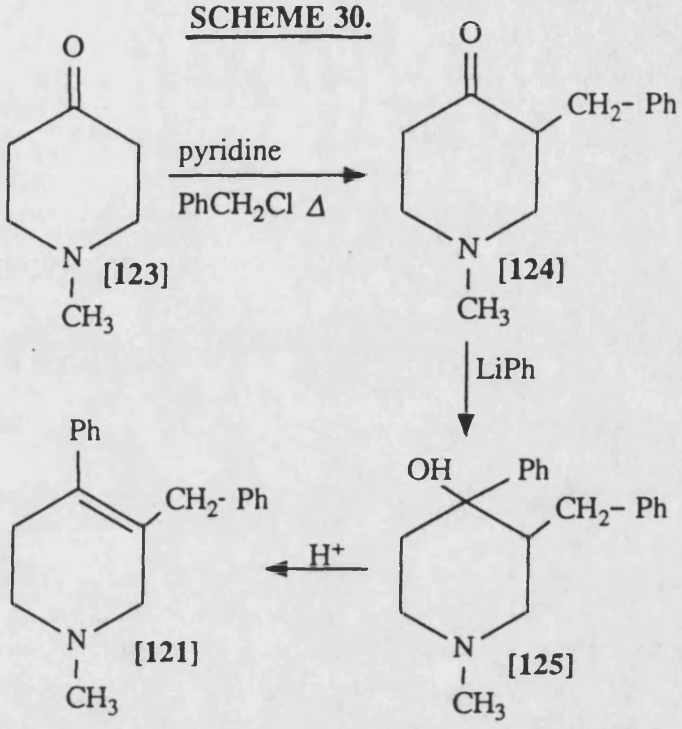


[122]

Further work on this topic would be to re-examine the synthesis of 3-benzyl-1-methyl-4-phenyl-1,2,5,6- tetrahydropyridine **[121]** *via* the pathway depicted

in Scheme 30, which utilises 1-methyl-4-piperidone [123] as the starting material.

SCHEME 30.



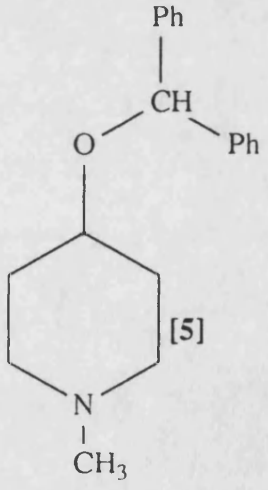
This route (the enamine route) would in fact be useful as various aromatic substituents may be inserted in compounds [124] and [125] to produce different analogues.

CHAPTER 3.
THE HISTRYL WORK.

3.1 INTRODUCTION.

This chapter deals with the synthesis and conformational studies of novel diastereomers of Histryl as potential histamine H_1-antagonists. This work was undertaken as a result of the ^1H NMR evidence provided for the precise structure of Histryl, which was shown to exist as two clearly defined conformers (See section **3.12.2**).

Histryl [5] (1-methyl-4-piperidyl benzhydryl ether hydrochloride), was first synthesised in 1949[73], and was found to be a potent antihistaminic with sedative side effects[74]. Histryl is still in clinical use today and is marketed by SmithKline Beecham[189,190]. Histryl is also used in combination with other drugs to counter the effects of the common cold[191]. Apart from its antihistaminic activity, Histryl was found to have marked anticholinergic and anaesthetic properties. Histryl had negligible sympathetic and narcotic activity[74].



[5]

3.1.1 Aims and Objectives.

The primary aim of this work is to examine conformational aspects of Histryl using ^1H NMR spectroscopy. A second aim will be to prepare and fully characterize diastereomeric analogues of Histryl as potential H_1-histamine antagonists.

The detailed aims and objectives of part of this work entails:-

1) An examination of the conformation of Histryl using modern NMR techniques.

2) The synthesis of 1,2- and 1,3-dimethyl-4-piperidones.

3) The synthesis and separation of diastereomeric 1,2- and 1,3-dimethyl-4-piperidinols.

4) Conformational studies of the piperidinols using NMR experiments.

5) Synthesis and stereochemical studies of diastereomeric Histryl analogues.

6) Biological evaluation of the Histryl analogues synthesised.

3.12 Structure of Histryl.

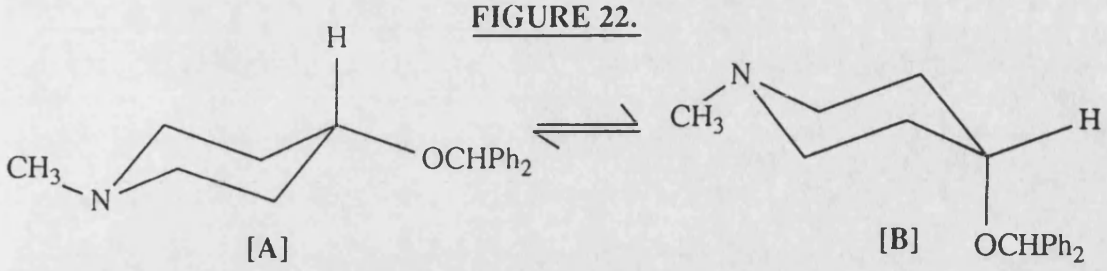
The structure of Histryl was derived from the diphenylhydramine "backbone", however, a piperidyl ring was introduced. Histryl, like many other classical antihistamines contains not only the CH_2CH_2N fragment, but also the X-$CHAr_2$ group (See section **1.2**). Due to the presence of the piperidyl ring in the molecule, Histryl may exhibit two different conformers, the significance of which is discussed next.

3.12.1 Conformation of Histryl.

Histryl can exist as two conformers, one in which the 4-methine proton of the ring is in the equatorial position, and the other when it is in the axial plane (Figure **22**). The two conformers come about by the interconversion of the two possible chair structures of

the molecule. Chemical shifts and coupling constants of these protons in both conformers would be different for both structures.

FIGURE 22.

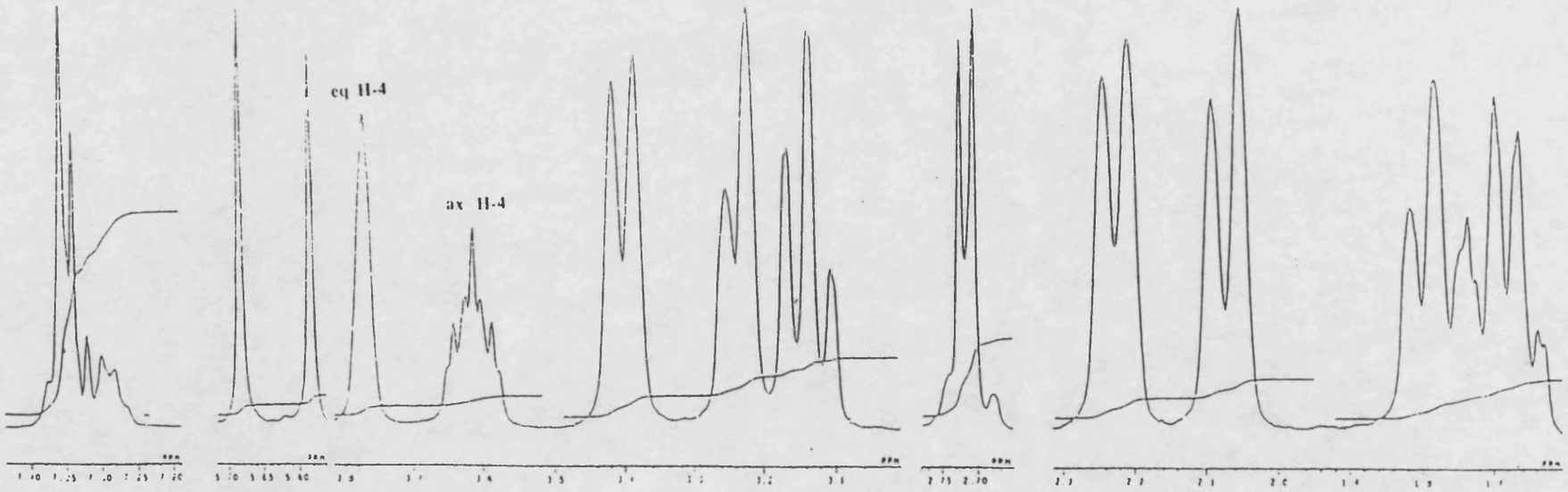


3.12.2 Conformational Analysis of Histryl.

A 400MHz ^{1}H NMR of Histryl (Spectrum **13**) showed a broad signal at δ3.8 and a septet at δ3.61 each signal integrating to 0.5 of a proton. The chemical shifts of both signals were consistent with literature value for the methine signal of the general structure RCH-OR (δ3.7 where R is an alkyl group)[170]. Poor resolution of most of the signals led to the use of a technique of measuring base widths and half widths of the undefined signals previously reported by Ison and Cas; [81]. The base width is a measure of the base of the signal (in Hz), and the half width is a measure of the width of the signal at half its height (also in Hz).

The broad signal (δ3.8) had a base width of 24 Hz, and a more accurate half width of 9 Hz, which corresponds to a signal of a proton experiencing two axial/equatorial and two equatorial/equatorial couplings. The literature[170] average of axial/equatorial and equatorial/equatorial is in the region of 5-6 Hz. This confirms that the 4-methine proton is in an equatorial position. The apparent septet (δ3.6) corresponds to two di-axial and two axial/ equatorial couplings. The base width is 40 Hz. Moreover, the ^{1}H NMR spectrum of histryl, shows a doubling-up of all the remaining signals confirming that there are two conformers present in the compound. The N-methyl signal shows two singlets (δ2.71 and δ2.73), similarly, two singlets are observed for the Ph_2CH-O- proton (δ5.6 and δ5.7).

SPECTRUM 13: 400 MHz ^{1}H NMR (D_2O) OF HISTRYL.



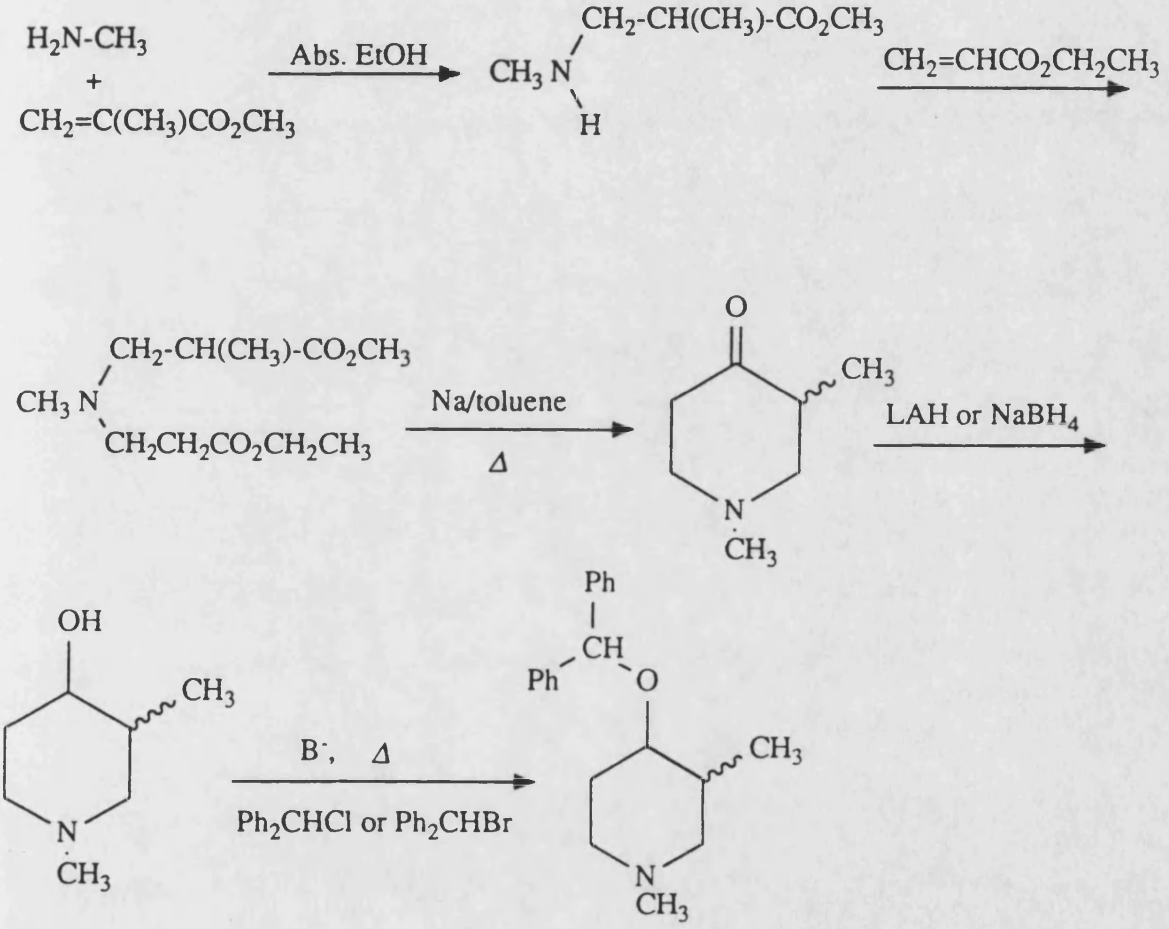
The remaining protons of the spectrum were assigned on chemical shift grounds. The equatorial H-2 proton was shown to be a broad signal at δ3.4. A broad signal was also observed at δ3.2 and was assigned to the equatorial H-6 protons. At δ3.1, an undefined triplet of doublets was assigned to the axial H-2. At δ2.7, the signal showed a multiplet which corresponded to 4 protons, this signal corresponds to the N-methyl proton with the extra proton assigned to the axial H-6 proton. The broad signals at δ2.2 and δ2.1 were assigned to the equatorial H-3 proton and the equatorial H-5 proton respectively. Lastly, a multiplet at the range δ1.8-1.7 which integrated to two protons were assigned to the axial H-3 and axial H-5 protons.

The fact that the 400MHz ^{1}H NMR of Histryl is showing two non-equivalent signals of the same protons indicates that interconversion rate of both possible conformers of Histryl is slow enough to be detected (Figure **22**). This phenomenon is known as NMR-slow. There are two possible reasons why most of the signals of the Histryl ^{1}H NMR spectrum are broad. One may be due to efficient relaxation and the other to environmental changes.

The "efficient relaxation" would not be acceptable in this case as it depends upon the interconversion of the histryl molecule from one conformer to the other being rapid enough as not to be detected within the NMR time scale (NMR-fast). In which case, an average signal of the same proton for both conformers would be observed as a broadened line (this is a consequence of the Heisenberg Uncertainty principle). It has already been discussed why there must be a slow NMR time scale.

The other alternative to why the signals are broadened must hence lie with the environmental exchange. This occurs when the rate constant for the exchange from one

SCHEME 31


H2N-CH3
+
CH2=C(CH3)CO2CH3
Abs. EtOH
CH2-CH(CH3)-CO2CH3
CH3 N
H
CH2=CHCO2CH2CH3
CH2-CH(CH3)-CO2CH3
CH3 N
CH2CH2CO2CH2CH3
Na/toluene
Δ
O
CH3
N
CH3
LAH or NaBH4
OH
CH3
N
CH3
B-, Δ
Ph2CHCl or Ph2CHBr
Ph
CH
Ph
O
CH3
N
CH3

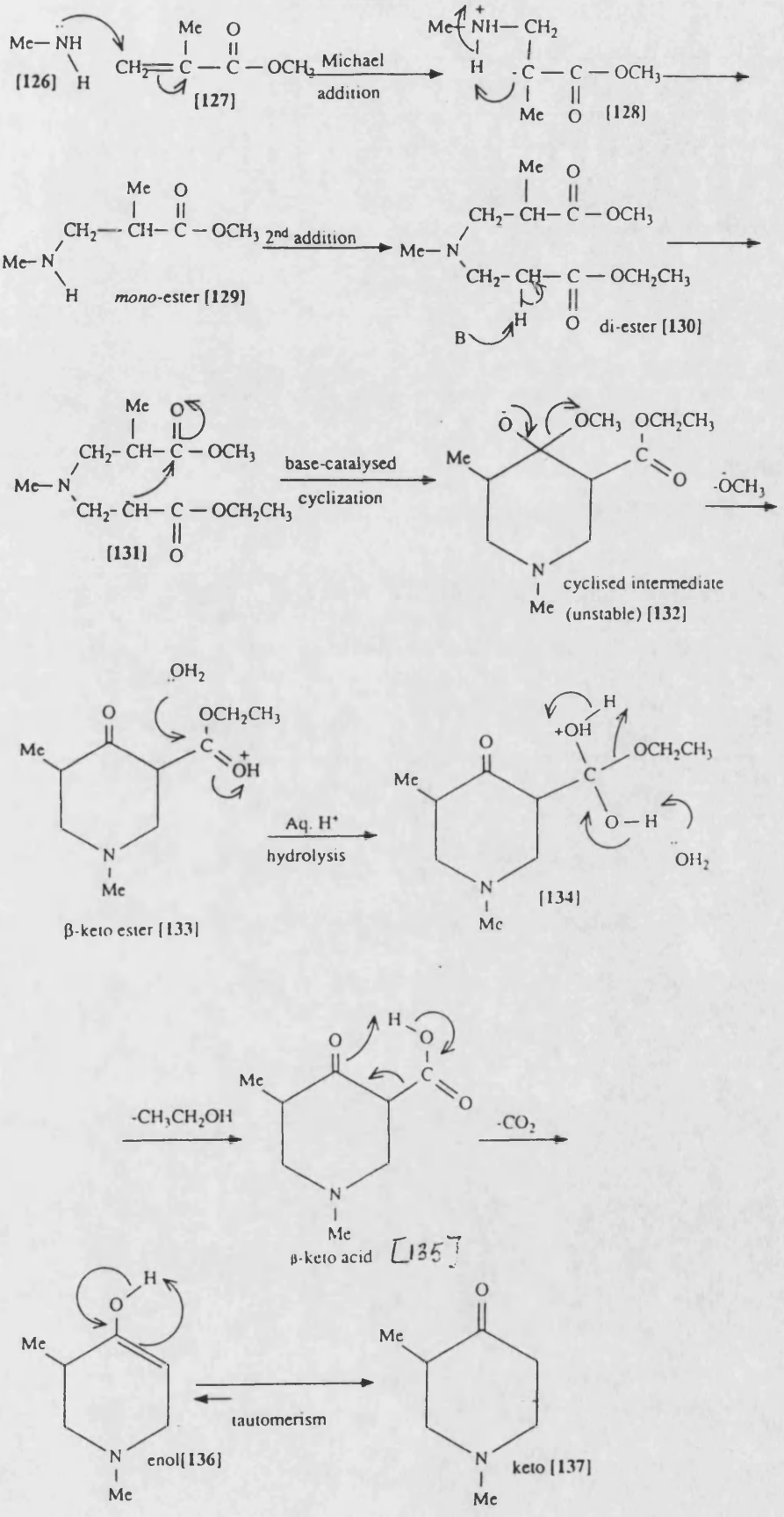
environment to another is greater than the frequency difference of the proton resonances in the separate environments. Thus at one extreme, if the rate of exchange is very slow, the proton will appear as separate signals, and at the other, when the rate of exchange is very fast, they appear as a single line. In between, as is the case in this example, when the rate constant is comparable to the frequency difference, broadened lines are detected.

From these deductions, it can be said that histryl exists as a 1:1 ratio of the 4-axial and 4-equatorial Ph_2CHO- conformers. As a consequence it was decided to try and synthesise and isolate conformationally restricted analogues of Histryl. It was considered this could be achieved by synthesising and separating analogues of novel diastereomeric analogues of Histryl by inserting a methyl group at the 2- and 3-positions of the piperidyl ring. This would enable pharmacological studies to be carried out to determine which conformer of Histryl confers biological activity and test the proposal[151] that three-dimensional Ar/Ar$^{\cdot}$ and N+ arrangement is an important criterion for activity. The pathway outlined in Scheme **31** was utilised for the synthesis of diastereomeric 1,3-dimethyl-4- piperidyl benzhydryl ethers. The first part of the synthesis involves the synthsis of 1,3-dimethyl-4- piperidone, which is discussed next.

3.2 1,3-DIMETHYL-4-PIPERIDONE.

The overall mechanistic pathway for the formation of 1,3-dimethyl-4-piperidone is shown in Scheme **32,** in which methylamine **[126]** takes part in a 1,4-conjugate Michael addition to methyl methacrylate **[127]**. The product anion **[128]** is formed which, in turn abstracts the available proton from the positively charged methylamine cation to yield methyl 2-methyl-3-(methylamino)propanoate **[129]**. A second Michael addition with ethyl acrylate takes place to give methyl

SCHEME 32.


Me— NH
H
[126]
Me O
CH2 = C — C — OCH3
[127]
Michael addition
Me— NH— CH2
H
C — C — OCH3
Me O
[128]
CH2— CH— C — OCH3
Me— N
H
mono-ester [129]
2nd addition
CH2— CH— C — OCH2CH3
di-ester [130]
B
CH2— CH— C — OCH3
CH2— CH— C — OCH2CH3
[131]
base-catalysed cyclization
OCH3 OCH2CH3
-OCH3
cyclised intermediate (unstable) [132]
OH2
OCH2CH3
OH
β-keto ester [133]
Aq. H+ hydrolysis
+OH
[134]
-CH3CH2OH
-CO2
β-keto acid [135]
enol [136]
tautomerism
keto [137]

3-[N-(2-ethoxycarbonylethyl)-N-methylamino]-2- methylpropanoate **[130]**.

In a Dieckmann cyclization, the base abstracts an acidic hydrogen α to one of the ester substituents. Out of the two possible α-hydrogens from the diester product **[130]**, the α-hydrogen of the methyl methacrylate chain is more stable, due to the +I effect of the methyl group, and hence less acidic than the α-hydrogen of the ethyl acrylate chain. Consequently, the abstraction occurs at the latter chain yielding an ester enolate **[131]**: a nucleophilic addition to the second ester substituent giving the cyclized intermediate **[132]**. The intermediate is not stable and hence expels the methoxide ion to yield the β-keto ester **[133]**. The expelled methoxide ion converts the product into the ketone. This drives the reaction to completion.

In the presence of aqueous acid, the ester is first activated **[134]** towards nucleophilic attack by the protonation of the carboxyl oxygen atom. Nucleophilic attack by water, followed by the transfer of a proton and elimination gives the β-keto acid **[135]**. On heating (over 100°C), the β-keto acid **[135]** is decarboxylated by a cyclic mechanism. The initial product is an enol **[136]**, which rapidly converts to the corresponding ketone **[137]**.

The next section deals with the synthesis and separation of diasteromers of 1,3-dimethyl-4-piperidinols.

3.3 1,3-DIMETHYL-4-PIPERIDINOLS.

Reductions of cyclic ketones are well documented in the literature[192,193,194], both chemically and catalytically. By increasing the size of the reducing agents, the more of the thermodynamically less stable axial alcohol is thought to be produced. It is

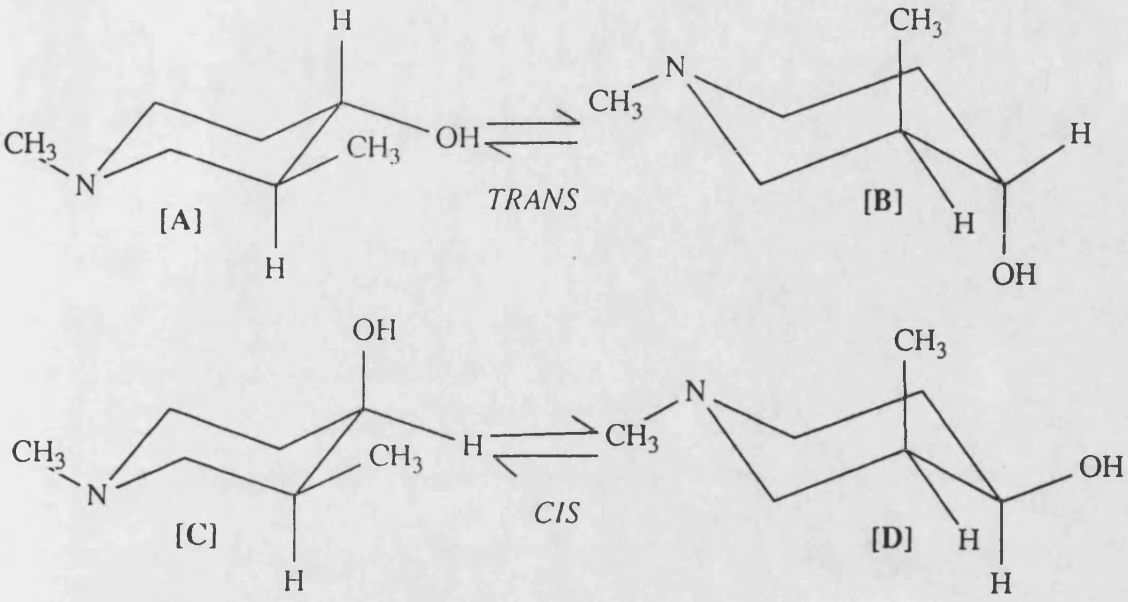
generally accepted that catalytic hydrogenation is thought to occur through *cis* addition of hydrogen to that side of the molecule which presents the least steric hinderance to adsorption by the catalyst[195].

Casy and Jeffries[196] reduced 1,3-dimethyl-4-piperidone **[137]** with lithium aluminum hydride (LAH) to give a diastereomeric mixture of 1,3-dimethyl-4-piperidinols **[138]** and **[139]**. They successfully isolated the α-isomer **[138]** as its hydrochloride salt. The β-isomer **[139]** was isolated as its methyl ester, which was then converted back to β-1,3-dimethyl-4-piperidinol **[139]**. The same authors[196] also postulated the conformation of the α- and β-isomers, which is discussed next.

3.31 Conformation of 1,3-Dimethyl-4-Piperidinols.

1,3-Dimethyl-4-piperidinol has two chiral centres, one in the 3-position and the other in the 4-position of the ring. This gives rise to four possible isomers (Figure 23). Two *trans* and two *cis* with respect to the positions of the 3-methyl and 4-hydroxyl substituents.

FIGURE 23.



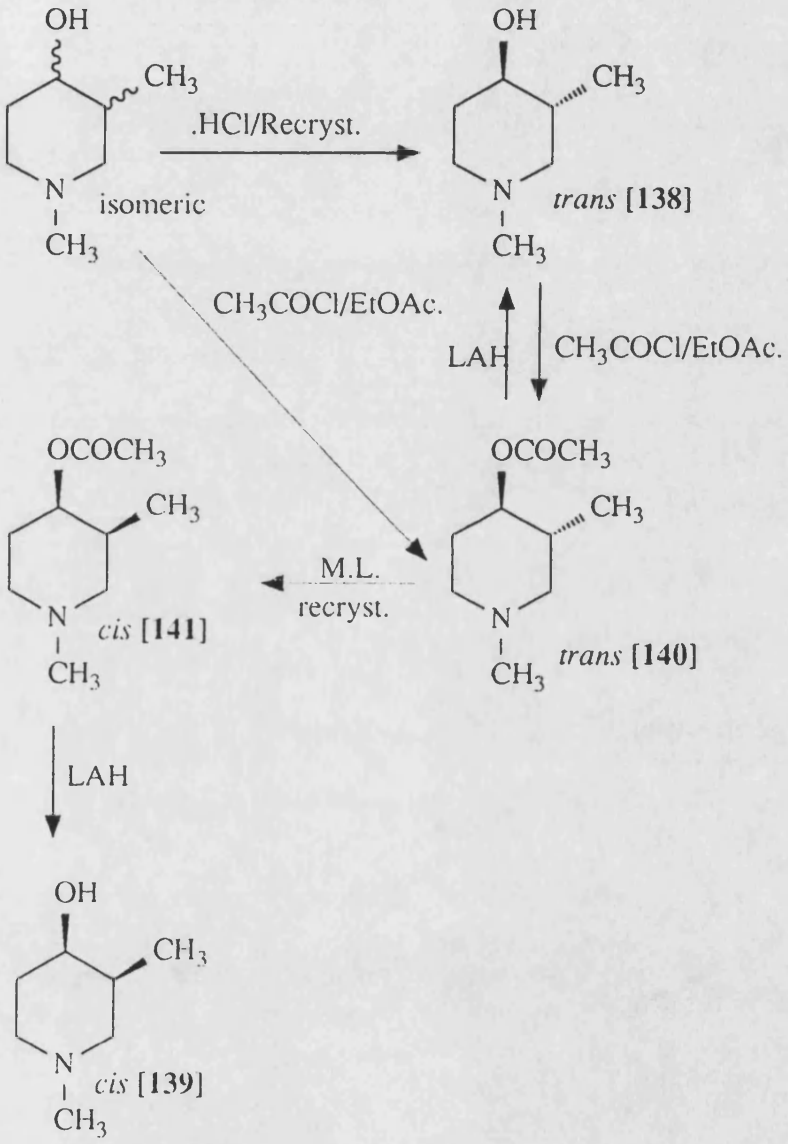
Casy and Jeffries[196] characterized the diastereomers of 1,3-dimethyl-4-piperidinols using a 60 MHz ^{1}H NMR and stipulated that the α-isomer was the *trans*-(*t* 3-Me r-4-OH)-1,3,-dimethyl-4-piperidinol of conformation **[A]** and the β-isomer was the *cis*-(*c* 3-Me r-4-OH)-1,3-dimethyl-4- piperidinol of conformation **[C]**. These findings were based on base width and half width measurements of the most deshielded protons (the 4-methines).

3.32 Synthesis of Diasteromeric 1,3-Dimethyl-4- Piperidinols.

The same procedure adopted by Casy and Jeffries[196] was used in this work (Scheme **33**), in which a mixture of isomeric 1,3-dimethyl-4-piperidinols (from LAH reduction) was converted to its hydrochloride salt and then recrystallized to give α-1,3-dimethyl-4-piperidinol HCl **[138]**. The only difference encountered from published results[196] was that the free base of α-1,3-dimethyl-4-piperidinol **[138]** synthesised in this work, was infact a low melting solid (34-36°C), and not an oil.

Derivatization of the diastereomeric piperidinols to the corresponding acetate esters **[140]** and **[141]** and subsequent recrystallization gave the pure β-acetate ester **[141]**. Reduction of the β-acetate ester **[141]** with LAH gave the β-1,3-dimethyl-4-piperidinol **[139]**.

SCHEME 33.



A number of reductive reactions were carried out on 1,3-dimethyl-4-piperidone **[137]** to give the corresponding piperidinols. When 1,3-dimethyl-4-piperidone **[137]** was reduced with lithium aluminum hydride (LAH) or aluminum isopropoxide, a mixture of isomers resulted. Similarly, when the piperidone was reduced catalytically with

platinum oxide at 50 psi a mixture of diastereomers of 1,3-dimethyl-4-piperidinols **[138]** and **[139]** was also afforded. In all of the reductive conditions, the piperidinols afforded were distilled under reduced pressure to give colourless oils.

3.33 Evidence of Structure of 1,3-Dimethyl-4-Piperidinols.

The infra red spectra of the 1,3-dimethyl-4-piperidinols showed the presence of a large signal at 3200 cm^{-1} corresponding to the OH stretch, which was absent in the starting material.

In order to ascertain the conformation of the piperidinols synthesized, the most deshielded signal of the ^1H NMR spectra, which was assigned to the 4-methine proton, was analysed. It was thought that the multiplicity of this signal, may provide coupling constants which would give sufficent information about the position of the 4-hydroxy and 3-methyl groups. Previous ^1H NMR characterization of the 1,3-dimethyl-4-piperidinols, were based base width and half width measurements of the 4-methine signals on 60 MHz ^1H NMR spectrometer[196] (See section **3.12.2**).

The ^1H NMR spectra of isomeric mixture of 1,3-dimethyl-4- piperidinols showed the presence of two lowest field signals assigned to the 4-methine protons. One was in the region of δ3.8 and the other at δ3.1. Both signals integrated to one proton, in which the most deshielded signal was assigned to the 4-methine proton in the equatorial position, and the other assigned to the 4-methine in the axial position[170]. In all of these spectra, the signals assigned to the H-4 protons were undefined, however, base width and half width measurements were calculated. Defined signals of these protons were observed in the corresponding esters (See section **3.34.1**).

The 270 MHz ^{1}H NMR of isomeric 1,3-dimethyl-4-piperidinol isolated from the LAH reduction showed an undefined doublet of doublets at δ3.8 assigned to the 4-methine proton situated in the equatorial position. The base width of this signal was measured at 17.8 Hz, whilst the more accurate half-width corresponded to 10.1 Hz. The base width of 17.8 Hz is accounted for by one axial/equatorial and one equatorial/equatorial coupling constants (2x5 Hz) with the H-5 protons as well as an axial/equatorial coupling constant with the axial H-3 proton (approx. 5 Hz), giving a total value of 15 Hz. The same spectrum also showed an undefined triplet of doublets at δ3.1 corresponding to 4-methine proton situated in the axial plane. The splitting patterns accounts for two di-axial (with axH-5 and axH-3) and one axial/equatorial (with eqH-5) interactions. A signal centred at δ2.3 assigned to the N-C$\underline{H}_3$ protons was duplicated.

The ^{1}H NMR spectrum of isomeric piperidinol isolated from the platinum oxide reduction (at 20 psi) showed a doublet of doublets at δ3.8 assigned to the 4-methine signal in the equatorial position. Coupling constants of 3.3 Hz and 6.6 Hz were measured. These coupling constants also verify that the 4-methine proton is situated in the equatorial position. The same spectrum also showed an undefined sextet at δ3.1 corresponding to the 4-methine signal in the axial plane. The ratios of the α- to β-isomers in the isomeric mixtures of the piperidinols were calculated by measuring the integral of the 4-methine signals from ^{1}H NMR spectra (Table 3), where α denotes the α-isomer whilst β denotes the β-isomer.

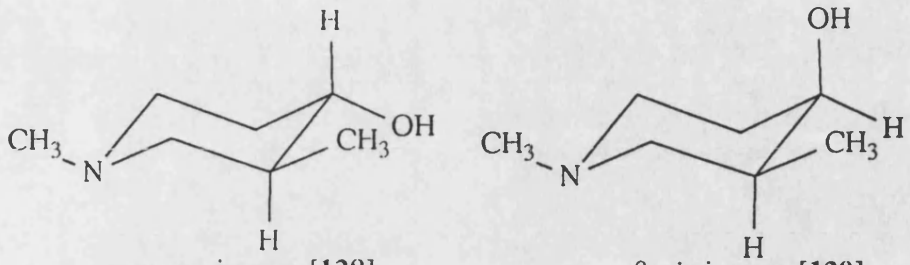
TABLE 3.

COMPOUND	CONDITIONS	α	β
1,3-Dimethyl-4-piperidone	$LiAlH_4$	30	70
1,3-Dimethyl-4-piperidone	$Al[OCH(CH_3)_2]_3$	50	50
1,3-Dimethyl-4-piperidone	Pt_2O / 50 psi	27	73
1,3-dimethyl-4-piperidone	Pt_2O / 20 psi	14	86

The 270 MHz ^1H NMR spectrum of the pure α-1,3-dimethyl-4- piperidinol HCl **[138]** gave an undefined triplet of doublets at δ3.1 integrating to one proton was assigned to the 4-methine proton in the axial plane. A singlet at δ2.2 was assigned to the N-$C\underline{H}_3$ protons.

The ^1H NMR spectrum of the β-1,3-dimethyl-4-piperidinol **[139]** showed an undefined doublet of doublets at δ3.8 was assigned to the 4-methine proton situated in the equatorial position. The base width was measured at 13.7 Hz and a half width measured at 7.8Hz.

To summerize, the ^1H NMR spectra of the various diastereomeric 1,3-dimethyl-4-piperidinols show conclusively that the α-piperidinol has the *trans* (*t*-3-Me r-4-OH) conformation with the 3-methyl and 4-hydroxyl groups of the ring equatorial to one another and that the β-piperidinol has *cis* (*c* 3-Me-r-4-OH) conformation with the 3-methyl group situated in the equatorial plane and the 4-hydroxyl group situated in the axial plane.



α-*trans*-isomer **[138]**
(*t* 3-Me-r-4-OH)

β-*cis*-isomer **[139]**
(*c* 3-Me-r-4-OH)

The next section deals with the conformation of the 1,3-dimethyl-4-piperidyl acetates to support the findings of the conformation of the 1,3-dimethyl-4-piperidinols discussed above.

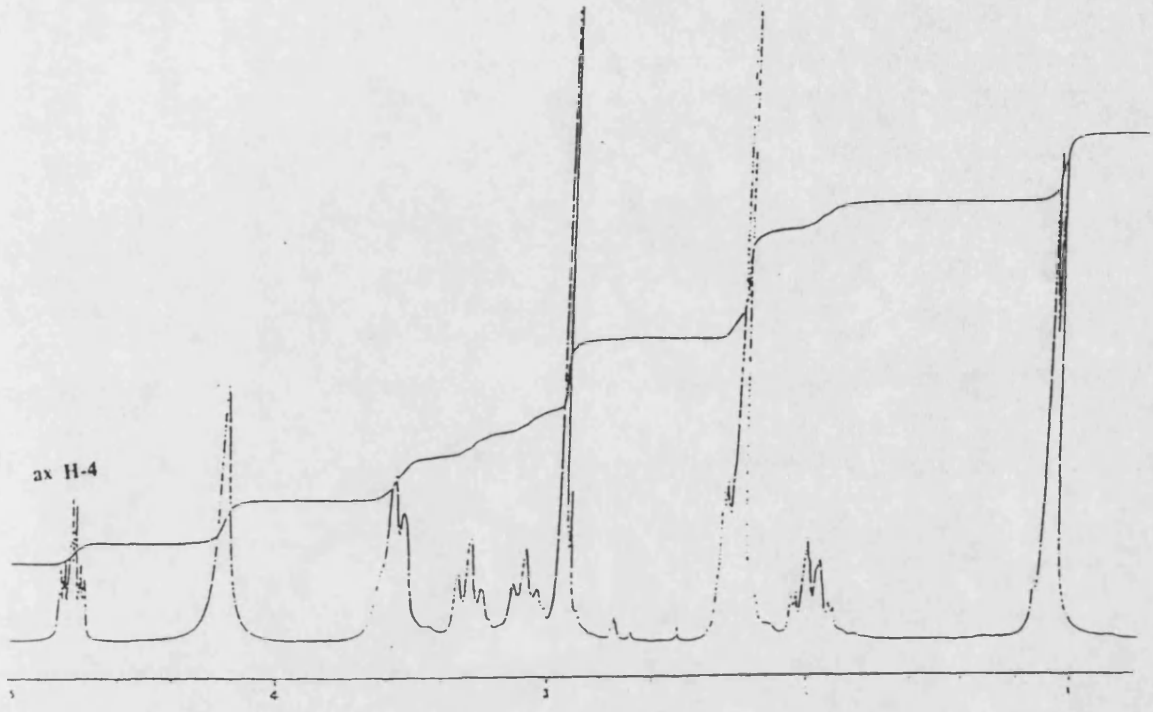
3.34 Synthesis of 1,3-Dimethyl-4-Piperidyl Acetate Esters.

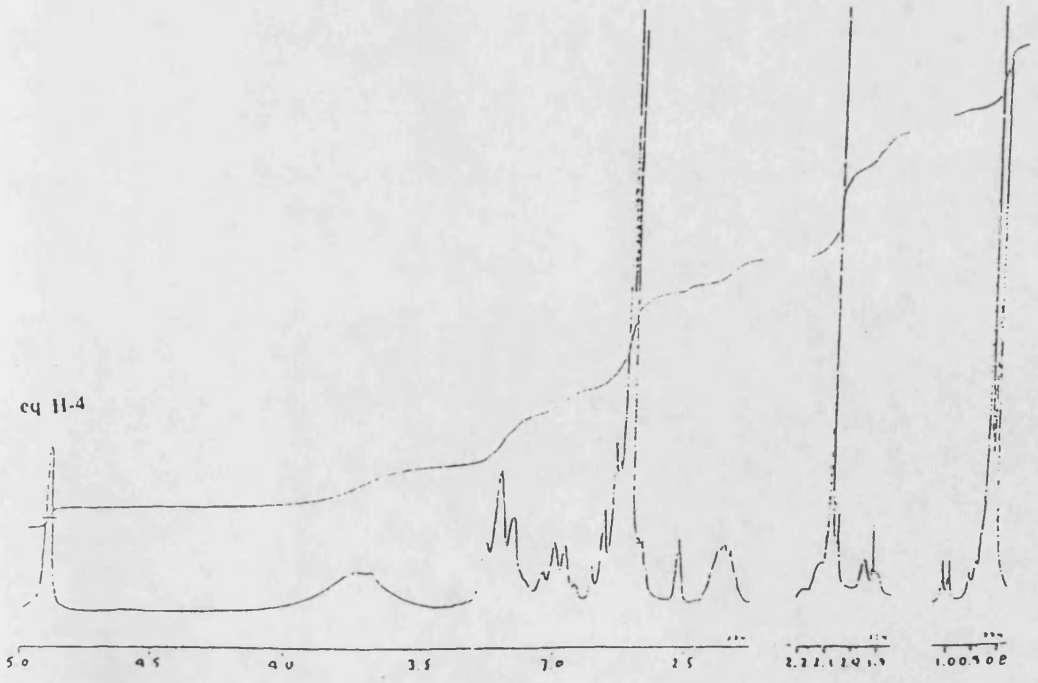
As discussed in section **3.32**, the α-isomer of 1,3-dimethyl-4-piperidinol **[138]** was isolated as the hydrochloride salt from the LAH reduction. Isolation of the β-isomer from the mother liquor was not achieved and so the crude residue (which contained mainly the β-isomer) was basified to liberate the free base which was treated with acetyl chloride to form the acetate ester. The β-1,3-dimethyl-4-piperidyl acetate HCl **[141]** was isolated from this reaction. The α-1,3-dimethyl-4-piperidinol **[138]** isolated as the hydrochloride salt, was basified and treated with acetyl chloride to yield the corresponding α-1,3-dimethyl-4-piperidyl acetate **[140]**. The acetates were prepared to validate the conformational assignments attributed to the precursor piperidinols.

3.34.1 Evidence of Structure of 1,3-Dimethyl-4-Piperidyl Acetate Esters.

The ^{1}H NMR spectrum of α-1,3-dimethyl-4-piperidyl acetate hydrochloride **[140]** (Spectrum **14**) showed a doublet of triplets centred at δ4.8. The peaks were resolved sufficiently to measure their coupling constants. Coupling constants of 6.1 Hz. were

SPECTRUM 14: 270 MHz ^{1}H NMR (DMSO-d_6) OF α-(*TRANS*)-1,3-DIMETHYL-4-PIPERIDYL ACETATE ESTER [140].





SPECTRUM 15: 270 MHz ^{1}H NMR (DMSO-d_6) OF β-(*CIS*)-1,3-DIMETHYL-4-PIPERIDYL ACETATE ESTER [141].

measured which corresponded to equatorial/equatorial or axial/equatorial interactions, and constants of 10.1 Hz corresponded to di-axial interactions. This signal confirms that the 4-methine proton must be situated in an axial position, which was expected as it is more stable, since the larger substituent prefers to be in the sterically less crowded equatorial position.

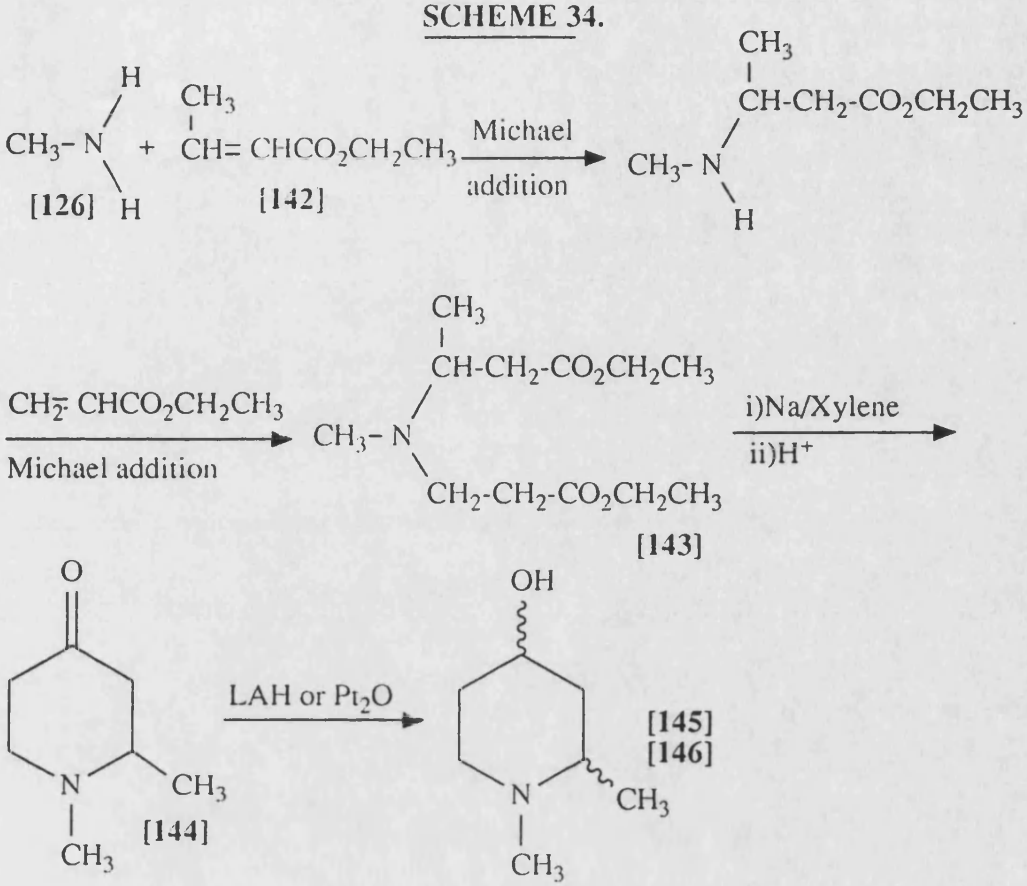
Spectrum **15**, shows the ^{1}H NMR of the pure β-1,3-dimethyl-4- piperidyl acetate ester hydrochloride **[141]**. The most deshielded proton was an unresolved signal at δ4.9 which was assigned to the 4-methine proton. The signal width was 21.0 Hz, and the half width was 6.0 Hz. These measurements confirm that the proton lies in the equatorial plane showing two equatorial/axial interactions with axial H-3 and axial H-5 as well as an equatorial/equatorial interaction with equatorial H-5.

Overall, the ^{1}H NMR evidence obtained from this work showed that the α-(*trans*)-isomers (*t*-3-Me r-4-OR) **[138]** and **[140]** had the 3-methine and 4-methine protons in the axial positions giving rise to the highly stable axial-axial conformation. The β(*cis*)-isomers (*c*-3-Me-r-4-OR) **[139]** and **[141]** had the 3-methine proton in an axial position whilst the 4-methine was in the equatorial position.

3.4 1,2-DIMETHYL-4-PIPERIDINOLS.

Other Histryl analogues may be synthesised by inserting a methyl substituent in the 2-position of the ring rather than in the 3-position. The synthesis (Scheme **34**) involved the stepwise Michael addition of ethyl crotonate **[142]** and then ethyl acrylate to methylamine **[126]** yielding the diester **[143]**. This diester in the presence of a strong base, underwent Dieckmann cyclization followed by decarboxylation gave 1,2-dimethyl-4-piperidone **[144]**.

SCHEME 34.



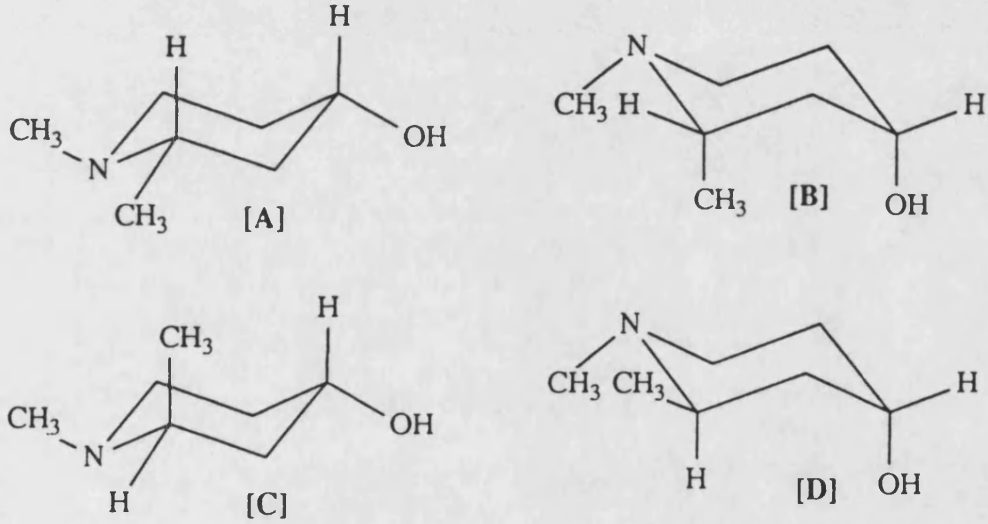
Reduction of 1,2-dimethyl-4-piperidone **[144]** with platinum oxide at room temperature, under hydrogen gave the β-1,2-dimethyl-4-piperidinol **[146]** exclusively as a white solid.

Reduction of 1,2-dimethyl-4-piperidone **[144]** with LAH gave a mixture of diastereomers (α-**[145]** and β-**[146]**). When the free bases were converted to the corresponding HCl salts, and recrystallized from ethanol, α-1,2-dimethyl-4- piperidinol HCl **[145]** crystallized out. Like the previous examples (See section **3.32**) it was not possible to obtain a pure sample of the β-isomer from the mother liquor.

3.41 Conformational Analyses of 1,2-Dimethyl-4- Piperidinols.

Like the 1,3-dimethyl-4-piperidinols, the 1,2-dimethyl-4- piperidinols possess two chiral centres and hence four conformers can be drawn (Figure 24). Conformer [A] is possibly the most stable as both the methyl and hydroxyl substituents are situated in the more spacious equatorial planes. Conformer [B] is the least stable as the 2-methyl and 4-hydroxyl could suffer 1,3-diaxial interactions. Conformer [C] is probably more stable than conformer [D] due to steric hinderence that is encountered in the latter by the 2-methyl substituent with the N-methyl group.

FIGURE 24.



The next section of this work deals with the conformational analyses of the 1,2-dimethyl-4-piperidinols synthesised using ^{1}H and ^{13}C NMR data.

3.42 Evidence of Structure of 1,2-Dimethyl-4-Piperidinols.

A similar spectroscopic procedure used for ascertaining the conformations of 1,3-dimethyl-4-piperidinols was adopted to evaluate the conformations of 1,2-dimethyl-4-piperidinols, whereby the most deshielded protons encountered in the ^{1}H NMR spectra were assigned to the 4-methine protons. These signals were used to validate the conformation of 1,2-dimethyl-4-piperidinols. As a rule is assumed that

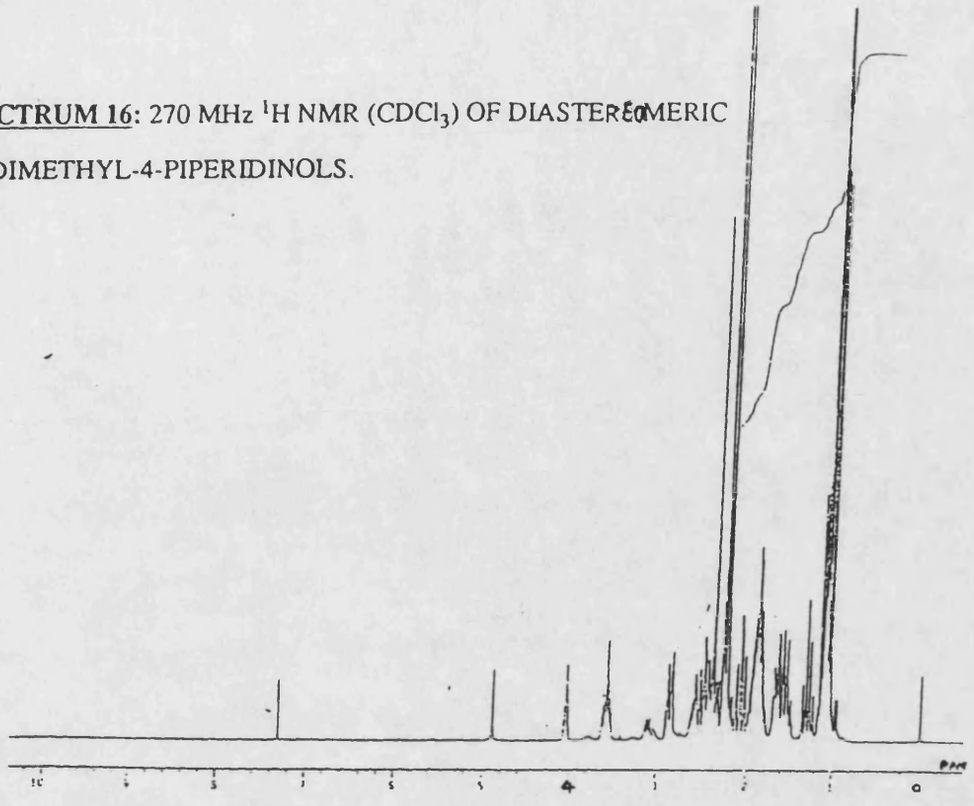
equatorial protons are more deshielded than axial ones[170] attached to the same carbon atom. This criterion was used to assign the equatorial and axial H-4 protons.

The ^{1}H NMR of diastereomeric 1,2-dimethyl-4-piperidinols (Spectrum **16**) (from LAH reduction) showed two signals, one at δ4.1 which integrated to 0.2 of a proton, and the other at δ3.66 which integrated to 0.8 of a proton, observed for the 4-methine proton. The quintet at δ4.1 with coupling constants of 3.4 Hz indicated that there are two axial/equatorial and two equatorial/equatorial interactions, and as such, this signal was assigned to the 4-methine signal in the equatorial position. The triplet of triplets at δ3.7 was assigned to the 4-methine in the axial position as coupling constants of 4.6 Hz were recorded for axial-equatorial interactions (with equatorial H-3 and H-5), and coupling constants of 11.2 Hz were recorded for axial-axial interactions (with axial H-3 and H-5).

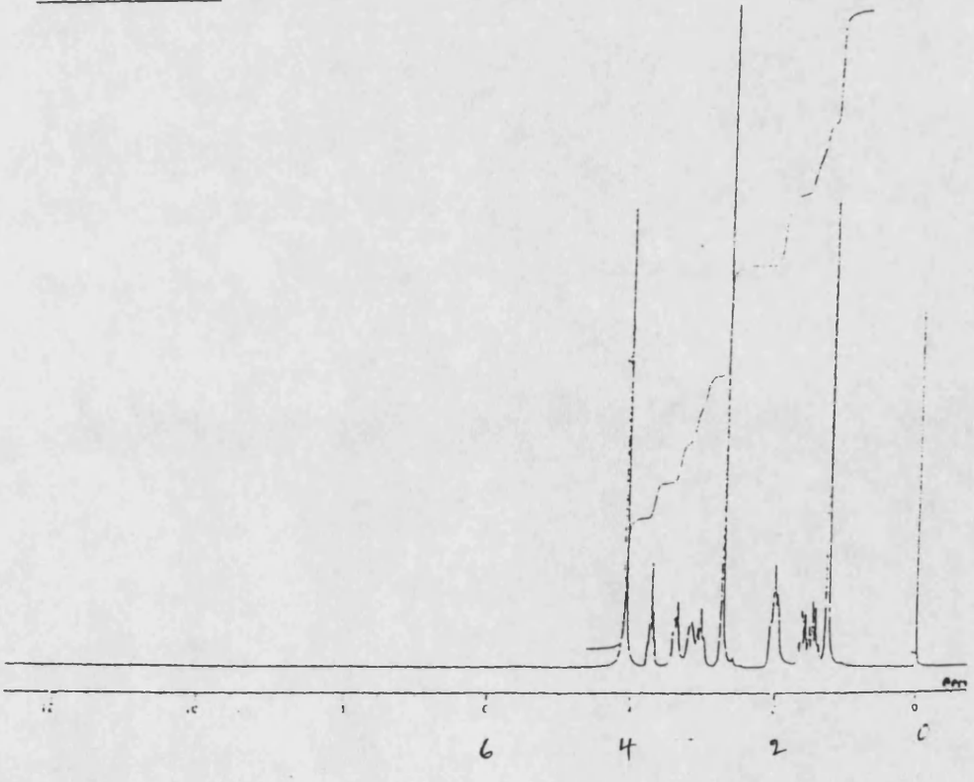
The ^{1}H NMR spectrum of α-1,2-dimethyl-4-piperidinol **[145]** (Spectrum **17**) showed only an undefined triplet of triplets at δ3.7 was present corresponding to the 4-axial methine proton (see above). The spectrum showed no signal at δ4.0 allocated to the 4-methine signal in the equatorial position. The β-1,2-dimethyl-4-piperidinol **[146]** isolated from the platinum oxide reduction, gave a broad peak at δ4.0 corresponding to the 4-methine signal in the equatorial position.

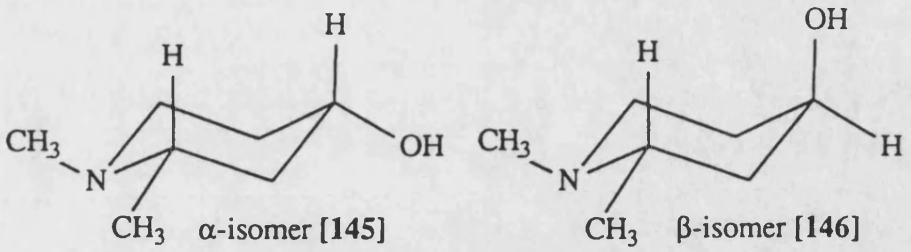
The ^{1}H NMR spectra of the 1,2-dimethyl-4-piperidinols confirm that the α-isomer has the 4-hydroxyl group in the equatorial position, and the β-isomer has the hydroxyl group in the axial position. The spectra however, did not provide sufficient information about the position of the of the 2-methyl substituent, although it was assumed that it was situated in the more spacious equatorial position.

SPECTRUM 16: 270 MHz ^{1}H NMR ($CDCl_3$) OF DIASTEREOMERIC 1,2-DIMETHYL-4-PIPERIDINOLS.



SPECTRUM 17: 270 MHz ^{1}H NMR ($CDCl_3$) OF α-1,2-DIMETHYL-4-PIPERIDINOL [145].





The ^{13}C NMR spectrum of diastereomeric 1,2-dimethyl-4- piperidinol showed doubling-up of most of the signals. Two different signals were clearly observed for the C-4 (δ68.37 and δ57.47), C-6 (δ55.07 and δ50.17), C-2 (δ43.40 and δ41.09), C-2 (δ42.68 and δ42.07) and C-5 (δ35.06 and δ32.92), although there was only one signal for the N-CH_3 (δ42.13) and for CH_3 at position 2 (δ20.47). The ^{13}C NMR spectrum of α-1,2-dimethyl-4-piperidinol showed the presence of only one signal for each carbon atom signifying that only one conformer was present.

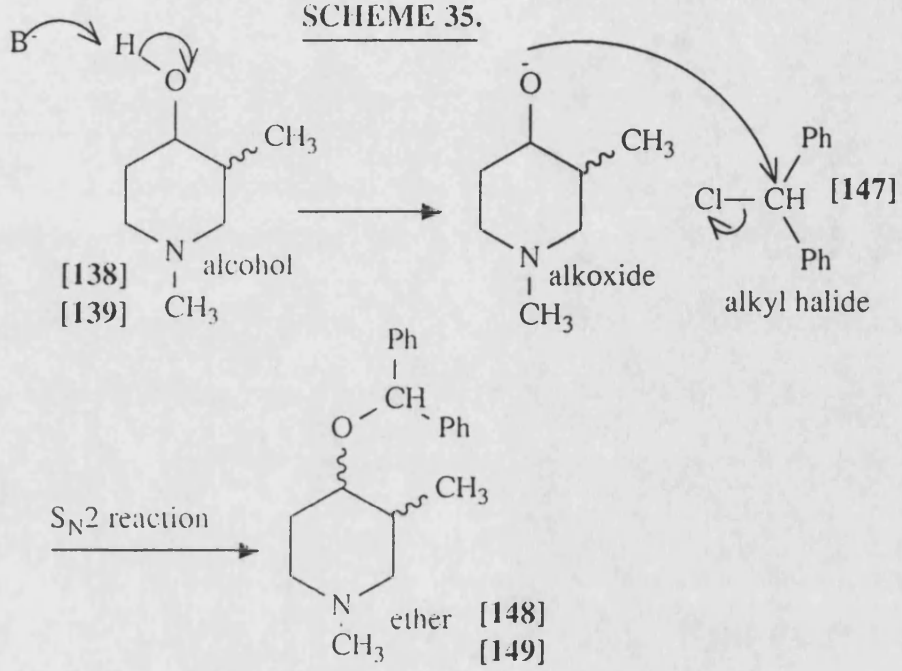
3.5 HISTRYL ANALOGES.

Papa and co-workers[197], synthesised a series of benzhydryl ethers by reacting the precursor alkyl piperidinols with benzhydryl bromides, and other aryl substituted benzhydryl halides in the presence of base. However, no conformational analyses were reported. Some of the compounds synthesised by Papa *et al.*,[197] exhibited prolonged antihistaminic effects as well as substantial anticholinergic properties. The next section of this work deals with the synthesis of novel conformationally restricted analogues of Histryl.

3.51 Synthesis of 1,3-Dimethyl-4-Piperidyl Benzhydryl Ethers.

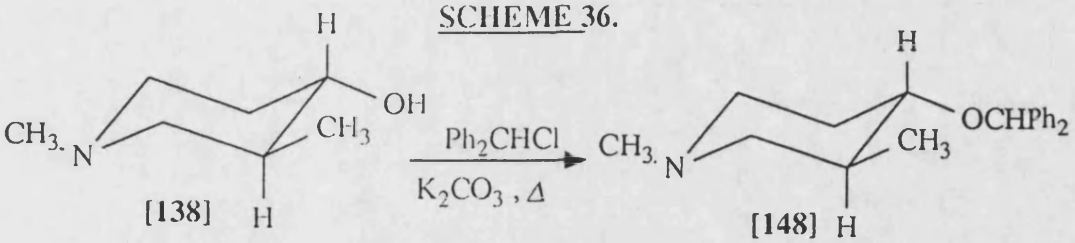
The Williamson synthesis (Scheme 35) depends upon the ionisation of the hydroxyl group of the alcohol by a suitable base, and the subsequent nucleophilic substitution by the alkoxide ion of the halide ion in the alkyl halide.

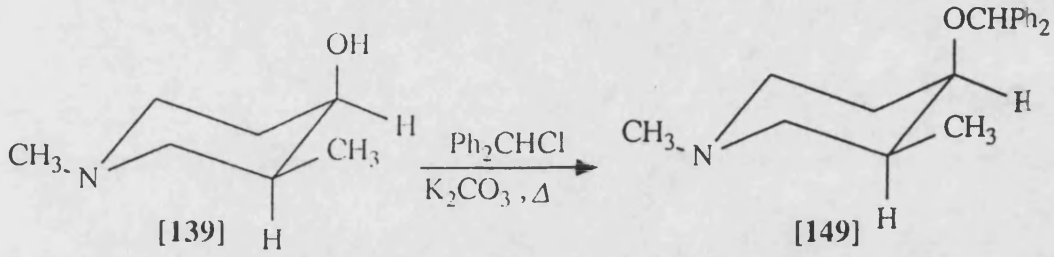
SCHEME 35.



As depicted in Scheme 36, the reaction of the *trans*-1,3-dimethyl-4-piperidinol **[138]**, in the presence of dry potassium carbonate, with chlorodiphenylmethane **[147]** was successful in yielding *trans*-1,3-dimethyl-4-piperidyl benzhydryl ether **[148]**. A similar reaction was employed using *cis*-1,3-dimethyl-4-piperidinol **[139]**. This reaction gave the desired product of *cis*-1,3-dimethyl-4-piperidyl benzhydryl ether **[149]**.

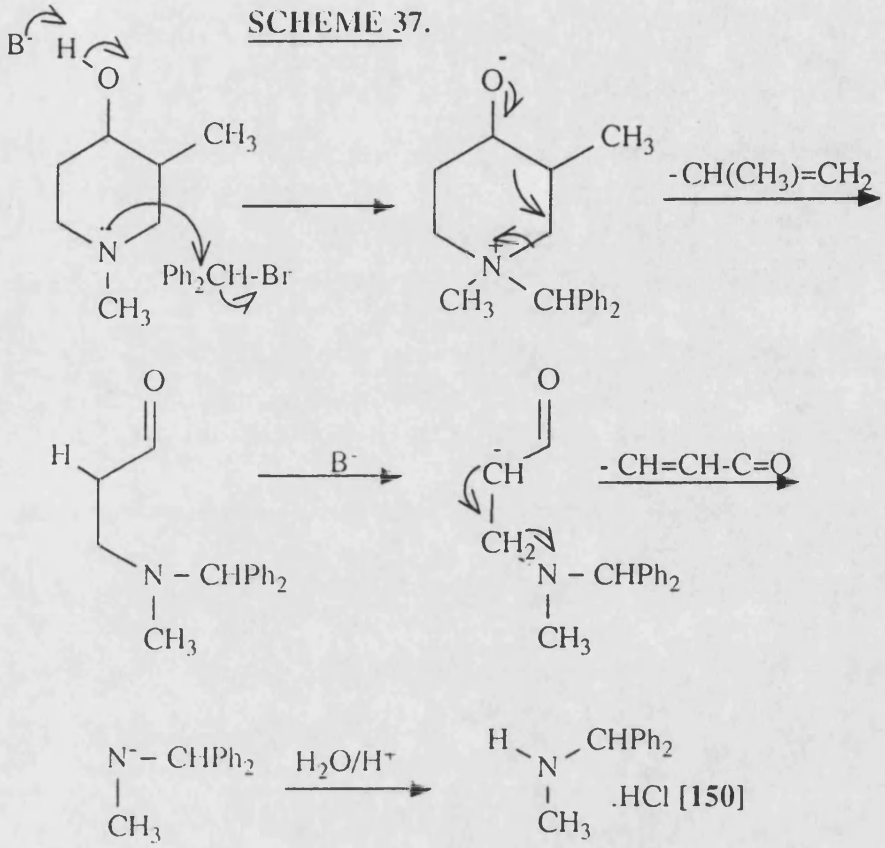
SCHEME 36.





Initial treatment of the *trans*-1,3-dimethyl-4-piperidinol **[138]** with bromodiphenylmethane in the presence of anhydrous potassium carbonate gave the starting material. A possible reason for the failure of the reaction was thought to have been concerned with steric hindrance. The bulky bromide atom may have impeded the reaction; this was overcome by using the alkyl chloride. When sodium hydride was employed as the base, only(N-diphenylmethyl) methylamine HCl **[150]** was isolatedin a 10% yield. This indicated that a degradation process of the type illustrated in scheme **37** had occurred, resulting in substitution by bromodiphenylmethane.

SCHEME 37.

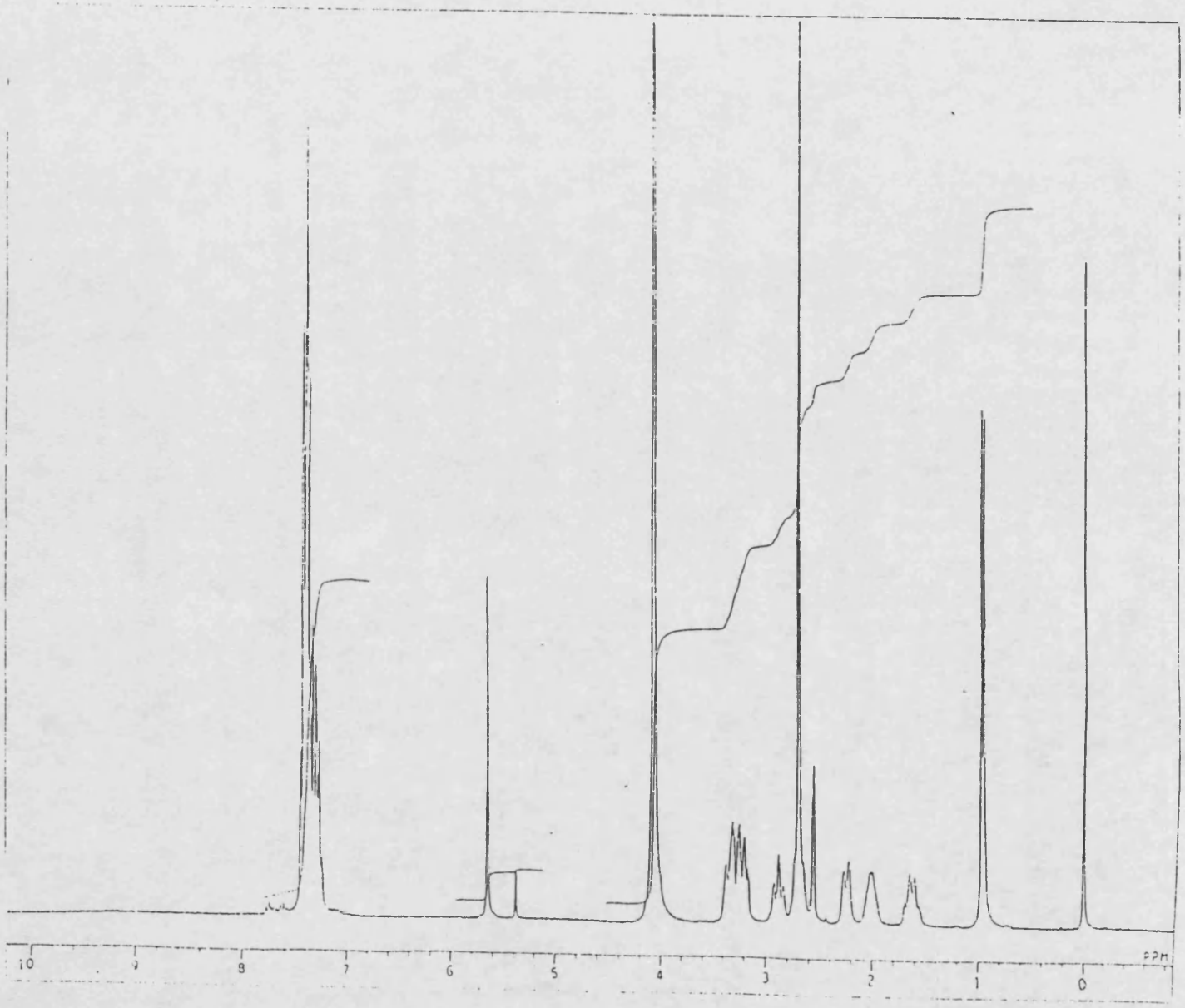


3.5.1.1 Evidence of Structure of 1,3-Dimethyl-4-Piperidyl Benzhydryl Ethers.

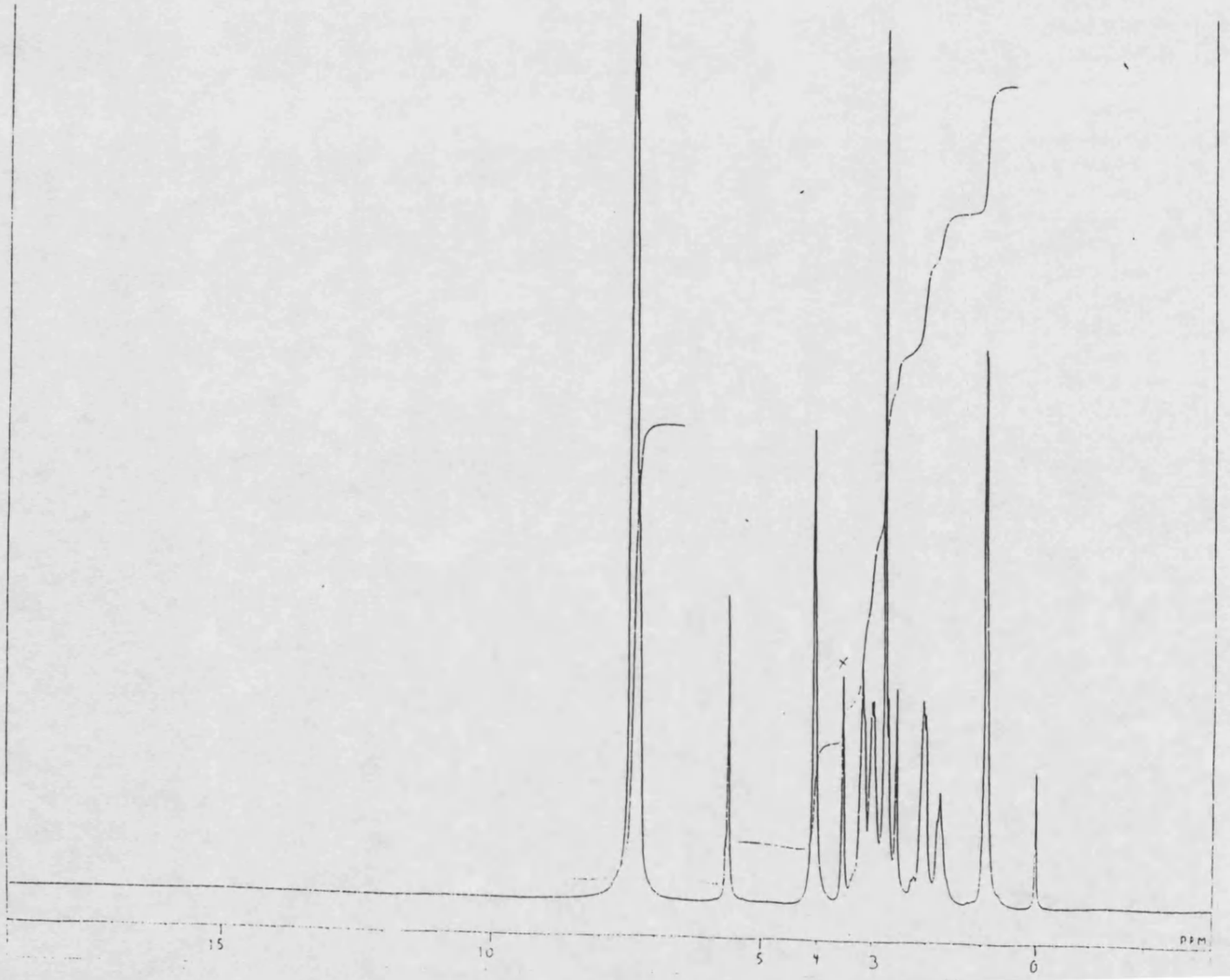
The ^{1}H NMR spectrum of *trans*-(*t*-3-Mer-4-OCHPh$_2$)- 1,3-dimethyl-4-piperidyl benzhydryl ether [**148**] (Spectrum **18**), derived from the pure *trans*-1,3-dimethyl-4-piperidinol, showed a multiplet at δ3.24 corresponding to three protons. This signal was assigned to the axial 4-methine, the equatorial H-2 and the equatorial H-6 protons. Due to the complexity of this signal, no conformational assignment was made.

The ^{1}H NMR spectrum of *cis*-(*c*-3-Me r-4-OCHPh$_2$)- 1,3-dimethyl-4-piperidyl benzhydryl ether [**149**] (Spectrum **19**) gave a broad signal at δ3.52 corresponding to one proton. This signal was assigned to the 4-methine proton an chemical shift grounds. The base width for this signal was calculated at 21.0 Hz, and the half width had a value of 9.0 Hz. These results were similar to those found for the precursor piperidinol

SPECTRUM 18: 270 MHz ^{1}H NMR (DMSO-d_6) OF *TRANS*-1,3-DIMETHYL-4-PIPERIDYL BENZHYDRYL ETHER HCl [148].



SPECTRUM 19: 270 ^{1}H NMR (DMSO-d_6) OF *CIS*-1,3-DIMETHYL-4-PIPERIDYL BENZHYDRYL ETHER OXALATE [149].

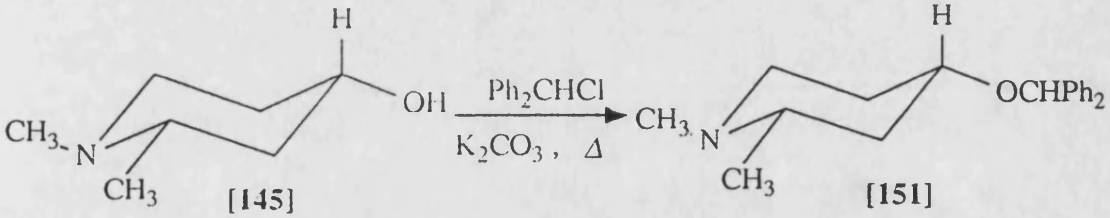


compound and hence the 4-methine proton was assigned to the equatorial position, with the benzhydryl substituent situated in the axial plane. This was unexpected as it was thought that a more stable conformer would be afforded by the bulky benzhydryl group occupying the equatorial plane through ring flipping.

3.52 Synthesis of 1,2-Dimethyl-4-Piperidyl Benzhydryl Ethers.

The free base of the α-1,2-dimethyl-4-piperidinol **[145]** was fused with chlorodiphenylmethane **[147]** in the presence of dried potassium carbonate in an anhydrous environment to give the corresponding α-1,2-dimethyl-4-piperidyl benzhydryl ether **[151]** (Scheme **38**).

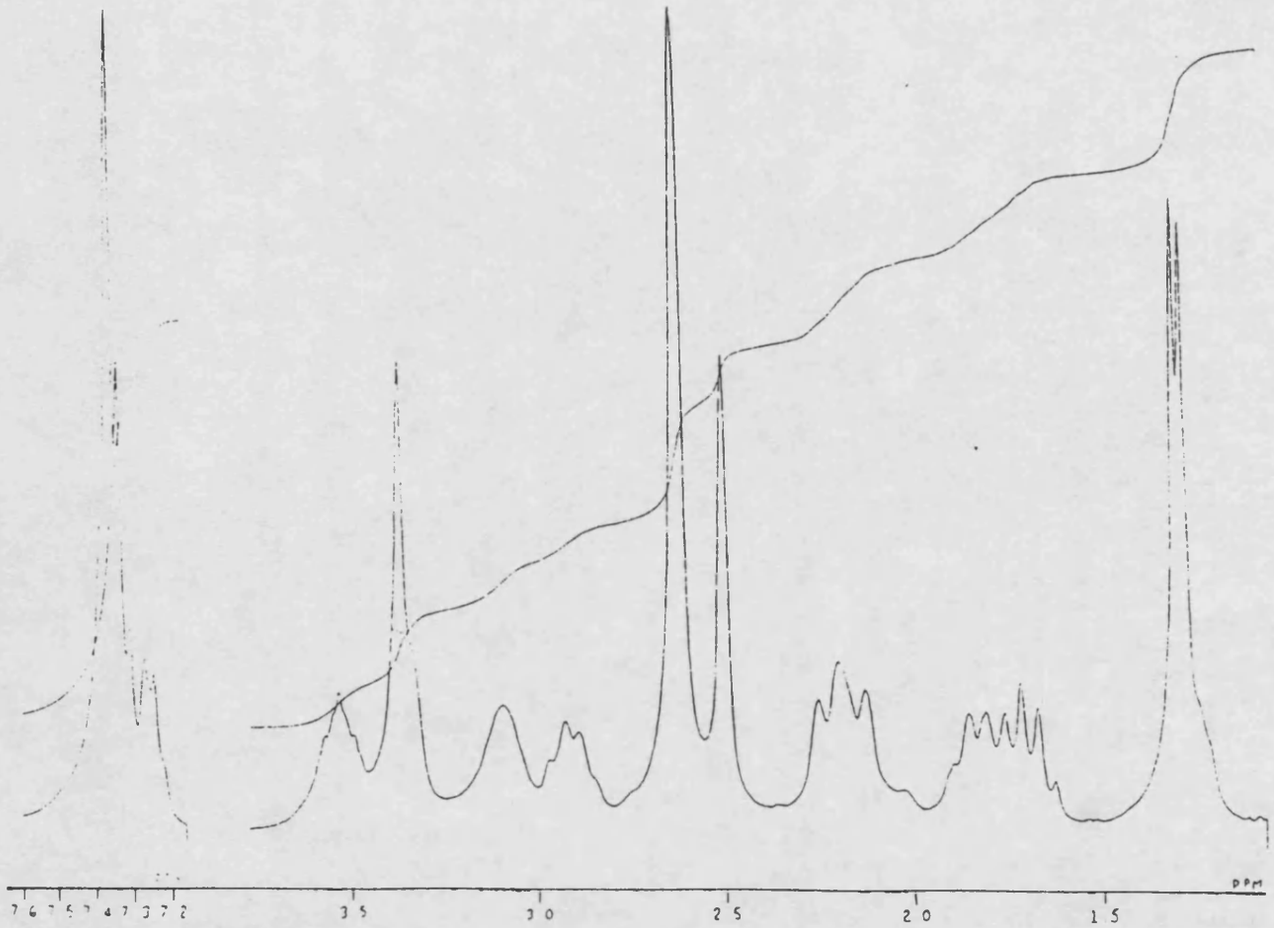
SCHEME 38.



3.52.1 Evidence of Structure of 1,2-Dimethyl-4-Piperidyl Benzhydryl Ether.

The ^{1}H NMR spectrum of α-1,3-dimethyl-4-piperidyl benzhydryl ether **[151]** (Spectrum **20**) showed that only one isomer was formed as no doubling-up of the signals occurred. The multiplet centred at δ7.3 integrated to ten protons and was assigned to the aromatic hydrogens. The most deshielded aliphatic signal (δ5.7) was assigned to OC<u>H</u>Ph$_2$. Equatorial protons attached to the same carbon atom were more downfield than the axial protons. On this basis , the equatorial <u>H</u>-6 proton (δ3.4) was more deshielded than the axial <u>H</u>-6 (δ3.1). When compared with the <u>H</u>-6 protons, the multiplet at δ2.9 was assigned to the <u>H</u>-2 proton as it experiences α-shielding from the 2-methyl group.

SPECTRUM 20: 270 MHz ^{1}H NMR ($CDCl_3$) OF α-1,2-DIMETHYL-4-PIPERIDYL BENZHYDRYL ETHER HCl [151].



A singlet at δ2.6 corresponding to three protons was allocated to the N-methyl substituent. A doublet at δ1.3 was assigned to the 2-methyl group. The multiplet at δ2.2 (2H) was assigned to the equatorial H-3 and equatorial H-5 protons. Similarly, the multiplet at δ1.7 was allocated to the axial protons at C-3 and C-5. The most deshielded proton of the piperidyl ring was a multiplet at δ3.5. This signal assigned to the H-4 proton.

In order to ascertain the conformation of α-1,2-dimethyl-4- piperidyl benzhydryl ether **[137]**, the positions of the benzhydryl and 2-methyl substituents needed to be investigated. However, both the H-4 and axial H-2 protons overlapped to some extent with neighbouring signals, so, the base width were not measured. Nevertheless, the half width of H-2 signal was measured at 21 Hz, indicating that it lies in the axial plane thus, leaving the methyl to occupy the more spacious equatorial position. The half width measurements of the H-4 signal was calculated at 30 Hz, this, also indicates that the proton lies in the axial plane. Consequently, the benzhydryl substituent occupies the equatorial position.

Further work should include the synthesis of the β-1,2-dimethyl-4-piperidyl benzhydryl ether for comparative pharmacological studies against the α-isomer **[151]** and Histryl.

CHAPTER 4.
PHARMACOLOGY.

4 PHARMACOLOGY.

In general terms, a drug interacts reversibly with a receptor to form a drug-receptor complex which then in some way produces a response. Under these conditions, the drug may be described as an agonist which will have an affinity for the receptor and also an efficacy or intrinsic activity at the receptor which results in the response. The potency of the drug is its ability to provoke the response; this is essentially a product of the affinity and the efficacy. So, a drug may have a poor affinity for the receptor but have a large effect there and appear to be very potent.

If another molecule is able to compete with the drug for binding sites at the receptor and yet has no efficacy itself, it can thereby prevent the response to the drug and is described as an antagonist. The term partial agonist also exists to describe drugs of low efficacy which does not provoke a full response.

4.1 PHARMACOLOGY OF PHENINDAMINE TARTRATE.

The biological activity of phenindamine tartrate is discussed in the literature[161,162]. Phenindamine tartrate was found to antagonise histaminic activity at H_1-receptor sites. What was interesting at the time was that phenindamine tartrate also protected dogs and rats, to some extent, against gastric acid secretion[163]. Phenindamine tartrate also possessed more potent anaesthetic actions than procaine hydrochloride[161].

Phenindamine tartrate differed from other antihistaminic drugs studied in that it produced evidence of central excitation, of the nervous system, rather than depression. This effect of phenindamine was increased by amphetamine and caffeine, but the depressant action of promethazine was potentiated by phenindamine.

4.2 *IN VITRO* EVALUATIONS AT HISTAMINE H_1-RECEPTORS.

4.21 Protocol.

Guinea Pig Ileum Preparation.

Female guinea pigs (approx 500g in weight) were killed by cervical dislocation and a piece of distal ileum, approximately 3 cm in length, was removed from the ileo-caecal junction. The tissue was suspended isotonically in a 10 ml organ bath under a tension of 1g and gassed with carbogen (95% oxygen and 5% carbon dioxide). The tissue was perfused with Tyrodes solution of the following composition:

NaCl, 40g/5L; KCl, 2g/5L; $CaCl_2$, 9 ml of 1M solution/5M; $NaHCO_3$, 0.5g/5L; NaH_2PO_4, 0.325g/5L; $MgCl_2.6H_2O$, 2g/5L; Glucose 5g/5L.

All drug solutions and their serial dilutions were made up in Tyrodes solution.

The Tyrodes solution was maintained at 32°C and the tissue allowed to equilibrate with its bathing solution for 20 min before addition of any agonists. One end of each tissue preparation was attached to a hook on the gassing side arm while the other end was attached to a Washington T2 or T3 isotonic transducer which was linked to a Washington 400 MD2R oscillograph *via* a Washington FC 117 isotonic/isometric coupler. A 3 min time cycle was used which allowed histamine to remain in contact with the tissue for 30 seconds before it was washed out, the tissue being allowed to recover for 2.5 min before the next agonist addition.

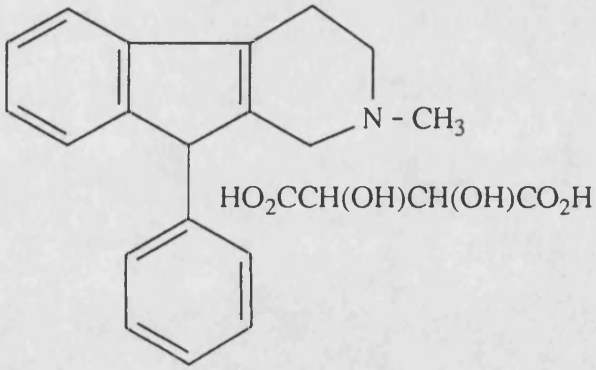
Dose response curves were constructed for histamine in the absence and presence of phenindamine tartrate **[14]**, and compounds **[51]**, **[59]**, **[60]**, **[70]**, **[71]**, **[82]**, **[88]** and **[89]** the tissue being allowed to equilibrate with each concentration of antagonist for 30 min prior to retesting the agonist action of histamine.

Dose response curves were plotted as a percentage of the histamine maximum response in the absence of antagonists (y axis) against $\log_{10}$ of the histamine concentration (molar).

The standard error of the means were within 10% in all cases and are omitted for the sake of clarity.

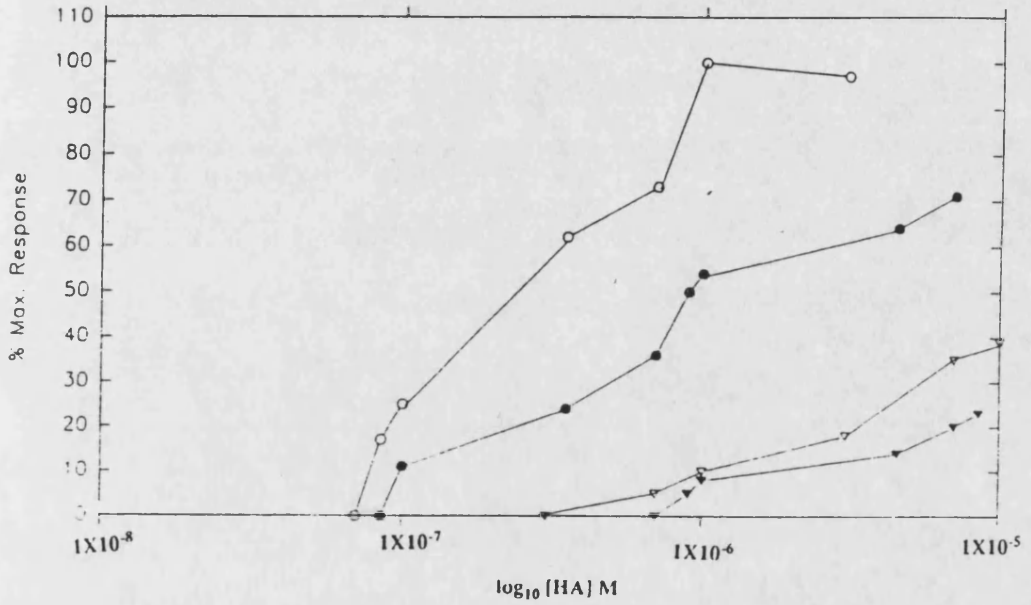
4.22 *In Vitro* Results.

COMPOUND: Phenindamine Tartrate **[14]** (Thephorin).

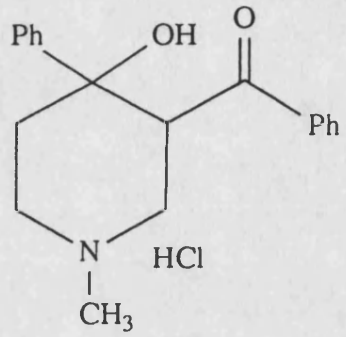


The dose-response curve (Figure **25**) showed that phenindamine tartrate was, as expected, a good histamine H_1 antagonist. However, what was interesting was that at high concentration of the drug ($1x10^{-6}$ M), Thephorin becomes a non-competitive inhibitor.

FIGURE 25: DOSE-RESPONSE CURVE OF THEPHORIN [14] AGAINST HISTAMINE ON ISOLATED GUINEA PIG ILEA AT 10^{-8}(●), 10^{-7}(◓) AND 10^{-6}(▲) MOLAR CONCENTRATIONS OF THEPHORIN.

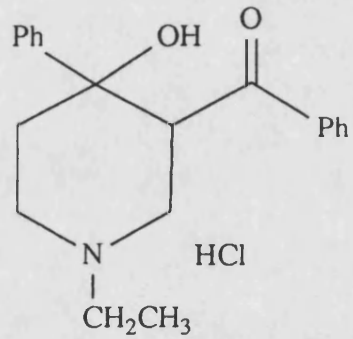


COMPOUND: 3-Benzoyl-4-hydroxy-1-methyl-4-phenylpiperidine HCl **[59]**.



Unlike Thephorin, piperidine **[59]** exhibits a dose-response curve (Figure **26**) that is typical of a non-competitive antagonist, when compared to histamine (agonist).

COMPOUND: 3-Benzoyl-1-ethyl-4-hydroxy-4-phenylpiperidine HCl **[60]**.



At a concentration of $1x10^{-8}$ and $1x10^{-7}$ M, piperidine **[60]**, appears to act as a good antagonist of histamine at the H_1-sites. At higher concentration ($1x10^{-6}$ M), the drug shows non-competitive antagonism (Figure **27**).

FIGURE 26: DOSE-RESPONSE CURVE OF PIPERIDINE [59] AGAINST HISTAMINE ON ISOLATED GUINEA PIG ILEA AT 10^{-8}(●), 10^{-7}(△) AND 10^{-6}(▲) MOLAR CONCENTRATIONS OF [59].

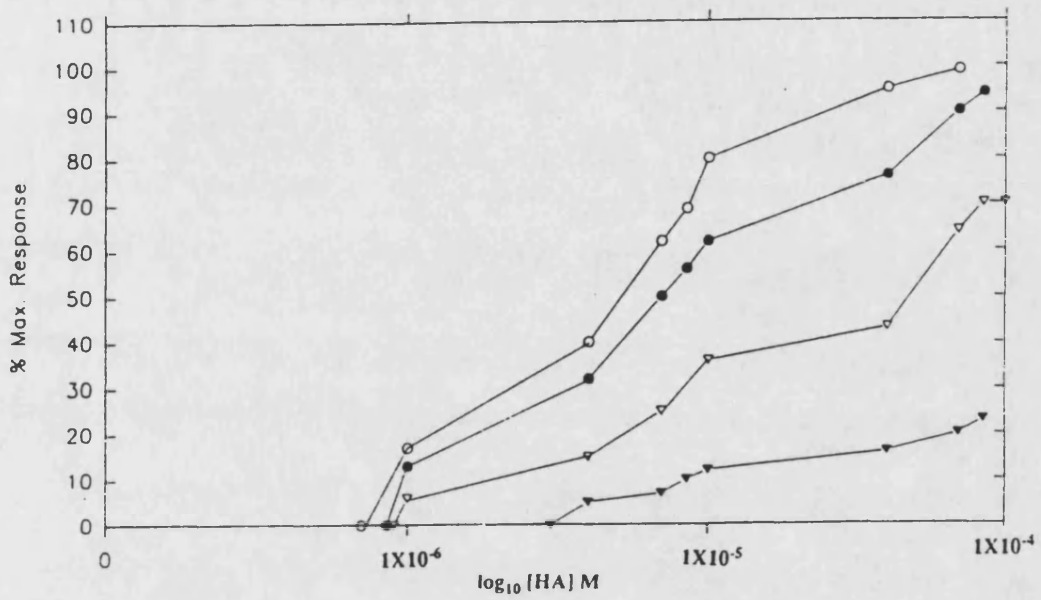
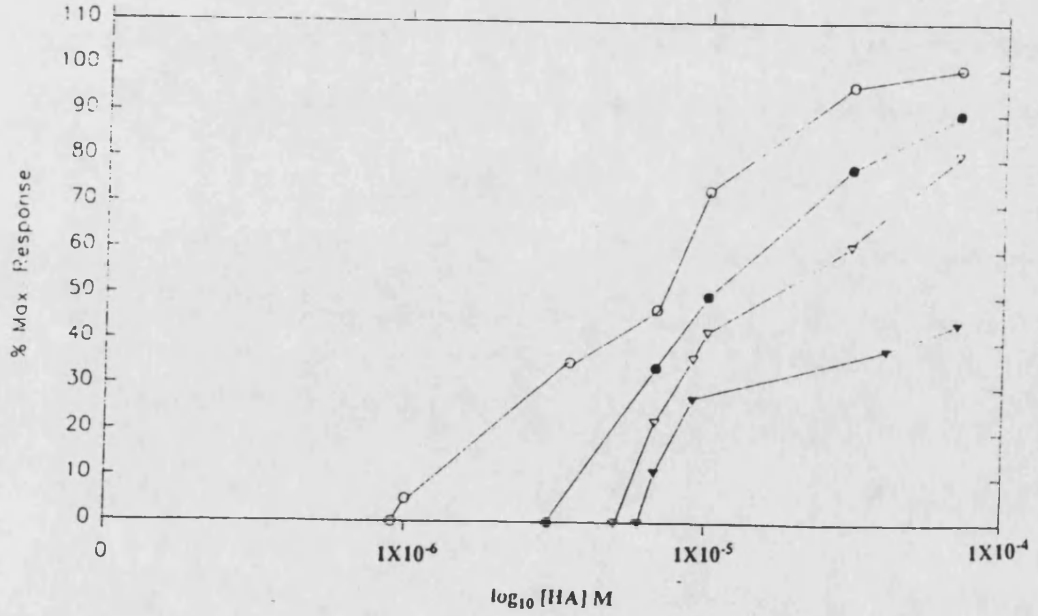
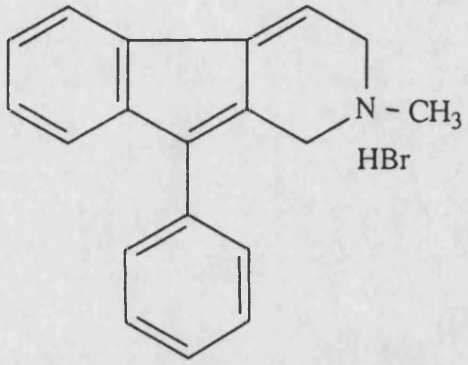


FIGURE 27: DOSE-RESPONSE CURVE OF PIPERIDINE [60] AGAINST HISTAMINE ON ISOLATED GUINEA PIG ILEA AT 10^{-8}(●), 10^{-7}(△) AND 10^{-6}(▲) MOLAR CONCENTRATIONS OF [60].



COMPOUND: 2-Methyl-9-phenyl-2,3-dihydro-1*H*- indeno[2,1-c]pyridine HBr **[70]**.



The dose-response curve (Figure **28**) shows that diene **[70]** is acting as antagonist to histamine, though, like Thephorin, it acts as a non-competitive inhibitor at high concentration of the drug ($1x10^{-6}$M).

COMPOUND: 2-Ethyl-9-phenyl-2,3-dihydro-1*H*- indeno[2,1-c]pyridine HBr **[71]**.

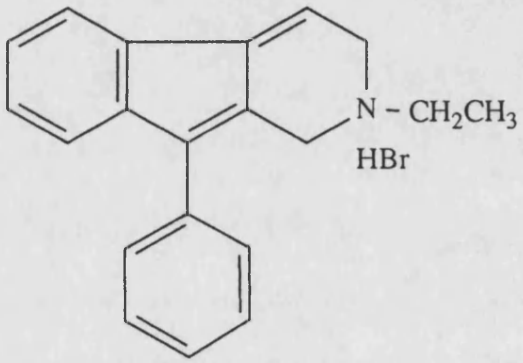


Figure **29** shows the drug to be a good inhibitor of histamine H_1 receptors even at high concentration. This drug **[71]** gave a better antagonistic dose-response profile than Thephorin **[14]**.

FIGURE 28: DOSE-RESPONSE CURVE OF DIENE [70] AGAINST HISTAMINE ON ISOLATED GUINEA PIG ILEA AT 10^{-8}(●), 10^{-7}(△) AND 10^{-6}(▲) MOLAR CONCENTRATIONS OF [70]

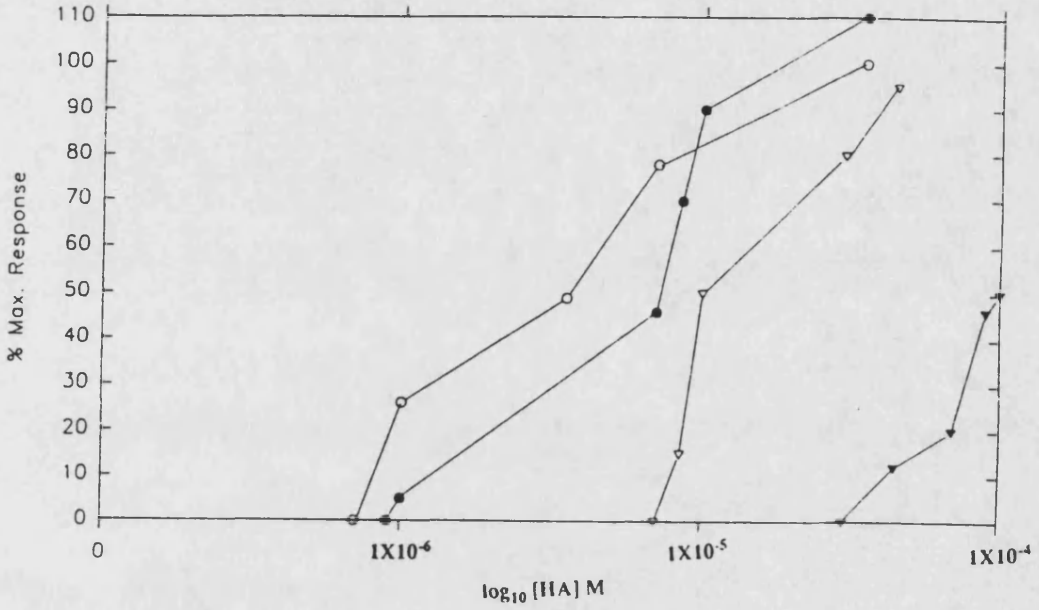
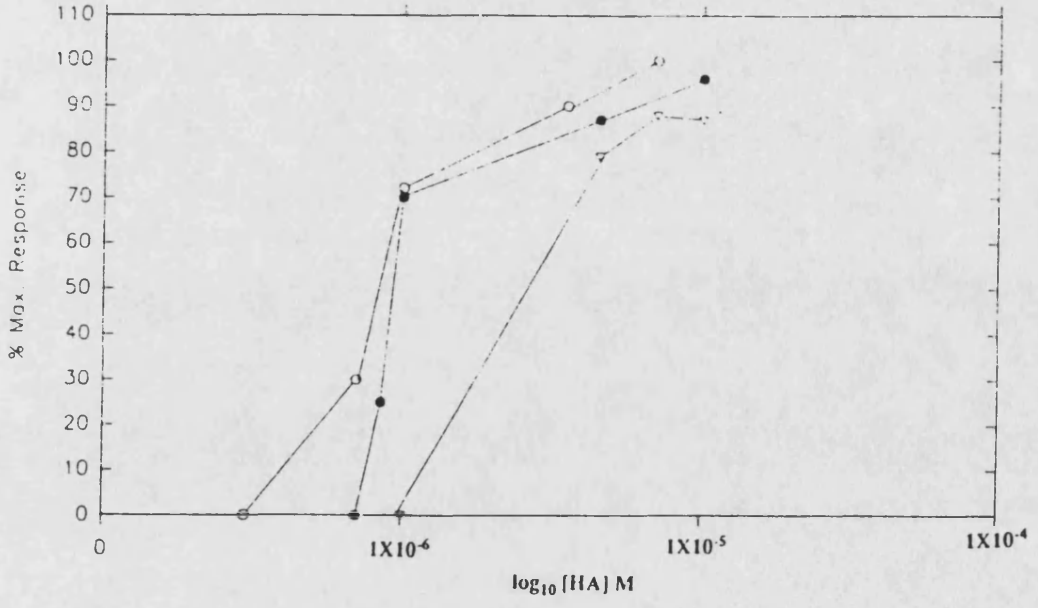
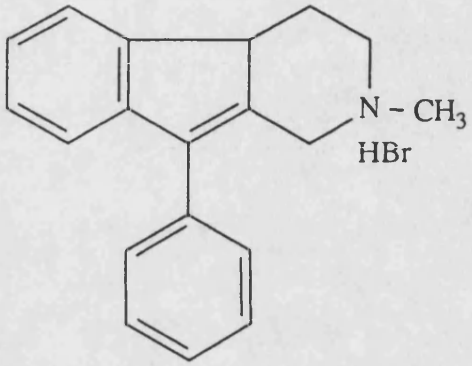


FIGURE 29: DOSE-RESPONSE CURVE OF DIENE [71] AGAINST HISTAMINE ON ISOLATED GUINEA PIG ILEA AT 10^{-7}(●) AND 10^{-6}(▲) MOLAR CONCENTRATIONS OF [71]

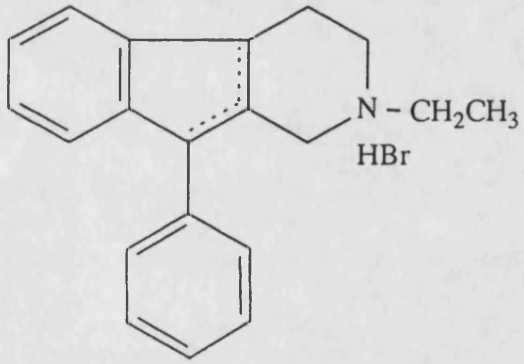


COMPOUND: 2-Methyl-9-phenyl-2,3,4,4a-tetrahydro-1*H*- indeno[2,1-c]pyridine HBr **[51]**.



The drug acts as a competitive inhibitor at a concentration of $1x10^{-8}$ M, but is non-competitive at $1x10^{-7}$M. The drug is inactive at $1x10^{-6}$M concentration (Figure **30**).

COMPOUND: Structural isomers of 2-Ethyl-9-phenyl- 2,3,4,4a and 2,3,4,9-tetrahydro-1*H*-indeno[2,1-c]pyridine HBr **[82]**.



The dose-response curve (Figure **31**) is analogous to the theoretical one that is obtainable for a non-competitive inhibitor.

FIGURE 30: DOSE-RESPONSE CURVE OF MONO-ENE (9,9a ISOMER) [51] AGAINST HISTAMINE ON ISOLATED GUINEA PIG ILEA AT 10^{-8}(●), 10^{-7}(▲) AND 10^{-6} MOLAR CONCENTRATIONS OF [51]

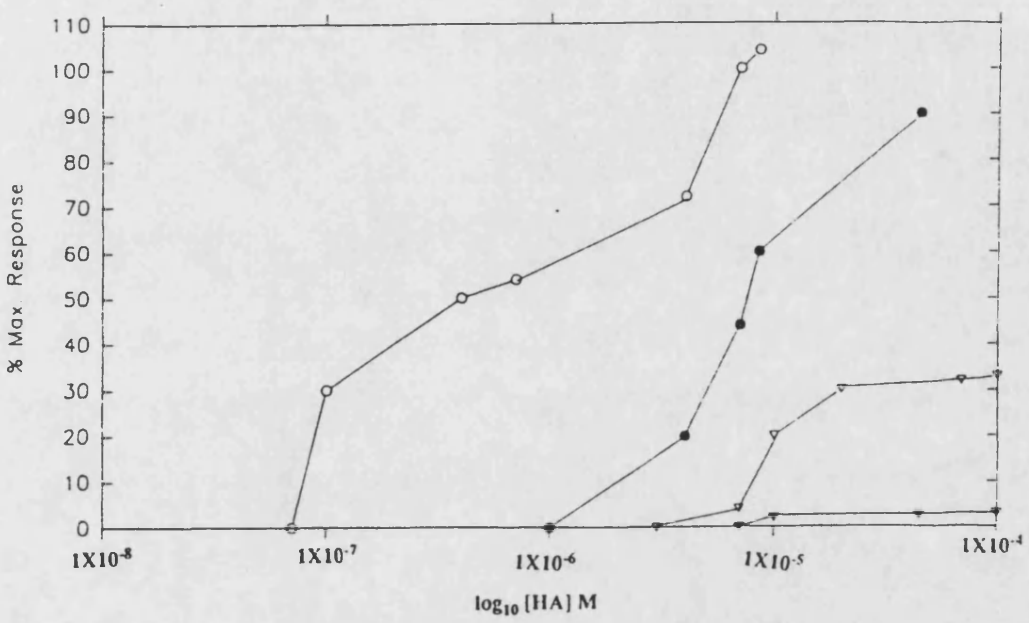
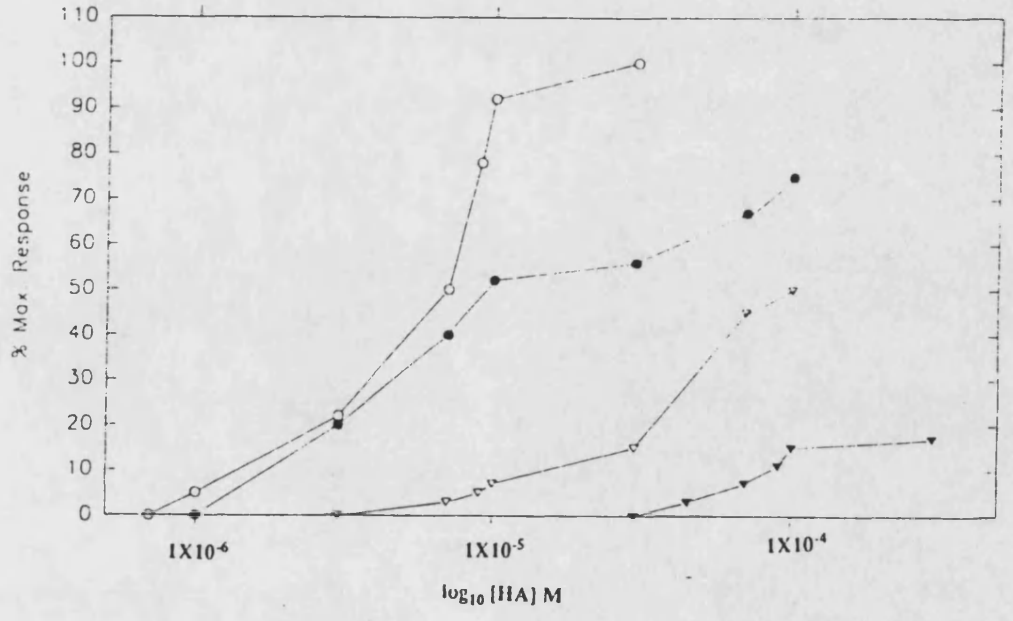
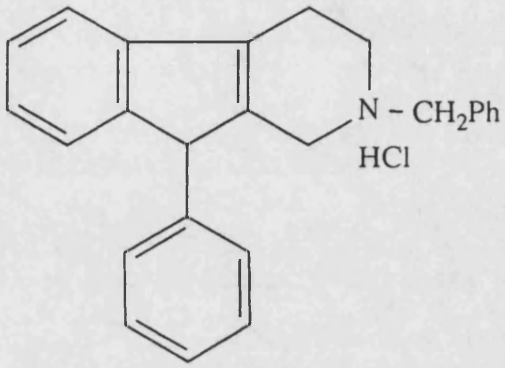


FIGURE 31: DOSE-RESPONSE CURVE OF ISOMERIC MONO-ENE [82] AGAINST HISTAMINE ON ISOLATED GUINEA PIG ILEA AT 10^{-8}(●), 10^{-7}(▲) AND 10^{-6} (▲) MOLAR CONCENTRATIONS OF [82]

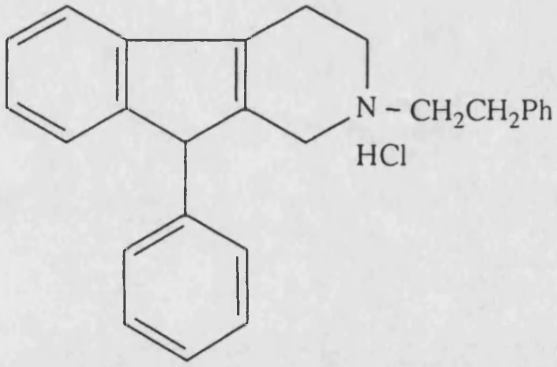


COMPOUND: 2-Benzyl-9-phenyl-2,3,4,9-tetrahydro-1*H*- indeno[2,1-c]pyridine HCl **[88]**.



The dose-response curve (Figure **32**) is similar to the theoretical plots that are obtainable for a reversible competitive antagonist. From these results, it appears that this drug is a better H_1-histamine antagonist than Thephorin in *in vitro* environments.

COMPOUND: 2-Phenethyl-9-phenyl-2,3,4,9-tetrahydro- 1*H*-indeno[2,1-c]pyridine HCl **[89]**.



The drug acts in a similar fashion to a non-competitive inhibitor (Figure **33**).

FIGURE 32: DOSE-RESPONSE CURVE OF MONO-ENE (4a,9a ISOMER) [88] AGAINST HISTAMINE ON ISOLATED GUINEA PIG ILEA AT 10^{-8}(●), 10^{-7}(△) AND 10^{-6}(▲) MOLAR CONCENTRATIONS OF [88].

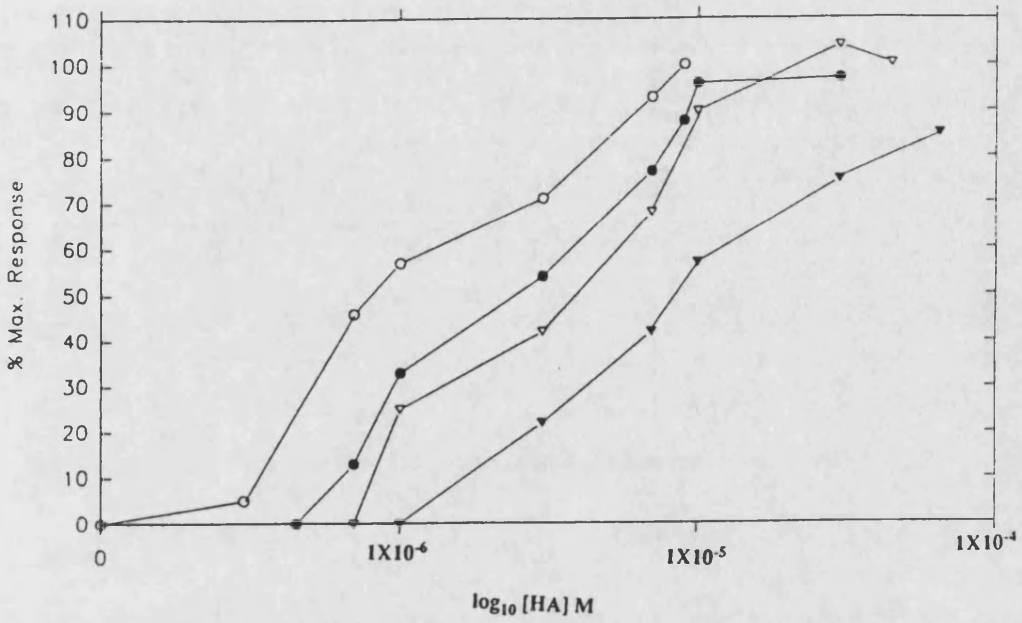
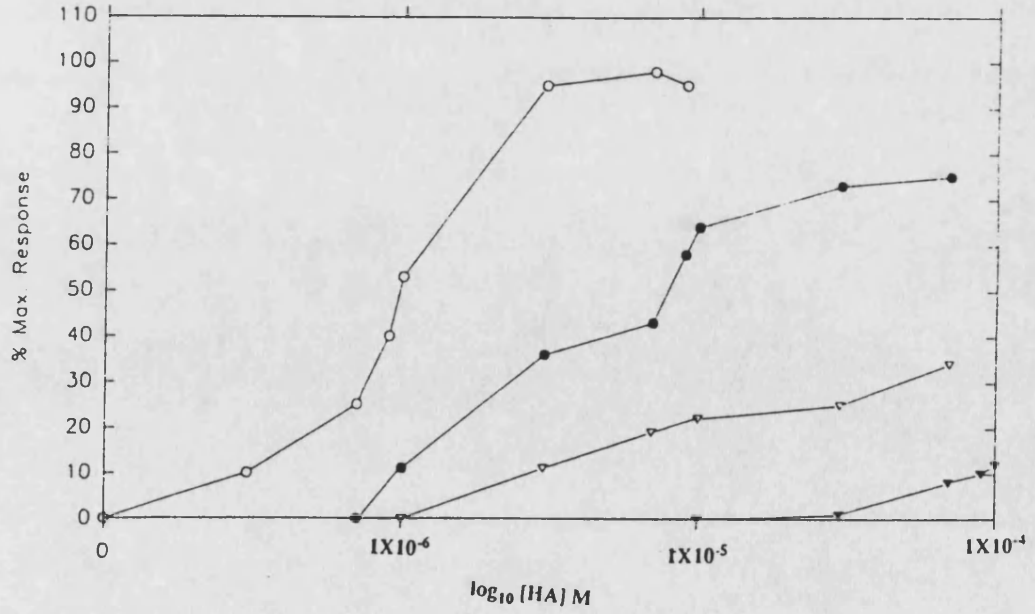


FIGURE 33: DOSE-RESPONSE CURVE OF MONO-ENE (4a,9a ISOMER) [89] AGAINST HISTAMINE ON ISOLATED GUINEA PIG ILEA AT 10^{-8}(●), 10^{-7}(△) AND 10^{-6}(▲) MOLAR CONCENTRATIONS [88].

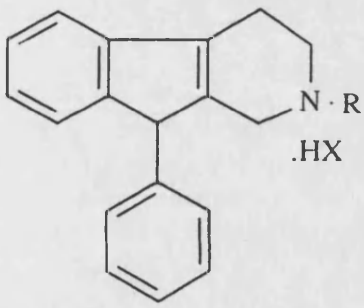


4.3 *IN VIVO* ANTIHISTAMINIC ACTIVITY.

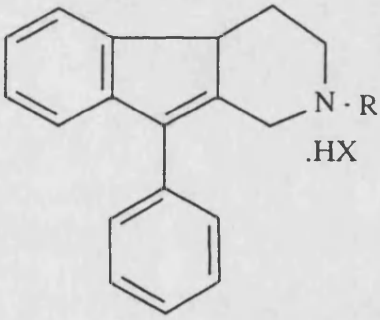
4.31 Protocol.

Compound 48/80, a recognised potent histamine releasing agent, was injected intravenously at a challenge dose of 0.5 mg/kg. The compounds tested were administered subcutaneously at 40 mg/Kg and at 10mg/Kg, with the exception of the commercial sample of Thephorin, which was administered at 10 mg/Kg and at 2.5 mg/Kg. Compounds which gave survival times of more than 240 minutes were considered as having useful antihistaminic activity. Results are summarized in Figure **35**. The compounds tested are presented in Figure **34**.

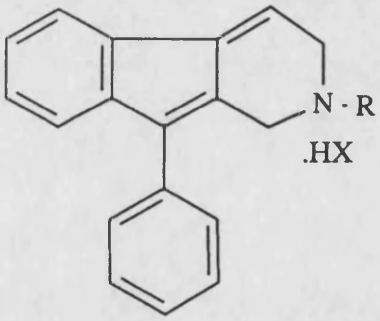
FIGURE 34.



R	X
[14] CH_3	tartrate
[88] CH_2Ph	Cl
[89] CH_2CH_2Ph	Cl



R	X
[51] CH_3	Br
[79] CH_2CH_3	Br
[80] CH_2Ph	Br
[81] CH_2CH_2Ph	Br
[87] * CH_2CH_3	Cl



R	X
[100] H	Cl

* Compound **[87]** is a mixture of the 9,9a- and 4a,9a-enes.

FIGURE 35.

SURVIVAL AT SUBCUTANEOUS DOSE LEVEL OF:			
COMPOUND	40mg/kg	10mg/kg	2.5mg/kg
[14]	-	2/2	1/2
[51]	2/2	1/2	-
[79]	1/2	0/2	-
[80]	0/2	0/2	-
[81]	1/2	0/2	-
[88]	0/2	0/2	-
[89]	0/2	0/2	-
[87]	2/2	1/2	-
[100]	1/2	0/2	-

Doses " - " means not tested at this level.

4.32 *In Vivo* Results.

40 mg/Kg Dose:

Compounds **[51]** (R=CH_3; X=Br) and **[87]** (R=CH_2CH_3; X=Cl) gave survival times for both rats of greater than 240 minutes. These compounds were classed as active at the administered dose.

For compounds **[100]** (diene R= H; X=Cl), **[81]** (R=CH_2CH_2Ph; X=Br), and **[79]** (R=CH_2CH_3; X=Br), one of the two rats survived more than 240 minutes. These compounds can be classed as less active than compounds **[51]** and **[87]**.

Compounds **[80]** (R=CH_2Ph; X=Br), **[88]** (R=CH_2Ph; X=Cl), and **[89]** (R=CH_2CH_2Ph; X=Cl) were inactive, as both rats did not survive past the required 240 minutes.

10 mg/Kg Dose:

Both rats which were treated with Thephorin **[14]** survived the required time. Compounds **[51]** and **[87]** were found to give a survival time of more than 240 minutes in one rat, but the other rat died before hand. Compounds **[51]** and **[87]**,though active were less active than Thephorin **[14]**.

The remaining compounds **[79]**, **[80]**, **[81]**, **[88]**, **[89]**, **[100]**, provided little or no protection against histamine, both rats died within the required time limit.

2.5 mg/Kg Dose:

When Thephorin **[14]** was administered at a lower dose of 2.5 mg/Kg subcutaneously, only one of the rats was protected. The ED_{50} of Thephorin was considered to be 2.5 mg/Kg (compared with astemizole 0.11 mg/Kg s.c and orally).

4.4 Conclusions.

Possible explanations for the drugs **[88]** and **[89]** having antagonistic effects *in vitro* and not *in vivo* could be accounted for by the toxicology of the drug to the animal, its distribution to the effector organs and its biotransformation largely by the liver. The drug may have physiological actions other than its antihistaminic effects and may therefore have adverse effects in the *in vivo* but not in the *in vitro* situation where a restricted array of physiological processes exist. The drug may be highly lipophilic and so be absorbed by tissue fats and therefore not reach the target organ.

A selection of the compounds synthesised in this work are currently being tested for H_2-histamine receptor antagonism.

CHAPTER 5.
EXPERIMENTAL.

5 EXPERIMENTAL.

5.1 Introduction.

The ^{1}H NMR spectra were recorded on a Jeol GX270MHz Fourier Transform(FT) NMR Spectrometer unless otherwise stated. The following abbreviations are used to describe resonance appearance in the ^{1}H NMR spectra: s, singlet; br, broad; d, doublet; t, triplet; q, quartet; m, multiplet plus combinations such as dd, doublet of doublets. The ^{13}C NMR spectra were recorded on a Jeol GX270MHz FT NMR Spectrometer operating at 67.8MHz. The multiplicity of the resonances were obtained from DEPT (Distortionless Enhancement by Polarisation Transfer) spectra, in which the phase of the signal indicated the number of protons attached to the carbon atoms giving rise to that signal.

The infra red spectra (liquid as films, solids as KBr discs or nujol mulls) were recorded on a Unicam SP1025 Spectrometer.

Mass spectra were recorded on a VG Micromass 707E Mass Spectrometer operating at low eV, 70 eV, or C.I.

Elemental analyses were carried out in the School of Chemistry, University of Bath.

Melting points were recorded on a Gallenkamp apparatus and are uncorrected.

Catalytic hydrogenations were performed using a COOK low pressure hydrogenator of 1 litre capacity.

The term *in vacuo* means that a rotary evaporator Buchi Rotavapor R110 was employed to remove solvents.

In the script, the term ether denotes diethyl ether and THF is tetrahydrofuran.

5.2 EXPERIMENTAL PROCEDURES.

5.21 MANNICH REACTIONS.

5.21.1 2-Benzoylethyl Benzylamine HCl [56].

A mixture of acetophenone (30.0g, 0.25mol), benzylamine (24.6g, 0.23mol), formaldehyde (10% w/v, 30ml) and hydrochloric acid (36% v/v, 20ml) was heated under reflux for 2 h. The homogeneous solution was cooled overnight with stirring. The product was extracted with chloroform (3x75ml), dried ($MgSO_4$) and evaporated *in vacuo*. The product was recrystallized from absolute ethanol to give **[56]** (30.92g, 49%), m.p. 179-180°C.

δ_H ($CDCl_3$, HCl salt): 9.95(2H, s, $N\underline{H}_2$), 7.89(10H, m, Ar-$\underline{H}$), 4.13(2H, t, J^3 5.5Hz., $C\underline{H}_2Ph$), 3.71(2H, t, J 7.3Hz., $CH_2C\underline{H}_2N$), 3.31(2H, m, $COC\underline{H}_2CH_2$).

δ_C ($CDCl_3$, HCl salt): 196.85 ($\underline{C}$=O), 135.58-128.51 (2xAr-$\underline{C}_q$), 133.03-128.60 (6xAr-$\underline{C}$H), 51.02 ($CO\underline{C}H_2$), 41.52 ($\underline{C}H_2Ph$), 34.67 ($CH_2\underline{C}H_2N$).

The above method was used for the synthesis of:-

2-Benzoylethyl tertiarybutylamine HCl **[57]** (43% yield), m.p.168-169°C.

δ_H ($CDCl_3$, HCl salt): 9.18(2H, s, $N\underline{H}_2$), 7.98(5H, m, Ar-$\underline{H}$), 3.61(2H, t, J^3 6.6Hz., $COC\underline{H}_2$), 3.21(2H, dt, $CH_2C\underline{H}_2N$), 1.34(9H, s, $NC(C\underline{H}_3)_3$).

δ_C ($CDCl_3$, HCl salt): 196.72 (C=O), 136.06 (Ar-C_q), 133.70-127.92 (3xAr-CH), 35.87($COCH_2$), 25.12 ($COCH_2CH_2N$), 25.13 (3xCH_3).

and 2-Benzoylethyl cyclohexylamine HCl [58] (47% yield), m.p.197-198°C.

δ_H ($CDCl_3$, HCl salt): 9.55(2H, s, NH_2), 7.96(5H, m, Ar-H), 3.82(2H, t, J^3 7.3Hz., NCH_2), 3.44(2H, t, J^3 7.3Hz., $COCH_2$), 3.07(1H, m, N-CH), 2.31-1.34(10H, m, ring-CH).

5.22 The Piperidines.

Method A.

5.22.1 3-Benzoyl-1-Butyl-4-Hydroxy-4-Phenylpiperidine HCl [65].

A mixture of acetophenone (12.0g, 0.1mol), butylamine (4.3g, 0.06mol), formaldehyde (38% w/v, 50 ml), and hydrochloric acid (50% v/v, 30ml) was heated under reflux for 2h. To the cooled mixture was added water (150ml) portionwise. The precipitate was collected and recrystallized from ethanol to give **[65]** (14.91g, 90%) as a white solid, m.p. 184-185°C (Lit.,[167] 182-184°C).

A similar procedure was adopted for other piperidines (See table 7).

Method B.

5.22.2 3-Benzoyl-1-Benzyl-4-Hydroxy-4-Phenylpiperidine [61].

A suspension of 2-benzoylethyl benzylamine HCl (13.75g, 0.05mol) was stirred with a solution of sodium hydroxide in water (2N, 100ml) for 18h at room temperature. The mixture was extracted with ether (5x50ml), dried ($MgSO_4$), and evaporated to yield a solid which was recrystallized from absolute ethanol to give **[61]** (12.14g, 61%) as a white solid, m.p. 203.5-204.5°C (Lit.,[167] 193-194°C).

The same procedure was adopted for the synthesis of 3-Benzoyl-1-cyclohexyl-4-hydroxy-4-phenylpiperidine **[68]**.

The analytical data for all of the piperidines synthesised are presented in Table **4** for ^{13}C NMR, Tables **5** and **6** for ^{1}H NMR, Table **1** for mass spectra, and Table **7** for % yield, m.p. and microanalytical data.

TABLE 4: ^{13}C NMR Data for 1-Alkyl-3-Benzoyl-4-Hydroxy-4-Phenylpiperidines.

COMPD	C-2	C-3	C-4	C-5	C-6	C=O	Ar (CH and C_q)	N-R [a]
[59]	51.57	46.19	71.19	36.59	50.66	201.16	124.28-134.70 (6xCH) 143.65 (C_q)	43.14 CH_3
[60]	51.57	45.99	71.79	36.39	50.09	201.52	127.66-133.34 (4xCH)	47.84 CH_2, 9.11 CH_3
[61]	49.75	45.80	70.77	35.42	46.41	199.90	123.67-133.28 (8xCH) 127.63-143.49 (C_q)	59.39 CH_2Ph
[62]	50.27	45.99	71.06	35.95	48.23	200.35	123.97-137.89 (7xCH) 135.35, 143.56 (C_q)	57.54 $\underline{CH_2}CH_2Ph$ 29.68 $CH_2\underline{CH_2}Ph$
[63]	52.87	50.40	73.27	39.70	49.40	204.41	124.52-133.79 (5xCH) 128.21, 147.32 (C_q)	38.24 CH 6.32, 6.16 2xCH_2
[64]	48.52	50.96	73.27	40.12	44.20	204.57	124.51-133.73 (5xCH)	54.62 CH 18.49, 18.26 2xCH_3
[65]	50.73	45.86	71.55	36.32	48.36	201.48	124.26-134.47 (5xCH) 134.73, 143.59 (C_q)	57.05-19.88 3xCH_3 13.26 CH_3
[66]	48.36	45.99	71.97	36.26	44.68	202.0	124.42-134.83 (5xCH) 134.64, 143.85 (C_q)	69.70 CH 23.00, 21.50 2xCH_3
[67]	50.68	46.02	71.68	36.36	48.46	201.68	124.39-134.83 (5xCH) 134.62, 143.76 (C_q)	57.41 NCH_2, 13.72 CH_3 30.94-22.22 4xCH_2
[68]	47.91	45.99	72.04	36.36	44.43	201.97	124.42-134.86 (5xCH) 134.67, 143.88 (C_q)	66.23 CH 27.21-24.91 3xCH_3
[69]	52.16	49.90	71.71	36.16	48.82	201.78	124.39-134.74 (6xCH) 143.82 (C_q)	63.96 NCH_2, 25.17 CH 31.46-25.33 4xCH_2

a) see Table 7 for structure of R.

Table 5: 270 MHz ^{1}H NMR Data for 1-Alkyl-3-Benzoyl-4-Hydroxy-4-Phenylpiperidines.

COMPD	H-2 / H-6	H-3	H-5	OH	Ar-H	N-R[a]
[59]	3.48, m	5.57, t, 6.96 Hz.	eq: 2.16[b] dt ax: 2.82, m	5.07, d 2.56 Hz.	8.07, m	2.90, s $\underline{CH_3}$
[60]	3.55, m	5.63, dd 4.03, 11.73 Hz.	eq: 2.01[b], dt ax: 2.93, m	5.08, d 2.93 Hz.	8.13, m	1.55[b], t, $\underline{CH_3}$ 3.19[b], q, $\underline{CH_2}CH_3$
[62]	3.60, m	5.60, t 9.52 Hz.	eq: 2.01[b] d ax: 2.90, m	5.18, d 1.84 Hz.	8.04, m	3.60, m $\underline{CH_2}\underline{CH_2}Ph$
[63]	3.14, m	4.43, dd 3.67, 11.36 Hz.	eq: 1.83, m ax: 1.83, m	5.18, d 2.74 Hz.	7.98, m	0.59, m, 2x$\underline{CH_2}$ 2.03, m, N-C$\underline{H}$R
[64]	2.93, m	4.38, dd 4.03, 10.99 Hz.	eq: 1.86[b] dt ax: 2.03, m	5.17, d 2.39 Hz.	7.89, m	1.11, d, 6.6Hz. $CH(\underline{CH_3})_2$; 2.93, m, $\underline{CH}(CH_3)_2$
[66]	3.62, m	5.91, dd 3.66, 11.72 Hz.	eq: 1.99, m ax: 2.99, m	5.09, d 2.56 Hz.	8.16, m	1.17, 2xt, 7.7, 7.33, 15.03 Hz. $CH(CH_2\underline{CH_3})_2$; 2.14, m, $CH(\underline{CH_2}CH_3)_2$
[68]	3.58, m	5.85, dd 3.66, 11.36 Hz.	eq: 2.05, m ax: 3.17, m	5.09, d 2.56 Hz.	8.15, m	2.05, m; 2.45, m 3.58[b], tt

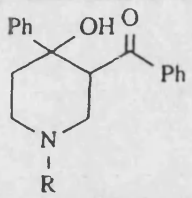
a) see Table 7 for structure of R.
b) unresolved signals.

Table 6: 270 MHz ^{1}H NMR Data for 1-Alkyl-3-Benzoyl-4-Hydroxy-4-Phenylpiperidines.

COMPD.	H-2 / H-6	ax-H-3	H-5	OH	Ar-H	N-R[b]
[61]	3.65, m	5.61, dd 4.03, 11.73 Hz.	eq: 1.91[a], d ax: 2.88, m	5.20, s	7.99, m	4.51, m
[65]	3.50, m	5.72, dd 4.03, 12.09 Hz.	eq: 1.99, m ax: 3.10, m	5.08, s	8.14, m	1.00, t 7.33 Hz. 1.99-3.06, m
[67]	3.49, m	5.71, dd 4.03, 12.09 Hz.	eq: 1.97, m ax: 3.04, m	5.01, s	8.14, m	0.91, m; 1.33, m; 3.04, m
[69]	3.50, m	5.91, dd 3.84, 11.90 Hz.	eq: 1.98, m ax: 3.05, m	5.06, s	8.12, m	1.89, m, 3.05, m, N-$\underline{CH_3}$

a) unresolved signal.
b) see Table 7 for structure of R.

Table 7: Analytical Data for 1-Alkyl-3-Benzoyl-4-Hydroxy-4-Phenylpiperidines.



COMPOUND FORMULA	R =	YIELD (%)	SOLVENT	M.p./°C (DECOMP.)	FOUND (%) (REQUIRED) C	H	N
[59][b] $C_{19}H_{21}NO_2.HCl$	CH_3	59	EtOH	183-184	68.8 (68.8	6.71 6.6	4.17 4.2)
[60][b] $C_{20}H_{23}NO_2.HCl$	CH_2CH_3	28	EtOH	132-133	69.1 (69.5	7.03 6.9	4.2 4.1)
[61][a] $C_{25}H_{25}NO_2.HCl$	CH_2Ph	61	EtOH	203.5-204.5	73.7 (73.6	6.43 6.4	3.34 3.4)
[62][b] $C_{26}H_{27}NO_2.HCl$	CH_2CH_2Ph	38	EtOH	189-190	73.6 (74.0	6.62 6.64	3.27 3.32)
[63][b] $C_{21}H_{23}NO_2$	Cyclopropyl	91	EtOH	153-154	78.3 (78.5	7.18 7.17	4.26 4.36)
[64][b] $C_{21}H_{25}NO_2.HCl$	$CH(CH_3)_2$	39	EtOH	163-164	70.2 (70.1	7.25 7.23	3.92 3.89)
[65][b] $C_{22}H_{27}NO_2.HCl$	Butyl	90	EtOH	184-185	70.8 (70.7	7.51 7.50	3.60 3.75)
[66][b] $C_{23}H_{29}NO_2.HCl$	$CH(CH_2CH_3)_2$	42	EtOH	180-181	71.4 (71.2	7.76 7.74	2.89 2.84)
[67] $C_{24}H_{31}NO_2.HCl$	Hexyl	84	EtOH	170-171	71.8 (71.7	8.13 7.97	3.45 3.49)
[68][a] $C_{24}H_{29}NO_2.HCl$	Cyclohexyl	49	EtOH	174-175	72.0 (72.1	7.47 7.51	3.45 3.50)
[69][b] $C_{25}H_{31}NO_2.HCl.H_2O$	Cyclohexyl-methyl	58	EtOH	183-184	70.3 (69.5	7.85 7.88	3.19 3.24)

a) synthesised from the *mono*-Mannich product, then converted to the HCl salt.
b) synthesised from the Mannich reaction.

5.3 The 2-Alkyl-9-Phenyl-2,3-Dihydro-1*H*- Indeno[2,1-c]pyridines.

5.31 2-Benzyl-9-Phenyl-2,3-Dihydro-1*H*-Indeno[2,1-c]pyridine Hydrobromide [72].

3-Benzoyl-1-benzyl-4-hydroxy-4-phenylpiperidine HCl (4.0g, 0.01mol) was stirred with hydrobromic acid (48% w/v, 10 ml) and distilled water (10 ml) for 2h at room temperature, and then heated at reflux for 2h. The cooled mixture was diluted with distilled water(50 ml), extracted with chloroform (3x50 ml), dried ($MgSO_4$), and evaporated *in vacuo* to give the yellow solid which was recrystallized from ethanol to give **[72]** (3.25g, 78%) as yellow crystals, m.p.196-197. (Lit.,[180] 188-190°C).

The same procedure was adopted for the synthesis of the remaining dienes.

For analytical data see Tables **8** (^{1}H NMR), and **9** (^{13}C NMR), **2** (mass spectra), and **10** (% yields, m.p., CHN microanalysis).

Table 8: 270 MHz ^{1}H NMR Data for the 2-Alkyl-9-Phenyl-2,3-Dihydro-1*H*-Indeno[2,1-c]pyridines.

COMPD.	H_2-1	H_2-3	H-4	Ar-H	N-R[a]	N-H
[70][b]	4.40, s	4.28, d 2.55 Hz.	6.60, t 3.00 Hz.	7.63, m	2.93, s	
[71][b]	4.46, s	4.16, s	6.63, t 4.03 Hz.	7.62, m	3.62, q, 7.33 Hz. N-C$\underline{H}_2$CH$_3$, 1.40, t 7.33 Hz.	
[72]	5.82, m	5.82, m	6.62, dd 3.12, 4.96 Hz.	7.68, m	5.82, m, N-C$\underline{H}_2$Ph	12.03, s
[73][b]	4.59, s	4.41, s	7.10[c], t	7.89, m	3.62, m, N-C$\underline{H}_2$CH$_2$Ph 3.13, m, N-CH$_2$C$\underline{H}_2$Ph	
[74]	eq: 4.54, dd 1.70, 13.12 Hz. ax: 4.30, dd 1.70, 15.57 Hz.	eq: 4.40[c],dt ax: 4.36[c] dt	6.60, t 3.66, 7.94 Hz.	7.61, m	3.11, 1.76, 1.31, m 3xC$\underline{H}_2$; 0.86, t 7.33 Hz., -C$\underline{H}_3$	11.64, s
[75]	eq: 4.59, brd. ax: 4.18[c] dd	4.48, m	6.68, t 4.27, 3.97 Hz.	7.66, m	3.18, m, N-C$\underline{H}$(R) 1.85, m, 2xC$\underline{H}_2$ 1.25, 1.04, t 7.33 Hz., 2xC$\underline{H}_3$	11.21, s
[76]	eq: 4.60, m ax: 4.80, m	eq: 4.47[c], dt ax: 4.32[c], dt	6.62[c] t	7.65, m	3.12, 2.04, m 5xC$\underline{H}_2$; 0.83[c], t -CH$_3$	11.73, s
[77]	4.03, m	4.29, d 3.66 Hz.	7.12, t 4.03 Hz.	7.88, m	3.49, m, N-C$\underline{H}$R 2.12, 1.87, 1.64 1.37, m, 5xC$\underline{H}_2$	10.17, s
[78]	eq: 4.74, dd 2.56, 15.76 Hz. ax: 4.06, brd.	eq: 4.64[c], dt ax: 4.25, m	6.63[c], dd	7.81, m	3.18, m, N-C$\underline{H}_2$R 1.90, m, 5xC$\underline{H}_2$	11.35, s

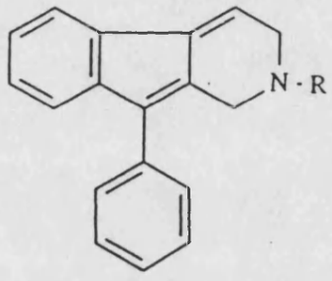
a) see Table 10 for structure of R.
b) duterated samples.
c) unresolved signals

Table 9: ^{13}C NMR Data for the 2-Alkyl-9-Phenyl-2,3-Dihydro-1*H*-Indeno[2,1-c]pyridimes.

COMPD	C-1	C-3	C-4	C-4a	C-9	C-9a	Ar-C (C-H and C-q)	N-R[a]
[70]	50.39	51.61	115.57	120.79	132.82	131.95	128.96-120.72 (6 signals) 142.33-130.79 (3 signals)	41.39 $\underline{C}H_3$
[71]	47.81	49.01	115.47	120.89	133.11	131.91	129.03-120.66 (6 signals) 142.45-139.24 (3 signals)	48.55 $\underline{C}H_2$, 10.05 $\underline{C}H_3$
[72]	47.00	48.91	114.88	120.30	133.18	131.82	131.01-120.72 (8 signals) 143.14-139.37 (3 signals)	55.89 $\underline{C}H_2Ph$
[73]	49.33	49.82	120.23	124.55	133.31	132.33	129.22-121.14 (9 signals) 141.87-136.94 (4 signals)	56.14 $\underline{C}H_2CH_2Ph$ 29.81 $CH_2\underline{C}H_2Ph$
[74]	48.59	49.43	115.14	120.56	133.05	131.85	128.99-120.69 (4 signals) 142.65-139.18 (3 signals)	53.32, 26.43, 19.85 3x$\underline{C}H_2$; 13.36 $\underline{C}H_3$
[75]	46.67	47.52	115.44	121.21	133.02	131.85	129.06-120.78 (5 signals) 142.49-139.89 (3 signals)	63.96 N-$\underline{C}H(R)_2$; 21.57, 21.05 2x$\underline{C}H_2$; 9.99, 9.86 2x$\underline{C}H_3$
[76]	48.46	49.50	115.08	120.46	133.05	131.83	129.01-120.72 (4 signals) 142.59-139.20 (3 signals)	53.42, 30.81, 26.12, 24.49 22.09 5x$\underline{C}H_2$; 13.65 $\underline{C}H_3$
[77]	46.06	46.80	115.73	121.31	133.08	131.91	129.06-120.72 (6 signals) 142.55-139.92 (4 signals)	61.98 N-$\underline{C}H$-; 28.32, 27.93 24.81, 24.29 4x$\underline{C}H_2$
[78]	49.30	49.85	114.79	120.30	133.08	131.75	129.64-120.76 (6 signals) 143.17-139.11 (3 signals)	58.77 N-$\underline{C}H_2$-; 33.73 $\underline{C}H$- 31.04, 25.46, 25.14 3x$\underline{C}H_2$

a) see Table 10 for structure of R.

Table 10: Analytical Data for the 2-Alkyl-9-Phenyl-2,3-Dihydro-1*H*-Indeno[2,1-c]pyridines.



COMPOUND FORMULA	R =	YIELD (%)	M.P. / ^{O}C (DECOMP.)	FOUND (%) (REQUIRED) C	H	N
[70] $C_{19}H_{17}N.HBr$	CH_3	70	208-209	67.2 (67.1	5.27 5.29	4.05 4.12)
[71] $C_{20}H_{19}N.HBr$	CH_2CH_3	68	194-195	- (-	- -	- -)
[72] $C_{25}H_{21}N.HBr$	CH_2Ph	78	196-197	72.1 (72.1	5.42 5.29	3.34 3.37)
[73] $C_{26}H_{23}N.HBr$	CH_2CH_2Ph	65	201-202	- (-	- -	- -)
[74] $C_{22}H_{23}N.HBr$	Butyl	87	198-199	68.9 (69.1	6.35 6.28	3.61 3.66)
[75] $C_{23}H_{25}N.HBr$	$CH(CH_2CH_3)_2$	83	207-208	69.6 (69.7	6.63 6.57	3.47 3.54)
[76] $C_{24}H_{27}N.HBr$	Hexyl	84	196-197	70.0 (70.2	6.84 6.63	3.37 3.41)
[77] $C_{24}H_{25}N.HBr$	Cyclohexyl	61	218-219	70.5 (70.6	6.47 6.37	3.39 3.43)
[78] $C_{25}H_{27}N.HBr$	Cyclohexyl-methyl	52	206-207	- (-	- -	- -)

5.4 PHENINDAMINE ANALOGUES.

5.41 The 2-Alkyl-9-Phenyl-2,3,4,4a-Tetrahydro-1*H*- Indeno[2,1-c]pyridines.

5.41.1 2-Phenethyl-9-Phenyl-2,3,4,4a-Tetrahydro-1*H*- Indeno[2,1-c] pyridine HBr. [81].

A solution of 2-phenethyl-9-phenyl-2,3-dihydro-1*H*- indeno[2,1-c]pyridine HBr [73] (4.3g, 0.01mol) in ethanol (250ml) was hydrogenated over palladium (0.4g, 10% on activated carbon), at a pressure of 100 psi for 6h at room temperature. The catalyst was removed through celite, and the residual ethanolic solution was concentrated at the pump. The product was recrystallized from an ethanol-ether to give **[81]** (2.98g, 69%) as a white solid, m.p. 122-123°C.

A similar method was used for the synthesis of
2-methyl-9-phenyl-2,3,4,4a-tetrahydro-1*H*-indeno[2,1-c] pyridine HBr **[51]**,
2-ethyl-9-phenyl-2,3,4,4a-tetrahydro-1*H*- indeno[2,1-c] pyridine HBr **[79]** and
2-benzyl-9-phenyl- 2,3,4,4a-tetrahydro-1*H*-indeno[2,1-c] pyridine HBr **[80]**.

5.41.2 2-Methyl-9-Phenyl-2,3,4,4a-Tetrahydro-1*H*- Indeno[2,1-c]pyridine HCl [86].

To 2-methyl-9-phenyl-2,3,4,4a-tetrahydro-1*H*-indeno[2,1-c] pyridine HBr **[51]** (1.0g, 2.9mmol) was added ammonia solution (pH 10). The green mixture was extracted with ether (3x50ml), and washed with a saturated solution of ammonium chloride (50ml). The dried ethereal extract was condensed to a small volume. Hydrogen chloride gas was bubbled into the ethereal solution to precipitate a yellow solid which was recrystallized from ethanol-ether to give **[86]** (0.68g, 79%), as a white solid m.p.

198-199°C (Lit.,[157] 169-171°C).

The ^{13}C NMR, ^{1}H NMR and microanalytical data for the 2-alkyl-9-phenyl-2,3,4,4a-tetrahydro-1*H*-indeno[2,1-c] pyridines are presented in Tables **11**, **14** and **17** respectively.

5.42 Geometric Isomers of 2-Alkyl-9-Phenyl-2,3,4,4a- and 2,3,4,9-Tetrahydro-1*H*-Indeno[2,1-c]pyridines.

5.42.1 2-Cyclohexyl-9-Phenyl-2,3,4,4a- and 2,3,4,9-Tetrahydro-1*H*-Indeno[2,1-c]pyridine HBr [84].

A solution of 2-cyclohexyl-9-phenyl-2,3-dihydro-1*H*- indeno[2,1-c]pyridine HBr [77] (4.10g, 0.01mol) in ethanol (250ml) was hydrogenated over palladium (0.4g, 10% on activated carbon), at a pressure of 100 psi for 16h at room temperature. The catalyst was removed through celite, and the residual ethanolic solution was condensed at the pump. The product was recrystallized from ethanol- ether to give [84] (3.80g, 92%) as a white solid, m.p. 149-151°C.

The same procedure was used for the synthesis of geometric isomeric 2-ethyl-9-phenyl-2,3,4,4a- and 2,3,4,9- tetrahydro-1*H*-indeno[2,1-c]pyridine HBr [82] and 2-(1-ethylpropyl)-9-phenyl-2,3,4,4a- and 2,3,4,9-tetrahydro-1*H*-indeno[2,1-c]pyridine HBr [83].

5.42.2 2-Ethyl-9-Phenyl-2,3,4,4a- and 2,3,4,9-Tetrahydro-1*H*-Indeno[2,1-c]pyridine HCl [86].

To 2-ethyl-9-phenyl-2,3,4,4a-tetrahydro-1*H*-indeno[2,1-c] pyridine HBr [51] (1.0g, 2.8mmol) was added ammonia solution (pH 10). The green mixture was extracted with ether (3x50ml), and washed with a saturated solution of ammonium chloride (50ml). The dried ethereal extract was condensed to a small volume. Hydrogen chloride gas was bubbled into the ethereal solution to precipitate a yellow solid which was recrystallized from ethanol-ether to give [86] (0.56g, 64%), as a white solid m.p. 178-180°C

5.42.3 2-Benzyl-9-Phenyl-2,3,4,4a- and 2,3,4,9-Tetrahydro-1*H*-Indeno[2,1-c] pyridine HBr [90].

To a solution of 2-benzyl-9-phenyl-2,3,4,4a-tetrahydro-1*H*- indeno[2,1-c] pyridine[62] (50mg, 0.12mmol), in absolute ethanol (10ml) was added palladium catalyst (10 mg, 5% on activated carbon). The mixture was stirred for three weeks at room temperature, the catalyst was removed, and the filtrate was evaporated *in vacuo* to give [90] (40mg,80%) as a yellow solid, m.p. 105-110°C. The product was not further purified.

The ^{13}C NMR, ^{1}H NMR and microanalytical data for the 2-alkyl-9-phenyl-2,3,4,4a- and 2,3,4,9-tetrahydro-1*H*- indeno[2,1-c]pyridines are presented in Tables **12**, **15** and **17** respectively.

5.43 The 2-Alkyl-9-Phenyl-2,3,4,9-Tetrahydro-1*H*- Indeno[2,1-c]pyridines.

5.43.1 2-Hexyl-9-Phenyl-2,3,4,9-Tetrahydro-1*H*- Indeno[2,1-c]pyridine HBr [85].

A solution of 2-hexyl-9-phenyl-2,3-dihydro-1*H*- indeno[2,1-c]pyridine HBr **[76]**(2.90g, 0.01 mol) in ethanol (250ml) was hydrogenated over palladium (0.3g, 10% on activated carbon), at a pressure of 100psi for 48h at room temperature. The catalyst was removed through celite, and the residual ethanolic solution was condensed at the pump. The product was recrystallized from ethanol-ether to give **[85]**(2.22g, 78%) as a white solid, m.p. 176-177°C.

5.43.2 2-Phenethyl-9-Phenyl-2,3,4,9-Tetrahydro-1*H*- Indeno[2,1-c]pyridine HCl [88].

A saturated solution of hydrogen chloride in dry ether was added dropwise to 2-phenethyl-9-phenyl-2,3,4,4a- tetrahydro-1*H*-indeno[2,1-c]pyridine (1.0g, 2.4mmol) in absolute ethanol until the solution went cloudy. The suspension was cooled and the product was collected and washed with ether (2x25ml) to give **[88]** (0.77g, 89%) as a white solid, m.p.140-141°C.

The above method was used to synthesise 2-phenethyl-9-phenyl-2,3,4,9-tetrahydro-1*H*-indeno[2,1-c] pyridine HCl **[89]**.

The ^{13}C NMR, ^{1}H NMR and microanalytical data for the 2-alkyl-9-phenyl-2,3,4,9-tetrahydro-1*H*-indeno[2,1-c] pyridines are presented in Tables **13**, **16** and **17** respectively.

Table 11: ^{13}C NMR Data for the 2-Alkyl-9-Phenyl-2,3,4,4a-Tetrahydro-1*H*-Indeno[2,1-c]pyridines.

COMPOUND	CH (non-Ar)	CH_2	Ar-CH	Ar-C_q	N-R[b]
[51]	45.28[a] 45.93	53.61[a], 52.71 51.38[a], 51.08 27.44[a], 23.92	121.31-128.96 (6 pairs)	129.12-144.92 (3 pairs)	43.11[a], 37.43 2 x CH_3
[79]	45.67	50.83, 27.05	120.36-128.83 (6 signals)	132.27-145.50 (4 signals)	9.02, CH_3 49.85, CH_2
[80]	45.90[a]	49.85[a], 49.59 47.78, 35.42 29.09	123.58-133.11[c] (9 signals)	134.41-143.27[c] (3 signals)	56.89[a], 56.05 2xCH_2
[81]	45.82[a]	50.79, 50.60 36.38	119.06-128.98[c] (6 pairs)	132.43-145.72[c] (6 signals)	56.47[a], 55.79 2 x CH_2

a) epimeric signals.
b) see Table 17 for structure of R.
c) includes signals in R.

Table 12: ^{13}C NMR Data for the 2-Alkyl-9-Phenyl-2,3,4,4a- and 2,3,4,9-Tetrahydro-1*H*-Indeno[2,1-c]pyridines.

COMPOUND	CH (non-Ar)	CH_2	Ar-CH	Ar-C_q	N-R[c]
[82]	45.97[a], 55.98[b]	52.03, 51.54 50.17, 49.66 48.39, 48.13 44.76, 24.16	118.81-129.11 (6 pairs)	129.03, 128.21 126.04	9.66, 9.50 2xCH_3 48.75, 48.59 2xCH_2
[83]	45.90[a], 55.85[b]	65.55, 49.90 47.48, 47.16 46.90, 46.38	118.68-128.96 (16 signals)	131.04-145.41 (10 signals)	69.05, 59.49 2xN-CH 27.02-19.20 6xCH_2 15.02-8.11 6xCH_3
[84]	45.93[a], 55.21[b]	47.10, 46.84 26.69, 26.11 25.92, 25.52 24.65, 24.49	120.17-128.83 (8 signals)	132.53-145.50 (5 signals)	64.25 N-CH
[102]	54.91[a], 45.80[b]	42.17, 41.84 40.90, 39.83 27.41, 19.01	118.65-128.77 (10 signals)	132.56-147.32 (10 signals)	

a) H-4a CH signals.
b) H-9 CH signals.
c) see Table 17 for structure of R.

Table 13: ^{13}C NMR Data for the 2-Alkyl-9-Phenyl-2,3,4,9-Tetrahydro-1*H*-Indeno[2,1-c]pyridines.

COMPOUND	CH (non-Ar)	CH_2	Ar-CH	Ar-C_q	N-R[a]
[85]	55.17	54.87, 49.33 30.68	119.00-128.93 (8 signals)	134.83-147.80 (5 signals)	48.64-19.56 5 x CH_2 13.85 CH_3
[88]	55.85[b], 56.05	48.81, 48.33 47.68, 47.10 18.75, 18.39	118.68-131.01 (6 pairs)	128.25-147.51 (6 pairs)	57.31, 57.07 2 x N-CH_2Ph
[89]	54.72[b], 55.14	55.59, 55.50 49.07, 48.88 48.49, 47.91 29.48, 29.32	118.81-128.80 (7 pairs)	134.57-147.74 (5 pairs)	

a) see Table 17 for structure of R.
b) epimeric signals of H-9.

Table 14: 270 MHz ^{1}H NMR Data for the 2-Alkyl-9-Phenyl-2,3,4,4a-Tetrahydro-1*H*-Indeno[2,1-c]pyridines.

Assignment of protons	[51]	[79]	[80]	[81]
axH-4 ^{2}J/Hz ^{3}J/Hz	1.79, dq 12.6 3.6	1.27, m	1.89, m	1.54[a], dq
eqH-4 ^{2}J/Hz ^{3}J/Hz	2.44, dd 12.6 5.4	2.80, br	2.50[a], dd	2.79[a], dd
H-4a ^{3}J/Hz	3.32, d 10.8	3.27, m	3.76[a], dd	3.43, m
H_2-3	3.58, m	3.66, m	3.70, m	3.81, m
axH-1	4.18, m	4.27, m	4.65, m	4.41, m
eqH-1	4.18, m	4.27, m	4.65, m	4.41, m
Ar-H	7.33, m	7.58, m	7.66, m	7.63, m
N-R[b]	2.72, s	1.27[a], t 3.27[a], q	3.53, m	3.43, m

a) unresolved signals.
b) see Table 17 for structure of R.

Table 15: 270 MHz ^{1}H NMR for the 2-Alkyl-9-Phenyl-2,3,4,4a- and 2,3,4,9-Tetrahydro-1*H*-Indeno[2,1-c]pyridines.

Assignment of protons	[82]	[83]	[84]	[102]
axH-4	1.58, m	1.50, m	1.45, dq[a]	1.42, dq[a]
H-4a/H_2-3	4.14, m	4.42, m	3.67, m	4.07, m
H_2-1				
eqH-4	2.72, m	2.65, m		2.84[a], dd
H-9	4.34, br	4.47, br	4.20, br	4.68, br
Ar-H	7.54, m	7.55, m	7.68, m	7.59, m
N-R[b]	1.23, t 6.96 Hz, $C\underline{H}_3$	1.56[a], t 2x$C\underline{H}_3$	1.90, m	
	3.5, q 6.96 Hz, $C\underline{H}_2$	3.51[a], q 2x$C\underline{H}_2$		

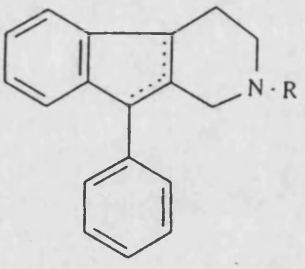
a) unresolved signals.
b) see Table 17 for structure of R.

Table 16: 270 MHz ^{1}H NMR Data for the 2-Alkyl-9-Phenyl-2,3,4,9-Tetrahydro-1*H*-Indeno[2,1-c]pyridines.

Assignment of protons	[85]	[88]	[89]
H_2-4	2.94, br	4.44, m	3.19, m
H_2-3	3.21, br		3.50, m
H_2-2	4.08, br		3.83, m
H-9	4.72, brd	4.89, brd	4.82, brd
Ar-H	7.62, m	7.67, m	7.61, m
N-R[a]	1.72, m	4.44, m	3.19, m

a) see table 17 for structure of R.

Table 17: Analytical Data for the N-2 Alkyl Substituted Phenindamine Analogues.



COMPOUND FORMULA	R =	YIELD (%)	SOLVENT	M.P. / °C (DECOMP.)	FOUND (%) (REQUIRED) C	H	N
[51][a] $C_{19}H_{19}N.HBr$	CH_3	59	EtOH/Et_2O	184-185	66.8 (66.7	5.81 5.85	3.97 4.09)
[79][a] $C_{20}H_{21}N.HBr$	CH_2CH_3	66	EtOH/Et_2O	182-184	67.2 (67.4	6.21 5.90	3.90 3.93)
[80][a] $C_{25}H_{23}N.HBr.2H_2O$	CH_2Ph	67	EtOH/Et_2O	185-187	66.1 (66.1	5.95 5.73	3.08 2.96)
[81][a] $C_{26}H_{25}N.HBr.H_2O$	CH_2CH_2Ph	69	EtOH/Et_2O	122-123	69.3 (69.5	6.00 6.22	3.11 3.12)
[83][b] $C_{23}H_{27}N.HBr$	Butyl	89	EtOH/Et_2O	159-161	68.9 (69.3	6.85 7.04	3.47 3.52)
[84][b] $C_{24}H_{27}N.HBr$	Cyclohexyl	92	EtOH/Et_2O	149-151	69.9 (70.2	6.74 6.83	3.36 3.41)
[85][c] $C_{24}H_{29}N.HBr$	Hexyl	78	EtOH/Et_2O	176-177	69.7 (69.9	7.34 7.28	3.34 3.40)
[87][b] $C_{20}H_{21}N.HCl.H_2O$	CH_2CH_3	64	EtOH/Et_2O	178-180	72.3 (72.8	7.11 6.96	4.20 4.25)
[88][c] $C_{25}H_{23}N.HCl.2H_2O$	CH_2Ph	92	EtOH/Et_2O	188-189	73.3 (73.3	6.59 6.51	3.42 3.30)
[89][c] $C_{26}H_{25}N.HCl.1.5H_2O$	CH_2CH_2Ph	89	EtOH/Et_2O	140-141	75.3 (75.1	6.76 6.97	3.38 3.35)

a) 9,9a-ene isomers.
b) a mixture of 9,9a- and 4a,9a-ene isomers.
c)4a,9a-ene isomers.

5.5 THE 2-Alkyl-9-Phenyl-2,3,4,4a,9,9a-Hexahydro-1*H*- Indeno[2,1-c]pyridines.

5.51 *All cis*-9-Phenyl-2,3,4,4a,9,9a-Hexahydro-1*H*- Indeno[2,1-c]pyridine HBr [93].

A solution of 2-benzyl-9-phenyl-2,3-dihydro-1*H*- indeno[2,1-c]pyridine HBr [72](14.0g, 34mmol) in ethanol (95%, 250ml) was hydrogenated with palladium (1.0g, 5% on activated carbon) at 70°C, and 100psi for 6h. The catalyst was removed and the filtrate was evaporated *in vacuo* to a small bulk. Ether was added until the solution went cloudy. Crystals of [93] were collected and dried. (7.60g, 68%), m.p. 235-237°C. (Lit.,[180] 275-277°C). (Found: C, 65.2; H, 6.11; N, 4.20 $C_{18}H_{20}BrN$ requires C, 65.5; H, 6.06; N, 4.24%).

The HBr salt (6.0g, 18mmol) was treated with ammonia solution (pH10), then extracted with ether (3x50ml), washed with a saturated solution of ammonium chloride (50ml), and dried. The ethereal solution was evaporated to give a colourless oil which solidified on standing, (4.21g, 94%), m.p. 84.5-85.5°C.

δ_H ($CDCl_3$, HBr salt) 8.93(1H, s, NH), 8.68(1H, s, NH), 7.35(9H, m, Ar-H), 4.56(1H, d, $J_{9,9a}$ 5.9Hz., H-9), 3.4(1H, brs, H-4a), 3.27(1H, m, $J_{9,9a}$ 5.9Hz., H-9a), 2.65(6H, m, H_2-1, H_2-3, H_2-4).

δ_C ($CDCl_3$, HBr salt) 142.81-136.32 (3 x Ar-Cq), 128.86-122.67 (6 x Ar-C), 42.13 (C-1), 40.28 (C-3), 20.86 (C-4), 39.76 (C-9a), 53.03 (C-9), 42.62 (C-4a).

5.52 *Trans-9-Phenyl*-2,3,4,4a,9,9a-Hexahydro-1*H*- Indeno[2,1-c] pyridine HCl [94].

The foregoing product [93](2.70g, 11mmol) was boiled under reflux with a solution of potassium hydroxide in n-butanol (25%, 50ml) for 24h. The cooled mixture was evaporated. The product was dissolved in ether and washed with brine (50ml). The ethereal extract was dried (Mg SO_4) and concentrated *in vacuo* to a give a colourless oil.

A solution of the oil in dry ether was treated with ethereal HCl, and the above named product was recrystallized from absolute ethanol, (2.52g, 80%), m.p. 249-250°C. (Found: C, 75.5; H, 6.92; N, 4.79 $C_{18}H_{20}ClN$ requires C, 75.7; H, 7.01; N, 4.90%).

δ_H ($CDCl_3$, HCl salt): 9.50(2H, s, NH_2), 7.39(9H, m Ar-H), 4.78 (1H, d, $J_{9,9a}$ 9.9Hz., H-9), 3.37(1H, m, J^3 6.2Hz., $J_{4a,9a}$ 5.2Hz., J^3 5.9Hz., H-4a), 3.22(2H, dd, $J_{4a,9a}$ 5.2Hz. $J_{9,9a}$ 9.9Hz., H-9a), 3.11(6H, m, H_2-1, H_2-3, H_2-4).

δ_C ($CDCl_3$, HCl salt) 145.83-142.10 (3 x Ar Cq), 128.57-123.54 (6 x Ar-C), 41.55 (C-1), 41.29 (C-3), 25.13 (C-4), 39.15 (C-9a), 50.08, (C-9), 45.93 (C-4a).

5.53 *Cis*-2-Phenethyl-9-Phenyl-2,3,4,4a,9,9a- Hexahydro-1*H*- Indeno[2,1-c]pyridine Hydrochloride [95].

To a stirred slurry of *all cis*-9-phenyl-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-c]pyridine [93](0.25g, 1.00mmol), dried potassium carbonate (0.15g, 1.10mmol) and potassium iodide (0.06g, 0.50 mmol) in dry acetonitrile (20ml) was added a solution of (2-bromoethyl)benzene (0.20g, 1.10mmol) in dry acetonitrile (5ml), the resulting mixture was refluxed gently for 18 h. The

(3x50ml). The ethereal layer was washed with water (2x10ml), dried ($MgSO_4$), and concentrated *in vacuo* to give a colourless oil, which was converted to the hydrochloride salt. The product was recrystallized from ethanol-acetone to give **[95]** (0.32g, 82%) as white crystals, m.p. 258-260°C. (Found: C 79.9, H 7.29, N 3.53 $C_{26}H_{27}N.HCl$ requires C 80.1, H 6.93, N 3.59%).

δ_H (DMSO-d_6, HCl salt): 10.98(1H, s, N<u>H</u>), 7.45(14H, m, Ar-<u>H</u>), 4.69(1H, d, $J_{9,9a}$ 5.9Hz., <u>H</u>-9), 3.48(2H, br, N-C<u>H_2</u>), 3.36(1H, brs, <u>H</u>-9a), 3.26(1H, m, <u>H</u>-4a), 3.07(2H, m, <u>H_2</u>-1), 2.96(2H, m, <u>H_2</u>-3), 3.26(4H, m, <u>H_2</u>-4, N-CH_2C<u>H_2</u>Ph).

δ_C (DMSO-d_6, HCl salt): 167.85-131.85 (5xAr-<u>C_q</u>), 129.12-123.41 (8xAr-<u>C</u>H), 56.66 (N-<u>C</u>H_2), 50.82 (<u>C</u>-1), 47.71 (<u>C</u>-3), 29.32 (<u>C</u>-4), 21.31 (N-CH_2<u>C</u>H_2Ph), 52.48 (<u>C</u>-9), 43.30 (<u>C</u>-9a), 39.37 (<u>C</u>-4a).

5.6 N-Debenzylation.

5.61 3-Benzoyl-4-Hydroxy-4-Phenylpiperidine-1- (2,2,2-trichloroethoxycarbonyl) Piperidine [96].

To a solution of the 3-benzoyl-1-benzyl-4-hydroxy-4- phenylpiperidine (16.0g, 43mmol) in dry toluene (75ml), was added 2,2,2-trichloroethylchloroformate (9.14g, 43mmol) portionwise. The mixture was stirred at room temperature for 24h. The solution was diluted with ether (100ml), and washed with water (50ml), then with a saturated solution of ammonium chloride (50ml). The organic layer was dried (Mg SO_4), filtered, and evaporated to dryness at the pump to yield a yellow oil which solidified overnight. Recrystallizatiom from absolute ethanol gave **[96]** (12.01g, 61%), m.p. 115-116°C (Found: C, 55.6; H, 4.56; N, 2.85. $C_{21}H_{20}Cl_3NO_4$ requires C, 55.2; H, 4,38; N, 3.07).

δ_H ($CDCl_3$): 7.91 (10H, m, Ar-H), 5.22 (1H, s, OH), 5.09 (0.5H, d, J^2 12.1Hz., $NCO_2CH_2CCl_3$), 4.95 (0.5H, d, J^2 11.7Hz., $NCO_2CH_2CCl_3$), 4.79 (0.5H, d, J^2 11.9Hz., $NCO_2CH_2CCl_3$), 4.66 (0.5H, d, J^2 12.1Hz., $NCO_2CH_2CCl_3$), 4.56 (1H, m, H-3), 4.27 (2H, m, H_2-2), 3.65 (2H, m, H_2-6), 1.96 (2H, m, H_2-5).

δ_C ($CDCl_3$): 146.15 (C=O carbamate), 134.28-124.39 (8 x Ar-C), 125.04 ($-CCl_3$), 75.28 ($COCH_2CCl_3$), 73.47 (C-4), 50.24, 49.75 (2 x C-3), 44.05, 43.56 (2 x C-1), 43.01, 40.90 (2 x C-6), 39.83, 39.54 (2 x C-5).

5.62 3-Benzoyl-4-Hydroxy-4-Phenylpiperidine HCl [97].

The foregoing carbamate [96](10.0g, 22mmol) was dissolved in acetic acid (150ml), zinc dust (11.40g, 180mmol) was added portionwise to the solution and the suspension was heated at reflux for 2h. The cooled mixture was stirred further for 2h. The zinc was removed. The filtrate was evaporated *in vacuo* to a small volume and treated with ammonia solution (pH10). The mixture was extracted with ether (5x50ml), dried (Mg SO_4) and evaporated to give a yellow oil, which was converted to the hydrochloride salt. The product was recrystallized from absolute ethanol to give [97] (3.81g, 55%) as a white solid, m.p. 145-146°C (Found C, 66.6; H, 6.28; N, 4.35. $C_{18}H_{20}ClNO_2.0.5H_2O$ requires C,66.2; H, 6.43; N, 4.29%). No NMR data were recorded.

5.63 2-Benzyl-9-Phenyl-2,3-dihydro-1*H*-Indeno[2,1-c] pyridine-2-(2,2,2-trichloroethyl) Carbamate[99].

2-Benzyl-9-phenyl-2,3-dihydro-1*H*-indeno[2,1-c]pyridine HBr [72] (16.64g, 40mmol) was basified with ammonia solution, and the green mixture was extracted with ether (4x50ml) and washed with brine. The ethereal extract was dried and evaporated to dryness to give a dark green oil, (12.60g, 94%).

The oil (12.60g, 38mmol) was dissolved in dry toluene (150ml), and to this was added 2,2,2-trichloroethyl- chloroformate (8.0g, 38mmol) dropwise. The green solution turned yellow. Stirring was continued in an anhydrous environment for 5 days. The solution was then washed with HCl (6N, 2x50ml), water (50ml). The dried solution was concentrated *in vacuo* to give a yellow solid. Recrystallization from absolute

δ_H ($CDCl_3$): 7.61(9H, m, Ar-H), 6.82(1H, dt, H-4a), 4.80(4H, m, H_2-1, -$CO_2CH_2CCl_3$), 4.55(2H, dd, $J_{ax/eq}$ 3.7Hz., $J_{ax/ax}$ 15.8Hz., H_2-3).

δ_C ($CDCl_3$): 133.83, 133.66 (2 x Ar-C_q), 128.77-122.31, (7 x Ar-CH), 119.94, 119.78 (2xC-4), 75.22 (-$CO_2CH_2CCl_3$), 44.01, 43.49, 42.07 (3 x CH_2).

5.64 9-Phenyl-2,3-Dihydro-1*H*-Indeno[2,1-c]pyridine HCl [100].

Zinc dust (10.92g, 170mmol) was added to the carbamate [88](9.00g, 12mmol) in acetic acid (150ml) at 0°C. The reaction mixture was stirred at room temperature for 2h., heated at reflux for 2h, and cooled to room temperature and stirred for 16h. The zinc was filtered off, and the solution was distilled at the pump. To the product was added water (30ml), and ammonia solution (50ml, pH > 10). The aqueous solution was extracted with ether (5x75ml). The ethereal extract was washed with brine (2x50ml), and dried, then condensed at the pump to a small volume. Ethereal HCl was then added portionwise to precipitate the solid which was recrystallized from ethanol-ether to give the above named product, (2.91g, 49%), m.p. 222-223°C. (Found: C, 72.5, H, 5.58; N, 4.64 $C_{18}H_{16}ClN.H_2O$ requires C, 72.1; H, 6.01; N, 4.67%).

δ_H (DMSO-d_6): 9.92(2H, s, NH_2), 7.86(9H, m, Ar-H), 7.11(1H, t, J^3 4.0Hz, H-4), 4.40(2H, s, H_2-1), 4.15(2H, d, J^3 4.0Hz., H_2-3).

δ_C (DMSO-d_6): 141.67-137.55 (3 x Ar-C_q), 129.12-120.85 (6 x Ar-CH), 133.60 (C-9), 132.62 (C-9a), 124.68, (C-4a) ,119.94 (C-4), 41.61, 40.51 (C-1, C-3).

5.65 2-Benzyl-9-Phenyl-2,3,4,9-Tetrahydro-1*H*-Indeno[2,1-c] pyridine-2-(2,2,2-trichloroethyl) Carbamate [101].

2,2,2-Trichloroethyl chloroformate (8.48g, 40mmol) was added dropwise to a solution of the free base of [81](13.35g, 40mmol) in dry toluene (200ml). The mixture was stirred for 3 days, and then diluted with ether (100 ml), washed with HCl (6N, 50ml), brine (50ml) and the organic layer dried ($MgSO_4$) and evaporated *in vacuo*. The product was purified through a silica bed (eluent: toluene), to give a thick yellow oil, (15.67g, 93%) b.p. was not recorded. The product was used without further purification.

5.66 9-Phenyl-2,3,4,4a and 2,3,4,9-Tetrahydro-1*H*- Indeno[2,1-c]pyridine HCl [102].

The foregoing carbamate [101](15.57g, 370mmol) was heated at reflux with zinc dust (17.33g, 270mmol) in acetic acid (150 ml) for 2.5h. The zinc was filtered and the acidic solution was concentrated to a small volume . Water (30 ml) was added and the suspension was basified with ammonium hydroxide solution (pH 10). The solution was extracted with ether (5x75 ml), dried ($MgSO_4$) and evaporated to dryness. The resulting yellow oil was converted to the hydrochloride salt to give a yellow solid which was purified with charcoal, and then recrystallized from acetone to give [102] (4.67g, 43%) as a white solid m.p. 206-207°C (Found: C, 74.9; H, 6.29; N, 4.78. $C_{18}H_{18}ClN.0.25H_2O$ requires C, 74.99; H, 6.47; N, 4.86%).

δ_H (DMSO-d_6, HCl salt): See Table 15.

δ_C (DMSO-d_6): 147.51-134.72 (9 x Ar-$\underline{C}_q$), 128.96-118.84 (10 x Ar-$\underline{C}$H), 55.10 ($\underline{C}$-9a), 45.99 ($\underline{C}$-4a), 42.33, 45.03, 41.09, 27.57, 19.20 ($\underline{C}$-1, $\underline{C}$-3, $\underline{C}$-4).

5.7 THE ARECOLINE ROUTE.

5.7.1 Diastereomeric Methyl 1-Methyl-4-Phenylpiperidine-3- Carboxylates.

Arecoline hydrobromide (Methyl 1-methyl-1,2,5,6- tetrahydronicotinate HBr(20.0g, 0.085mol) was basified with potassium carbonate (50% w/v, 2x50ml). The aqueous suspension was extracted with toluene, dried ($MgSO_4$), and condensed to give the yellow oil of arecoline, (12.35g, 94%).

A suspension of magnesium turnings (3.74g, 154mmol) in dry ether (50ml) was placed in a 3-necked flask fitted with a condenser and a separating funnel. A drying tube was placed at the top of the condenser. Bromobenzene (24.18g, 154mmol) in dry ether was added dropwise from the separating funnel to the stirred mixture. The reaction was initiated with a crystal of iodine. After addition, reflux was maintained for a further 0.5 h, then cooled to -10°C in an ice-acetone bath. Arecoline (11.90g, 77mmol) was added dropwise with stirring at -10°C. The reaction mixture was added to crushed ice (50g) and acidified with cold hydrochloric acid (6N, 80ml). The aqueous layer was collected and treated with potassium carbonate (50% w/v, 150ml), and the insoluble magnesium hydroxide was removed by centrifuge. The aqueous layer was extracted with ether (8x100ml), dried over Mg SO_4. The ethereal layer was evaporated *in vacuo* to give the yellow oil (16.10g, 90%) of the above named product, b.p. 126-130°C/0.4mm Hg. (Lit.[187] 124-128°C/0.5 mmHg).

δ_H($CDCl_3$, free base): 7.33(5H, m, Ar-H), 3.94(1H, m, H-4, H-3, eq H-2), 3.42(3H, 2xs, CO_2CH_3), 3.37(3H, m, eq H-6, ax H-6, ax H-2), 2.98(3H, 4xs, N-CH_3), 2.73(1H, m, eqH-5), 2.24(1H, m, ax H-5).

δ_C($CDCl_3$, free base): 170.77 (C=O), 139.99, 138.69 (2x C_q), 128.70-126.76 (6x Ar-CH), 54.85-54.20 (2x C-2, 2x C-6), 51.96, 51.70 (2x CO_2CH_3), 45.63-35.65 (4x CH), 43.59, 43.46 (2x N-CH_3), 29.45, 28.87 (2xC-5).

5.72 Separation of the Diastereomers of Methyl 1-Methyl-4-Phenylpiperidine-3-Carboxylates.

5.72.1 α-*Trans*-(*t* 3-CO_2Me r-4-Ph)-Methyl 1-Methyl-4-Phenylpiperidine-3-Carboxylate HCl [104].

A saturated solution of hydrogen chloride in dry ether was added dropwise to a solution of diastereomers of methyl 1-methyl-4-phenylpiperidine-3-carboxylate (16.10g, 69mmol) in dry ether. The white precipitate was washed with ether (2x50 ml) and recrystallized from ethanol to give **[104]** (2.66g, 14.3%) as colourless crystals, m.p. 216-217°C, . (Found: C, 62.1; H, 7.59; N, 5.26. $C_{14}H_{20}ClNO_2$ requires C, 62.3; H, 7.59; N, 5.19%).

m/z: 233(M^+, 100), 174(13), 160(7), 155(3), 44(19).

5.72.2 β-*Cis*-(*c* 3-CO_2Me r-4-Ph)-Methyl 1-Methyl-4- Phenylpiperidine-3-Carboxylate HCl [105].

The mother liquor from **[104]** was condensed at the pump to give a white solid which was recrystallized from acetone giving **[105]** (8.69g, 47%) as a white solid, m.p. 190-192°C.

A small portion of the salt (0.5g) was then basified with aqueous ammonia, and

extracted with ether (4x25ml). The ethereal solution was dried and evaporated to dryness to give *cis*-methyl 1-methyl-4-phenylpiperidine-3-carboxylate, m.p. 53-54°C. (Lit.[187] 55-58°C).

m/z: 233(M^+, 78), 174(34), 155(26), 96(13), 70(12), 44(100).

5.73 α-*Trans*-(*t* 3-COOH r-4-Ph)-1-Methyl-4-Phenylpiperidine- 3-Carboxylic Acid HCl [106].

To a solution of the α-methyl 1-methyl-4-phenylpiperidine- 3-carboxylate HCl **[104]** (1.0g, 3.7mmol) in water (5ml) in a round-bottomed flask was added concentrated hydrochloric acid (6ml) and a few boiling stones. The mixture was then heated at 90-95°C for 0.5 h, at which time methanol and excess HCl was collected. The residue was evaporated to dryness and the product was recrystallized from absolute ethanol to give **[106]** (0.64g, 68%) as colourless prisms, m.p. 215-216°C, (Lit.,[187] 214-216°C) (Found: C, 60.0; H, 7.07; N, 5.31 $C_{13}H_{17}NO_2.HCl.0.5C_2H_5OH$ requires C, 60.32; H, 7.59; N, 5.02%).

δ_H (400 MHz, DMSO-d_6, HCl salt): 7.35(5H, m, Ar-H), 3.65(1H, m, eq H-2), 3.45(1H, m, ax H-2), 3.39(1H, td, $J_{ax/eq}$ 3.6Hz., $J_{ax/ax}$ 8.2Hz., ax H-4), 3.18(2H, t, J^3 12.2Hz., H_2-6), 2.97(1H, td, $J_{ax/eq}$ 3.6Hz., $J_{ax/ax}$ 8.2Hz., axH-3), 2.79(3H, s, N-CH_3), 2.21(1H, qd, $J_{ax/eq}$ 3.6Hz., J^3 12.6Hz.,eqH-5), 1.91(1H, dd, J^3 12.2 Hz., axH-5).

5.74 β-*Cis*-(*c* 3-COOH r-4-Ph)-1-Methyl-4-Phenylpiperidine- 3-Carboxylic Acid HCl [107].

A solution of the β-methyl 1-methyl-4-phenylpiperidine- 3-carboxylate **[105]**(7.5g, 27mmol) dissolved in water (25ml) and concentrated hydrochloric acid (30ml) was distilled at 90-95°C for 1 h. The residue was evaporated to dryness and the product was recrystallized from absolute ethanol to give **[107]** (5.13g, 74%) as flake-like crystals, m.p. 205-206°C, (Lit.,[187] 212-213°C) (Found: C, 59.8; H, 7.14; N, 5.41 $C_{13}H_{17}NO_2.HCl.0.5C_2H_5OH$ requires C, 60.32; H, 7.59; N, 5.02%).

δ_H(400 MHz, DMSO-d_6, HCl salt): 7.32(5H, m, Ar-H), 3.68(1H, d, J 12.9Hz., eqH-2), 3.63(1H, m, axH-2), 3.40(2H, m, axH-4, eqH-3), 3.15(2H, m, H_2-6), 2.80(3H, s, N-CH_3), 2.47(1H, qd, $J_{ax/eq}$ 3.6Hz., J^3 13.7Hz., eq H-5), 1.95(1H, m, ax H-5).

5.75 2-Methyl-9-Oxo-2,3,4,4a,9,9a-Hexahydro-1*H*- Indeno[2,1-c]pyridine HCl **[110]**.

To the α-acid HCl **[106]**(0.5g, 2.0mmol) was added thionyl chloride (10ml) with cooling. The mixture was left to stand for 4 h. Excess thionyl chloride was removed by vacuum distillation. The product was azeotroped with tetrachloromethane (2x20ml) to remove the last trace of thionyl chloride.

To this acid chloride (crude) dissolved in tetrachloromethane (10ml), was added anhydrous aluminium chloride (1.35g, 10mmol) portionwise with stirring at 40°C, until no more gas evolved. The mixture was stirred for 0.5h at 40°C, cooled and poured into crushed ice (20g). The aqueous layer containing the keto product was separated, and concentrated HCl (10ml) was added. The aqueous layer was washed with ether (2x50 ml), and then treated with ammonia solution (pH=10). The product was extracted with

ether (5x50ml), dried ($MgSO_4$), concentrated, and converted to the HCl salt, which recrystallized from ethanol-ether to give **[110]** (0.12g, 26%), m.p. 190.5-191°C. (Lit.,[187] 208-210°C).

A similar procedure was adopted for the β-acid **[96]**, to give **[110]** in a 40% yield, m.p. 189-190°C.

IR(ν_{max}/cm^{-1}, nujol mull): 3400(NH), 3100(CH-Ar), 2900(CH), 2600(N-Me), 1710(C=O), 1600(Ph).

δ_H(DMSO-d_6, HCl salt): 11.75 (1H, 2xs, +N-H), 7.7 (4H, m, Ar-H), 3.86(1H, brs., eq H-1), 3.63(1H, dd, $J_{ax/eq}$ 6.0Hz., J_{gem} 14.9Hz., axH-1), 3.30(3H, m, H_2-3, H-9a), 2.79(3H, 2xs, N-CH_3), 2.41(2H, m, eq H-4, H-4a), 1.53(1H, m, ax H-4).

δ_C(DMSO-d_6, HCl salt): 201.81 (C=O), 156.56, 133.86 (2x Ar-C_q), 135.22-123.80 (4 x Ar-CH), 51.28 (C-1), 48.32 (C-3), 28.99 (C-4), 45.24 (C-9a), 33.92 (C-4a), 42.84 (N-CH_3).

m/z: (M^+, 100%), 184(37), 44(18).

5.76 9-Hydroxy--2-Methyl-9-Phenyl-2,3,4,4a,9,9a-Hexahydro-1*H*-Indeno[2,1-c]pyridine [111].

To a solution of bromobenzene (80 mg, 0.1mmol) in dry THF(30 ml), was added butyllithium (1.0 M solution, 5ml) dropwise at -78°C. The solution was stirred at that temperature for 15 mins. To the mixture was added 2-methyl-9-oxo-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-c] pyridine **[110]** (100mg,

0.5mmol) dropwise at the same temperature. The suspension was allowed to warm to room temperature, and then poured into iced water (50 ml). Hydrochloric acid (25ml) was added, and the aqueous layer was washed with ether (4x20ml). The acidic solution was then neutralized with ammonia, and the product was extracted with ether (4x25ml), dried, and condensed at the pump to give a crude oil, (99mg, 71%). The above named product was used in the next step without further purification.

5.7.7 2-Methyl-9-Phenyl-2,3,4,4a-Tetrahydro-1*H*- Indeno[2,1-c]pyridine HCl **[86]**.

Thionyl chloride (10ml) was added to 9-hydroxy-2-methyl-9-phenyl-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-c]pyridine HCl **[111]** (90mg, 0.3mmol) with stirring. The mixture was stoppered and left to stand at room temperature for 24 h. Excess thionyl chloride was removed by distillation, and the product was basified with ammonia solution (20ml), and stirred at room temperature for 24 h. The product was extracted with ether (4x50ml). dried ($MgSO_4$), evaporated *in vacuo* to give a dark yellow oil which was converted to the HCl salt. Recrystallization from ethanol-ether gave **[86]** (60mg, 67%) as a white solid m.p.195-196°C. (Lit.,[157] 169-171°C).

5.7.8 9-Hydroxy-2-Methyl-9-(2-pyridyl)-2,3,4,4a9,9a-Hexahydro-1*H*-Indeno[2,1-c]pyridine HCl **[115]**.

To a solution of 2-bromopyridine (16mg, 0.1mmol) in dry THF(10 ml), was added butyllithium (1.0 M solution, 1ml) at -78°C. The solution was stirred at that temperature for 15 mins. To the mixture was added 2-methyl-9-oxo-2,3,4,4a,9,9a-Hexahydro-1*H*-indeno[2,1-c]pyridine (20mg, 0.1mmol) dropwise at the same temperature. The suspension was allowed to warm to room temperature, and then

poured into iced water (10ml). Concentrated hydrochloric acid (10ml) was then added, and the aqueous layer was washed with ether (4x20ml). The acidic solution was then basified with ammonia, and the product was extracted with ether (4x25ml), dried ($MgSO_4$), and evaporated *in vacuo* to give a yellow oil. To the oil, was added ethereal HCl, and the resulting yellow solid was collected, (13mg, 36%). The product was not further purified. ^1H NMR showed a broad peak at 5.18ppm corresponding to the O<u>H</u> which disappeared with a D_2O shake.

m/z: 280(M^++H, 1), 262(M^+-H_2O, 3), 78(Py, 4), 71(41), 57(100), 44(63).

5.8 Other Analogues of Phenindamine.

5.81 3-Benzyl-4-Hydroxy-1-Methyl-4-Phenylpiperidine HCl [120].

A mixture of 3-benzoyl-4-hydroxy-1-methyl-4- phenylpiperidine (1.0g, 3.38mmol) anhydrous hydrazine (5.0g, 156mmol) was heated under reflux for 2 h. Excess hydrazine was removed by distillation under vacuum. To the formed hydrazone was added triethylene glycol (30ml), and potassium hydroxide (0.5g). The suspension was heated under reflux for 3h, at which time the evolution of gas (N_2) had ceased. The product was extracted with ether (4x50ml). The ethereal layer was dried ($MgSO_4$) and then condensed at the pump to give a yellow oil, which was fractionated to give **[120]** (0.20g, 21%) as a colourless oil b.p. 121-124°C /2mmHg.

IR (ν_{max}/cm^{-1}, liquid film): absence of C=O stretch at 1690.

5.82 3-Benzyl-1-Methyl-1,2,3,6-Tetrahydropyridine [121].

A solution of 3-benzyl-4-hydroxy-1-methyl-4- phenylpiperidine (50 mg) in acetic acid (5ml) and concentrated hydrochloric acid (5ml) was heated under reflux for 6 h. The cooled mixture was then condensed to dryness at the pump, and then basified with ammonia solution. The product was extracted with ether (5x30ml). The ethereal extract was dried over $MgSO_4$, and then evaporated *in vacuo* to give a dark oil. TLC showed a multicomponent mixture which was not further investigated.

5.83 4-Hydroxy-3-(α-hydroxybenzyl)-4-Phenylpiperidine HCl [98].

To a solution of 3-benzoyl-1-benzyl-4-hydroxy-4- phenylpiperidine HCl [61](2.50g, 7.54mmol), in absolute ethanol(50ml), was hydrogenated with palladium hydroxide (25mg, 5% on activated carbon) at 70°C for 2h at 50 lbs psi. The catalyst was removed and the filtrate was condensed at the pump. The remaining solid was recrystallized from acetone to give crystals [98] (2.06g, 82%), m.p. 193-194°C, (Found: C, 67.2; H, 6.82; N, 4.34 $C_{18}H_{22}ClNO_2$ requires C; 67.6; H, 6.89; N, 4.38). The absence of the C=O stretching at 1690 cm^{-1} was noted.

δ_H (DMSO-d_6, HCl salt): 9.21(2H, brs, N$\underline{H}_2$), 7.51(10H, m, Ar-$\underline{H}$), 3.38(1H, s, O$\underline{H}$), 5.15(1H, d, J^3 3.7Hz., O$\underline{H}$), 4.48(1H, d, J 2.9Hz., C$\underline{H}$), 3.39(3H, m, eq$\underline{H}$-6, ax$\underline{H}$-2, eq$\underline{H}$-2), 2.85(2H, m, eq$\underline{H}$-5, ax$\underline{H}$-6), 2.22(1H, td, J 9.16Hz., J 12.8Hz., ax$\underline{H}$-3), 1.70(1H, d, J 14.6Hz., ax$\underline{H}$-5).

δ_C (DMSO-d_6, HCl salt): 147.16-143.13 (3x Ar-$\underline{C}_q$), 127.89-125.00 (6 x Ar-$\underline{C}$H), 71.10 ($\underline{C}$H), 47.74 ($\underline{C}$-4), 41.90 ($\underline{C}$-2), 39.47 ($\underline{C}$-6), 37.43 ($\underline{C}$-5).

5.84 Attempted Synthesis of 3-(benzylidene)-4-Phenyl- 1,2,5,6-Tetrahydro-pyridine Oxalate.

4-Hydroxy-3-(α-hydroxybenzyl)-1-methyl-4-phenylpiperidine HCl [98] (1.70g, 5.3mmol) was boiled under reflux with concentrated hydrochloric acid (50ml) and acetic acid (25ml) for 5h. The cooled mixture was reduced to a small volume at the pump, basified with concentrated ammonia solution, and extracted with ether (4 x 50ml). The ethereal extract was dried($MgSO_4$), and then titrated with a saturated solution of ethereal oxalic acid to give a product, which was recrystallized from

analysed and found to be (N-benzoylethyl)-N-(3-E-{phenyl}prop-2-ene)- amine oxalate **[122]**, (1.18g, 68%) as white crystals, m.p. 179-180°C (Found: C, 67.3; H, 6.16; N, 4.71 $C_{20}H_{21}NO_5$ requires C, 67.6; H, 5.92; N, 3.94%).

IR (ν_{max}/cm^{-1}, KBr disc): 1700(C=O), 1500(Ar), 1600 cm^{-1}(Ar), 1650(C=C) cm^{-1}.

δ_H (DMSO-d_6, oxalate salt): 9.68(2H, brs., N$\underline{H}_2$), 8.00(10H, m, Ar-$\underline{H}$), 6.87(1H, d, J_{trans} 16.1Hz., CH=C$\underline{H}$Ph), 6.14(1H, m, C$\underline{H}$=CHPh), 3.82(2H, d, J^3 6.0Hz., C$\underline{H}_2$), 3.56(2H, brs, C$\underline{H}_2$), 3.31(2H, bsr., C$\underline{H}_2$).

δ_C (DMSO-d_6, oxalate salt): 197.17($\underline{C}$=O), 165.16-135.77 (3 x $\underline{C}_q$), 136.45-128.05 (6 x Ar-$\underline{C}$), 126.66 (CH=$\underline{C}$HPh), 120.53 ($\underline{C}$H=CHPh), 48.52 ($\underline{C}H_2$), 41.16 ($\underline{C}H_2$), 34.70 ($\underline{C}H_2$).

5.9 SYNTHESIS OF 1,3-DIMETHYL-4-PIPERIDONE.

Methyl 2-Methyl-3-(methylamino)propanoate [129].

A solution of methyl methacrylate (189g, 1.89mol) in absolute ethanol (125ml) was added dropwise with stirring to an ice-cooled solution of methylamine (33% w/v in IMS, 125ml, 1.35mol) over a period of 3 h. The clear solution was stirred for a further 3 h, and then left to stand in the dark at room temperature for 4 days. The resulting pale yellow solution was condensed *in vacuo*, and fractionated to give **[129]** (125.0g, 51%) as a colourless oil, b.p.42-44°C/3.0 mmHg. (Lit.[198] 48.8-49.5°C/8 mmHg).

IR (ν_{max}/cm^{-1}, liquid film): 3320(N-H), 1740(C=O), 1100(C-O-C).

δ_H ($CDCl_3$): 3.70(3H, s, $CO_2C\underline{H}_3$), 2.98(1H, m, CH_2-C<u>H</u>[CH_3]), 2.71(2H, m, N-C<u>H</u>$_2$), 2.42(3H, s, N-C<u>H</u>$_3$), 1.19(3H, d, J^3 7.0Hz, CH[C<u>H</u>$_3$]).

δ_C ($CDCl_3$): 176.09 (<u>C</u>=O), 54.78 (<u>C</u>H$_2$), 51.41 ($CO_2\underline{C}H_3$) 39.54 (<u>C</u>H[CH_3]), 36.23 (N-<u>C</u>H$_3$), 15.08 (CH[<u>C</u>H$_3$]).

Methyl 3-Methyl-3-[N-(2-ethoxycarbonylethyl)-N- methylamino]-2-methylpropanoate [130].

A solution of methyl 2-methyl-3-(methylamino)propanoate **[129]** (34.88g, 0.266mol) and ethyl acrylate (26.63g, 0.266mol) was left in the dark for 10 days. The resulting amber-coloured mixture was fractionated to give **[130]** (45.1g,73%) as a colourless oil b.p. 120°C/3.0 mm Hg. (Lit.,[198] 105-107°C/4mmHg).

δ_H ($CDCl_3$): 4.17(2H, q, J^3 7.1Hz., $CO_2C\underline{H}_2CH_3$), 3.67(3H, s, $CO_2C\underline{H}_3$), 2.72(4H, m, 2 xN-$C\underline{H}_2$), 2.46(2H, m, N-$CH_2C\underline{H}_2$), 2.30(1H, m, C$\underline{H}$[CH_3]), 2.23(3H, s, N-$C\underline{H}_3$), 1.28(3H, t, J^3 7.1Hz., $COCH_2C\underline{H}_3$), 1.14(3H, d, J^3 6.8Hz.,CH[$C\underline{H}_3$]).

δ_C ($CDCl_3$): 176.22, 172.42 (2x$\underline{C}$=O); 60.59 ($\underline{C}H_2CO$); 53.13, 52.45 (2xN-$\underline{C}H_2$); 32.60 ($CO_2\underline{C}H_2$); 51.38 ($CO_2\underline{C}H_3$); 42.10 (C$\underline{H}$); 38.37 (N-$\underline{C}H_3$); 15.28 (CH[$\underline{C}H_3$]); 14.08 ($CH_2\underline{C}H_3$).

1,3-Dimethyl-4-piperidone [137].

To a stirred suspension of bird shot sodium (4.6g, 0.2mol) in dry xylene (100ml) was added methyl 3-[N-(2-ethoxycarbonylethyl)-N-methylamino]-2-methylpropano ate [130] (46.25g, 0.2mol) dropwise. The mixture, protected from moisture, was heated in an oil bath at 60°C. When the initial reaction had subsided, the mixture was heated under reflux for 3 h, by which time all the sodium had reacted. The resulting dark coloured liquid was cooled and added with stirring to iced water (200g). The aqueous layer was collected, washed with diethyl ether (2x100ml), and acidified with concentrated hydrochloric acid. The acidic mixture was heated under reflux for 4 h (a negative result was obtained with ferric chloride solution). The reaction mixture was cooled, concentrated to a small bulk, and basified with solid potassium hydroxide. The crude product was extracted with ether (18x100 ml), dried ($MgSO_4$), and evaporated *in vacuo* to give a yellow oil which was fractionated to give [137] (9.91g, 39%) as a colourless oil b.p. 40-42°C/2mm Hg. (Lit.,[198] 43-43.5°C/5.5 mm Hg).

δ_H (DMSO-d_6): 3.02(2H, m, $\underline{H}_2$-2), 2.74(3H, m, $\underline{H}_2$-6, $\underline{H}$-3), 2.27(3H, s, N-$C\underline{H}_3$), 2.20(2H, m, $\underline{H}_2$-5), 0.88(3H, d, J^3 6.6Hz., CH[$C\underline{H}_3$]).

δ_C (DMSO-d_6): 210.18 (C=O), 63.09 (C-2), 55.98 (C-6), 45.12 (C-3), 43.95 (N-CH_3), 40.64 (C-5) 11.68 (CH[CH_3]).

5.91 REDUCTION OF 1,3-DIMETHYL-4-PIPERIDONE.

5.91.1 Lithium Aluminium Hydride Reduction.

A suspension of lithium aluminium hydride (1.90g, 0.05mol) in dry ether (30ml) was stirred vigorously for 0.5 h. To the resulting slurry was added a solution of 1,3-dimethyl-4-piperidone (6.35g, 0.05mol) in dry ether (30ml) dropwise (at a rate sufficient to maintain gentle reflux). The mixture, protected from moisture, was heated under reflux for a further 10 h. The reaction mixture was cooled, and the excess LAH was decomposed carefully. The ethereal layer was collected, dried ($MgSO_4$), and evaporated *in vacuo* to give a colourless oil of diastereomeric 1,3-dimethyl-4-piperidinols, which was fractionated, (5.56g, 86%), b.p. 78-80°C/2 mm Hg. (Lit.,[196] 78.0°C / 1mm Hg).

A mixture of isomers was detected in the ^1H NMR (2.4:1 ratio of *trans* to *cis* respectively).

5.91.2 *Trans*-(*t* 3-Me r-4-OH)-1,3-Dimethyl-4-Piperidinol [138].

The foregoing 1,3-dimethyl-4-piperidinol (5.0g, 39mmol) from the LAH reaction were dissolved in dry ether (20ml). Dry hydrogen chloride gas was bubbled into the solution until no more solid precipitated. The white solid was collected, and recrystallized from

absolute ethanol-ether to give colourless crystals of the title product, m.p. 183-185°C. (Lit.,[192] 183-184°C). The free base was liberated by treatment with ammonia solution and extracted with ether. The ethereal layer was dried, evaporated *in vacuo* and fractionated to give **[138]** as a colourless liquid which solidified on standing, (3.37g, 67%), m.p. 32-32.5°C.

δ_H ($CDCl_3$): 3.84(1H, s, O<u>H</u>), 3.05(1H, td, ax<u>H</u>-4), 2.81(1H, m, eq<u>H</u>-2), 2.77(1H, m, eq<u>H</u>-6), 2.23(3H, s, N-C<u>H</u>$_3$), 1.98(1H, dd, ax<u>H</u>-2), 1.93(1H, m, ax<u>H</u>-6), 1.66(3H, m, <u>H</u>$_2$-6, ax<u>H</u>-3), 0.98(3H, d, J^3 5.7Hz., CH[C<u>H</u>$_3$]).

δ_C ($CDCl_3$): 73.72 (<u>C</u>-4), 61.85 (<u>C</u>-2), 54.59 (<u>C</u>-6), 45.70 (<u>C</u>-3), 38.53 (N-<u>C</u>H$_3$), 34.48 (<u>C</u>-5), 15.60 (CH[<u>C</u>H$_3$]).

m/z: 129(M^+, 60), 128(62), 112(33), 96(9), 84(26), 70(30), 58(48), 43(100), 27(9).

<u>5.91.3 Aluminium *Iso*propoxide Reduction.</u>

1,3-Dimethyl-4-piperidone **[137]** (3.23g, 25mmol) in distilled *iso*propanol (60 ml) was added to a solution of aluminium *iso*propoxide (3.21g, 25mmol) in *iso*propanol (30ml) in a 250 ml flask fitted with a Vigreux column and a condenser. Reflux was maintained for 16 h, whereby most of the *iso*propanol was removed by distillation. The residue was hydrolysed with ice-cold ammonia solution and the product extracted continuously with chloroform for 36 h. The extract was dried ($MgSO_4$), evaporated to dryness and fractionated to give a mixture of diastereomers of 1,3-dimethyl-4-piperidinols (3.04g, 94%).

A mixture of isomers was detected in the NMR (1:1 ratio of the α-*trans* and β-*cis* isomers).

5.91.4 Platinum Oxide Reduction.

A solution of 1,3-dimethyl-4-piperidone **[137]** (0.5g) in absolute ethanol (30ml) was catalytically hydrogenated with platinum oxide (0.1g) at 50 psi, and at room temperature for 16 h. The catalyst was removed through a bed of celite, and the filtrate was evaporated to dryness and fractionated to give a colourless oil (86%).

^{1}H NMR investigation showed a mixture of the α-*trans* and β-*cis* diastereomers of 1,3-dimethyl-4-piperidinols were present in the ratio of 1:2.7.

The same procedure was repeated at 20psi. A 6:1 ratio of the *cis*:*trans* isomers were detected in the ^{1}H NMR.

IR (ν_{max}/cm^{-1}, liquid film): 3200(O-H).

5.92 SEPARATION OF THE ISOMERS OF 1,3-DIMETHYL-4- PIPERIDINOL.

5.92.1 *Trans*-(*t* 3-Me r-4-OCOMe)-1,3-Dimethyl-4-Piperidyl Acetate Hydrochloride [140].

A solution of 1,3-dimethyl-4-piperidinol (1.0g, 7.8mmol) in ethyl acetate (30ml), was added dropwise to a solution of acetyl chloride (0.16g, 20mmol) in ethyl acetate (30ml) with stirring over a period of 1 h. The mixture was heated at reflux for 24 h and left to stand for a further 48 h at room temperature, at which time, crystals of the above named

product precipitated. The product was collected and recrystallized from absolute ethanol, (1.43g, 89%), m.p. 212-213°C. (Lit.,[196] 208-210°C). The mother liquor was retained.

δ_H (DMSO-d_6): 11.50(1H, s, +N-H), 4.81(1H, td, $J_{eq/ax}$ 4.4Hz., $J_{ax/ax}$ 10.3Hz., axH-4), 3.59(4H, m, H-2, H-6), 2.95(3H, s, $COCH_3$), 2.92(5H, brs, N-CH_3, axH-5, axH-3), 2.01(1H, qd, eqH-5), 1.10(3H, d, J^3 6.3Hz., CH[CH_3]).

δ_C (DMSO-d_6): 170.15 (C=O), 75.77 (C-4), 61.12 (C-6), 53.58 (C-2), 45.57 (N-CH_3), 35.48 ($OCOCH_3$), 30.62 (C-5), 20.98 (CH[CH_3]), 15.47 (CH[CH_3]).

5.92.2 *Trans*-(*t* 3-Me r-4-OH)-1,3-Dimethyl-4-Piperidinol **[138]**.

A suspension of LAH (0.37g, 10mmol) in sodium dried ether (20ml) was stirred vigorously for 15 mins. To the resulting slurry was added a solution of *trans*-1,3-dimethyl-4- piperidyl acetate **[140]** (1.67g, 10mmol) dropwise at a sufficient rate to keep the solution refluxing. The mixture, protected from moisture, was heated under reflux for 8 h. The reaction mixture was cooled to 0°C, and the unreacted LAH was decomposed carefully with water (0.4ml), sodium hydroxide (5N, 0.2ml) and water (0.6ml). The ethereal layer was decanted, dried ($MgSO_4$), evaporated *in vacuo* and fractionated to give **[138]** as a colourless oil. The oil solidified on standing, (1.13g, 88%), m.p. 32-33°C. (mixed m.p. 32-33°C with earlier method).

5.92.3 *Cis*-(*c* 3-Me r-4-OCOMe)-1,3-Dimethyl-4-Piperidyl Acetate Hydrochloride [141].

The mother liquor from the *trans*-1,3-dimethyl-4-piperidyl acetate was basified with ammonia solution and the free base was extracted with ether. The ether was dried ($MgSO_4$) and evaporated to dryness. The acetate ester (1.50g, 12mmol) was dissolved in ethyl acetate (50ml) and added dropwise to a solution of acetyl chloride (2.40g, 30mmol) in ethyl acetate (50ml) with stirring. The solution was refluxed for 24 h in an anhydrous environment. The solvent was removed and the solid was recrystallized from ethanol-ether at 5°C to give **[141]** (2.27g, 88%) as colourless crystals, m.p 138-140°C. (Lit.,[196] 145-146°C).

δ_H (DMSO-d_6): 11.35(1H, s, +NH), 4.90(1H, brd, b_w 21.0Hz., $b_{0.5}$ 6.0 Hz., eq H-4), 3.22(2H, m, H_2-2), 2.96-2.77(2H, m, H_2-6), 2.74(3H, s, N-CH_3), 2.36(1H. m, ax H-3), 2.09(3H, s, OCOCH_3), 1.96(2H, m, H_2-5), 0.85(3H, d, J^3 6.6Hz., CH[CH_3]).

δ_C (DMSO-d_6): 169.83 (COCH_3), 66.85 (COCH_3), 53.58 (C-6), 47.75 (C-2), 42.36 (N-CH_3), 31.20 (C-4), 26.89 (C-5), 20.73 (CH[CH_3]), 14.01 (CH[CH_3]).

5.92.4 *Cis*-(*c* 3-Me r-4-OH)-1,3-Dimethyl-4-Piperidinol [139].

A suspension of LAH (0.37g, 10mmol) in sodium dried ether (20ml) was stirred vigorously for 15 mins. To the resulting slurry was added dropwise a solution of *cis*-1,3-dimethyl-4- piperidyl acetate **[141]** (1.67g, 10mmol) at a sufficient rate to keep the solution refluxing. The mixture, protected from moisture, was further refluxed for 8 h. The reaction mixture was cooled to 0°C, and the unreacted LAH was decomposed carefully with water (0.4ml), sodium hydroxide (5N, 0.2ml) and water (0.6ml) again.

The ethereal layer was decanted, dried ($MgSO_4$), and evaporated *in vacuo* to give the crude *cis*-1,3-dimethyl-4-piperidinol, which was fractionated to give **[139]** (1.03g, 80%) as a colourless oil, b.p. 100-104°C/1.0mm Hg.

δ_H ($CDCl_3$): 3.75(1H, dd, b_w 13.7Hz., $b_{0.5}$ 7.8Hz., eq H-4), 3.28(1H, brs, OH), 2.38(3H, m, H_2-2, eq H-6), 2.25(3H, 2xs, N-CH_3), 2.10(1H, m, ax H-6), 1.87-1.64(3H, m, H_2-5, H-3), 0.98(3H, 2xd, J^3 7.0Hz., CH[CH_3]).

δ_C ($CDCl_3$): 73.76, 67.12 (2 x C-4), 61.95, 57.34 (2 x C-2), 54.69, 50.01 (2 x C-6), 46.19, 45.80 (2 x N-CH_3), 38.63, 35.13 (2 x CH[CH_3]), 34.61, 32.60(2 x C-5), 15.63, 14.69(2 x CH[CH_3]).

m/z: 129(M^+, 60), 128(63), 112(33), 96(9), 84(27), 70(30), 58(49), 43(100), 27(9).

5.93 SYNTHESIS OF 1,2-DIMETHYL-4-PIPERIDONE.

Ethyl 3-Methylaminobutyrate.

To ethyl crotonate (39.55g,0.35mol) was added to methylamine (32ml, 33% in IMS, 0.36mol), and absolute ethanol (35ml). The mixture was left to stand in the dark at room temperature for 5 days and then heated under reflux for 8h. The solvent was removed, and the orange liquid was fractionated to give the above named compound (40.61g, 80%) as a light yellow oil,, b.p. 70°C/10 mm Hg, (Lit.,[199] 72°C/12.5 mm Hg).

IR (ν_{max}/cm^{-1}, liquid film): 1730(C=O).

δ_H($CDCl_3$): 4.16(2H, q, OCH_2CH_3), 2.95(1H, m, CH[CH_3]), 2.50(3H, s, N-CH_3),

2.29(2H, d, CHC$\underline{H}_2$CO), 1.36(3H, d, CH(C$\underline{H}_3$)), 1.21(3H, t, $CH_2C\underline{H}_3$).

δ_C ($CDCl_3$): 172.0 ($\underline{C}$=O), 60.03 (O$\underline{C}H_2CH_3$), 52.28 ($\underline{C}$H[CH_3]), 41.50 (CH$\underline{C}H_2$CO), 33.75 (N-$\underline{C}H_3$), 20.15 (CH{$\underline{C}H_3$}), 14.35 ($CH_2\underline{C}H_3$).

Diethyl 3,4-Dimethyl-4-Azaheptanedioate **[143].**

A mixture of ethyl 3-methylaminobutyrate (34.88g, 0.24mol) and ethyl acrylate (24g, 0.24mol) was kept in the dark at room temperature for 10 days. The resulting amber coloured liquid was fractionated to give **[143]** (42.93g, 73%) a colourless oil b.p. 120°C/3.0 mm Hg. (Lit.,[192] 129°C/6 mm Hg)

IR (ν_{max}/cm^{-1}, liquid film): 1730, 1750(C=O).

δ_H ($CDCl_3$): 4.20(4H, q, 2 x OC$\underline{H}_2CH_3$), 3.33(1H, m, C$\underline{H}$[CH_3]), 2.49-2.83(6H, m, 2 x C$\underline{H}_2$CO, N-C$\underline{H}_2$), 2.33(3H, s, N-C$\underline{H}_3$), 1.43(6H, t, 2 x $CH_2C\underline{H}_3$), 1.20(3H, d, CH[C$\underline{H}_3$]).

δ_C ($CDCl_3$): 171.62 (2 x $\underline{C}$=O), 59.59 (2 x O$\underline{C}H_2CH_3$), 55.37 ($\underline{C}$H[CH_3]), 48.65 ($CH_2\underline{C}H_2$-N), 38.19 (CH$\underline{C}H_2$CO), 35.97 (N-$\underline{C}H_3$), 33.48 ($CH_2\underline{C}H_2$CO), 13.81 (2 x $CH_2\underline{C}H_3$).

1,2-Dimethyl-4-Piperidone [144].

Diethyl 3,4-dimethyl-4-azaheptanedioate (43.00g, 0.19mol) was added dropwise to a stirred suspension of bird shot sodium (4.30g, 0.19mol) in dry xylene (170ml). When the initial reaction had subsided, the mixture was refluxed for 3 h. The resultant dark liquid was cooled overnight and added with vigorous stirring to iced water (100g). The aqueous layer was separated, washed with ether (2 x 50ml) and made acidic with concentrated hydrochloric acid (150ml, pH 1.0). After refluxing for 4 h, the reaction mixture was condensed (75ml), and excess sodium chloride was filtered off. The filtrate was basified with potassium hydroxide pellets, and the product was extracted with ether (20 x 100ml), dried ($MgSO_4$), and distilled to give a dark yellow liquid, which was fractionated to give **[144]** (7.29g, 30%) as a light yellow liquid, b.p. 70°C/3.0 mm Hg. (Lit.,[200] 55-57°C/7 mmHg).

IR (ν_{max}/cm^{-1}, liquid film): 1730(C=O).

δ_H ($CDCL_3$): 1.20(3H, d, CH($C\underline{H}_3$)), 2.43(3H, s, N-$C\underline{H}_3$), 2.20(6H, m, $\underline{H}_2$-3, $\underline{H}_2$-5, $\underline{H}_2$-6), 3.00(1H, m, $C\underline{H}[CH_3]$).

δ_C ($CDCl_3$, Free base): 207.16 (C=O), 58.52 ($\underline{C}$-2), 54.55 ($\underline{C}$-6), 48.59 ($\underline{C}$-3), 41.44 (N-$\underline{C}H_3$), 41.12 ($\underline{C}$-5), 19.16 (CH[$\underline{C}H_3$]).

5.94 1.2-DIMETHYL-4-PIPERIDINOLS.

5.94.1 DIASTEREOMERIC 1,2-DIMETHYL-4-PIPERIDINOLS.

A suspension of lithium aluminium hydride (1.30g, 34 mmol) in dry ether (20ml) was stirred vigorously for 0.5 h. To the resulting slurry was added a solution of 1,2-dimethyl-4-piperidone **[144]** (4.30g, 34 mmol) in dry ether (20ml) dropwise, at a rate sufficient to maintain gentle reflux. The solution, protected from moisture, was heated under reflux for a further 1 h. The reaction mixture was cooled, and the excess LAH was decomposed carefully. The ethereal layer was collected, dried ($MgSO_4$), and evaporated to give a colourless thick oil of the above title compound, which was fractionated, (3.31g, 76%), b.p. 78-80°C/2 mm Hg.

δ_H ($CDCl_3$): 4.07(0.23H, quintet, J^3 3.4Hz., eq H-4), 3.63(0.77H, tt, $J_{eq/ax}$ 4.58Hz., $J_{ax/ax}$ 11.18Hz., ax H-4), 3.38(1H, brs, OH), 2.89(1H, dq, J^3=3.4Hz., H-2), 2.66(1H, m, eq H-6), 2.28(3H, 2 x s, N-CH_3), 2.13(1H, m, ax H-6), 1.99-1.49(4H, m, H_2-3, H_2-5), 1.15(3H, 2xd, J^3 6.6Hz., CH[CH_3]).

δ_C ($CDCl_3$): 68.37, 57.47 (2 x C-4), 55.07, 50.17 (2 x C-6), 43.40, 41.09 (2 x C-3), 42.68, 42.07 (2 x C-2), 42.13 (N-CH_3), 35.06, 32.92 (2 x C-5), 20.47 (CH[CH_3]).

5.94.2 α-1,2-Dimethyl-4-Piperidinol Hydrochloride [145].

Isomeric 1,2-dimethyl-4-piperidinols (1.0g, 7.8mmol) were dissolved in absolute ethanol (10ml), treated with hydrogen chloride gas until the solution turned cloudy. Crystals of the above named product precipitated (0.80g, 61%), m.p. 120-122°C.

δ_H (DMSO-d_6, HCl salt): 10.7(1H, s, +N-H), 3.67(1H, tt, ax H-4), 2.39(1H, m, H-2), 3.10(2H, m, H_2-6), 2.70(3H, s, N-CH_3), 2.00(2H, m, H_2-3), 1.75(2H, m, H_2-5), 1.15(3H, d, J^3 6.0Hz., CH[CH_3]).

δ_C (DMSO-d_6, HCl salt): 67.40 (C-4), 56.99 (C-6), 54.85 (C-3), 43.72 (C-2), 42.13 (N-CH_3), 35.23 (C-5), 20.66 (CH[CH_3]).

5.94.3 Reduction of 1,2-Dimethyl-4-Piperidone With Platinum Oxide.

To crude 1,2-dimethyl-4-piperidone (100mg) in absolute ethanol (10ml), was added platinum oxide (20mg), and the suspension was hydrogenated at room temperature for 24 h. The catalyst was removed, and the filtrate was concentrated to give a yellow oil. When acetone (10ml) was added to this oil, white solid of β-1,2-dimethyl-4-piperidinol **[146]** precipitated, (35mg, 35%).

The ^{1}H NMR showed that the 4-methine proton (δ4.1, br) to be in the equatorial position.

5.95 SYNTHESIS OF HISTRYL ANALOGUES.

5.95.1 *Trans*-1,3-Dimethyl-4-Piperidyl Benzhydryl Ether HCl [148].

Trans-1,3-Dimethyl-4-piperidinol **[138]** (0.5g, 3.89mmol) was added to anhydrous potassium carbonate (0.8g, 5.81mmol), and the mixture was agitated for 15 mins. A solution of chlorodiphenylmethane (1.05g, 4.26mmol) in dry toluene (10ml) was then added and the mixture was heated under reflux at 130°C for 3 h. The reaction mixture was diluted with water (10ml), and extracted with ether. The organic layer was

separated, dried ($MgSO_4$) and evaporated at the pump to give the ether as an oil. The oil was treated with ethereal HCl to precipitate a solid which was recrystallized from acetone to give **[148]** (0.24g, 15%) as colourless crystals, m.p. 125-126°C. (Found: C, 68.4; H, 7.89; N, 4.03. $C_{20}H_{25}NO.HCl.H_2O$ requires C,68.65; H, 8.07; N,4.00%).

δ_H (DMSO-d_6, HCl salt): 7.43(10H, m, Ar-H), 5.68(1H, s, Ph_2CH-), 3.24(3H, m, axH-4, eqH-2, eqH-6), 2.84(1H, m, axH-2), 2.66(3H, s, N-CH_3), 2.18(3H, m, axH-6, eqH-5, axH-5), 1.77(1H, dd, axH-3), 0.98(3H, d, J^3 6.2Hz., CH[CH_3]).

δ_C (DMSO-d_6, HCl salt): 143.17, 142.03 (2 x C_q), 128.28-126.24 (5 x Ar-CH), 79.30 ($OCHPh_2$), 75.32 (C-4), 56.92 (C-2), 51.51 (C-6), 41.97 (N-CH_3), 34.25 (CH[CH_3]), 20.72(C-5), 14.92 (CH[CH_3]).

5.95.2 *Cis*-1,3-Dimethyl-4-Piperidyl Benzhydryl Ether oxalate **[149]**.

Cis-1,3-Dimethyl-4-piperidinol **[139]** (1.0g, 7.75mmol) was agitated with anhydrous potassium carbonate (1.60g, 11.6mmol) for 15 min. a solution of chlorodiphenylmethane (1.73g, 8.54mmol) in dry toluene (10ml) was then added and the mixture was heated under reflux at 140°C for 3 h in an anhydrous condition. The cooled suspension was filtered and the filtrate was condensed to give a yellow oil. The oil was dissolved in ether, and to this was added oxalic acid in methanol. The mixture was left to stand for 2 h, at which time a white solid precipitated. The solid was collected, washed with ether (2x20ml), and recrystallized from ethanol-ether to give **[149]** (0.68g, 23%) as a white solid, m.p 142.5-143.5°C. (Found: C, 68.3; H, 7.12; N, 3.70. $C_{20}H_{25}NO.(CO_2H)_2$ requires C, 68.5; H, 7.01; N, 3.68%).

δ_H (DMSO-d_6, oxalate salt): 9.53(2H, s, $(CO_2\underline{H})_2$), 7.41(10H, m, Ar-$\underline{H}$), 5.66(1H, s, OC$\underline{H}Ph_2$), 3.52(1H, brs, b_w 21.0Hz., $b_{0.5}$ 9.0Hz., eq$\underline{H}$-4), 3.12(2H, m,$\underline{H}_2$-2), 2.95(2H, dd, $\underline{H}_2$-6), 2.71(3H, s, N-C$\underline{H}_3$), 2.05(2H, m, eq$\underline{H}$-3, eq$\underline{H}$-5), 1.79(1H, m, ax$\underline{H}$-5), 0.90(3H, d, J^3 6.6Hz., CH[C$\underline{H}_3$]).

δ_C (DMSO-d_6, oxalate salt): 165.16 ($\underline{C}$=O oxalate), 143.39, 142.32 (2 x Ar-$\underline{C}_q$), 128.41-126.49 (4 x Ar-$\underline{C}$H), 79.98 (O$\underline{C}$HPh$_2$), 70.02 ($\underline{C}$-4), 54.46 ($\underline{C}$-2), 48.42 ($\underline{C}$-6), 42.68 (N-$\underline{C}H_3$), 32.62 ($\underline{C}$H[CH_3]), 25.72 ($\underline{C}$-5), 14.63 ($\underline{C}$H[CH_3]).

5.95.3 α-1,2-Dimethyl-4-Piperidyl Benzhydryl Ether HCl **[151]**.

α-1,2-Dimethyl-4-piperidinol **[145]** (1.0g, 7.75mmol) was heated with anhydrous potassium carbonate (1.60g, 11.6mmol) and chlorodiphenylmethane (1.73g, 8.54mmol) at 140°C for 3h in an anhydrous condition. The cooled suspension was filtered and the filtrate was reduced *in vacuo* to give a yellow oil. The oil was dissolved in ether, and to this was added ethanolic HCl. The mixture was left to stand for 2 h, at which time a white solid of the above named product precipitated, (0.54g, 21%), m.p. 153-154°C.

δ_H ($CDCl_3$, HCl salt): 10.8(1H, brs, +N-$\underline{H}$), 7.35(10H, m, Ar-$\underline{H}$), 5.70(1H, s, OC$\underline{H}Ph_2$), 3.53(1H, m, ax$\underline{H}$-4), 3.36(1H, m, eq$\underline{H}$-6), 3.09(1H, m, ax$\underline{H}$-6), 2.93(1H, m, ax$\underline{H}$-2), 2.63(3H, s, N-C$\underline{H}_3$), 2.20(2H, m, eq$\underline{H}$-5, eq$\underline{H}$-3), 1.71(2H, m, ax$\underline{H}$-5, ax$\underline{H}$-3), 1.30(3H, d, J^3 6.2Hz, CH[C$\underline{H}_3$]).

CHAPTER 6.
REFERENCES.

6 REFERENCES.

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