PHD

On the investigation of the synthesis, stereochemistry and structure-activity relationship of opioid ligands related to 4-aryl-1-methylpiperidines and phencyclidine

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1989

Awarding institution:
University of Bath

بِسْمِ اللهِ الرَّحْمٰنِ الرَّحِيمِ

IN THE NAME OF ALLAH
THE MERCIFUL THE COMPASSIONATE

اَلْحَمْدُ لِلّٰهِ رَبِّ الْعٰلَمِيْنَ

وَالصَّلَاةُ وَالسَّلَامُ عَلٰى سَيِّدِنَا مُحَمَّدٍ خَاتَمِ النَّبِيِّيْنَ

ON THE INVESTIGATION OF THE SYNTHESIS, STEREOCHEMISTRY AND STRUCTURE-ACTIVITY RELATIONSHIP OF OPIOID LIGANDS RELATED TO 4-ARYL-1-METHYLPIPERIDINES AND PHENCYCLIDINE

Thesis

Submitted by OMAR A.A. AL-DEEB, B.SC., M.So.,

for the degree of Doctor of Philosophy

of the University of Bath

1989

This research has been carried out in the School of Pharmacy and Pharmacology under the supervision of Dr. Alan F. Casy and Dr. George H. Dewar.

Copyright

SIGNED:

O.A.A. AL-Deeb

To my parents,

all my brothers and sisters

and to my wife Fatin without whose

unfailing support and God's will made

the completion of this work possible.

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SUMMARY

A brief review of narcotic analgesics, with particular attention to the 4-arylpiperidine class, is presented in Chapter 1. Isomeric reversed esters of pethidine bearing 3-methyl substituents, together with the 4-alkyl-4-arylpiperidines, have been discussed from both a stereochemical and structure-activity point of view, and aspects of this are presented.

A brief general introduction to phencyclidine (PCP) is also presented, with particular reference to new analgesics derived from phencyclidine by introduction of a phenyl and hydroxyl moiety at position 4 of the piperidine ring of this agent.

In Chapter 2, the synthesis and characterisation of a novel series of potential analgesics based on 3-methyl substitution in the piperidine ring of this series of PCP analgesics is reported. This study was encouraged by the observation that such methyl substitution in the pethidine reversed ester significantly enhanced analgesic potency. The $\underline{\alpha}$-isomer of 4-hydroxy-3-methyl-4-phenyl-1-(1-phenylcyclohexyl)piperidine had a particularly interesting pharmacological profile, and therefore resolution of this compound was undertaken. The details of this resolution are reported.

The synthesis and characterisation of a series of 4-alkyl-4-arylpiperidines and their 3-methyl analogues is also described in Chapter 2. Extensive use of high field ^{1}H and ^{13}C NMR has been made in the conformational and, in appropriate cases, configurational analysis of the prepared compounds, and the data secured are discussed in detail.

Finally, those pharmacological results available at the time of writing this thesis are reported and discussed.

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ABBREVIATIONS

CPM	Cyclopropyl methyl
DCM	Dichloromethane
icv	Intracerebrovascular
ip	Intraperitoneal
iv	Intravenous
JP	Janssen Pharmaceutica
MHP	Mice Hot-Plate Test
MVD	Mouse Vas Deferens
NIH	National Institutes of Health
PPQ	p-Phenylquinone Writhing
TF	Tail-Flick Test
TFM	Tail-Flick Versus Morphine Test
THF	Tetrahydrofuran
TWR	Rat Tail Withdrawal Test
SC	Subcutaneous

1. INTRODUCTION

1.1 HISTORICAL INTRODUCTION

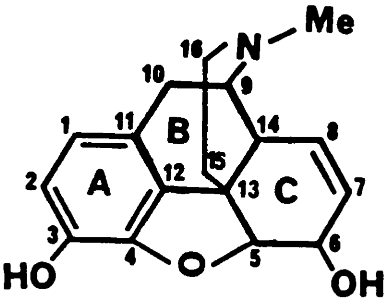
Pain is a universal syndrome with which everyone has had some personal experience. The earliest use of drugs for the relief of pain cannot be easily identified; nevertheless, opium is thought to have been used as a drug since ancient Greek times.

Alcohols, plants and their extracts were known in antiquity. However, it is probably the case that opium represented the best first line of therapy in this regard.

The Sumerians were believed to have used crude opium as early as 4,000 BC for its ability to relieve pain and produce a state of euphoria. However, despite the long history behind opium, it was not until 1803 that a German pharmacist isolated an alkaloid from opium which he called morphine (1). By the middle of the 19th century the use of pure morphine, rather than the crude opium preparations, had spread widely. Unfortunately, analgesia is not the sole pharmacological effect of morphine. Other undesired side effects, such as gastrointestinal disturbances, nausea, vomitting, and respiratory depression, are produced by affecting many of the vital centres in the brain. The most undesirable side effect of morphine is the development of rapid tolerance with repeated use, so that the user becomes addicted to the drug. The widespread use of morphine has resulted in a dramatic increase in addiction, so that it now presents itself as a significant social problem. This prompted the search for non-addictive synthetic opiates lacking the undesirable side effects of morphine, while maintaining the pain relieving property of the drug.

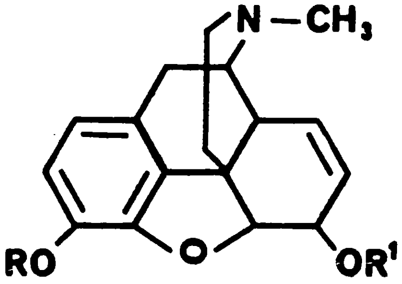
1.2 MORPHINE AND ITS DERIVATIVES

In 1952, Gates and Tschudi[1] confirmed the morphine structure as (1), and this was consistent with that originally suggested by Gulland and Robinson in 1923.[2] The addiction liability, and numerous undesirable side effects of morphine, have led to much modification of this molecule in an effort to produce the ideal centrally-acting analgesic.



(1)

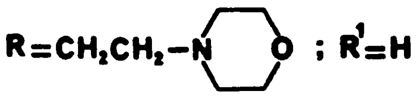
Early modification of morphine, in an attempt to produce analgesics superior to morphine, involved derivatisation of the 3- and 6-hydroxy groups. Diacetylmorphine (Heroin; 2) is one of the earlier known examples, and this substance has a greater analgesic activity than morphine, and intense dependence liability. On the other hand, etherification of the phenolic hydroxyl group decreased the analgesic potency, as illustrated by codeine (3) and peronine (4).



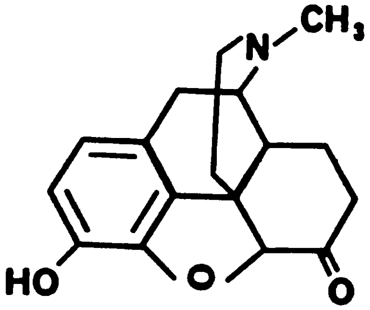
(2) $R = R^1 = COCH_3$

(3) $R = Me ; R^1 = H$

(4)

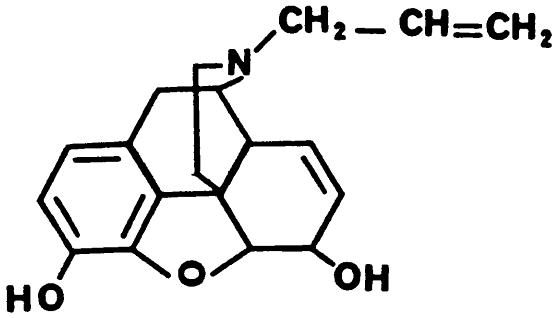


Other modifications involved chemical transformations within ring C of morphine which generated several drugs having morphine-like activities. However, these derivatives offer no real advantage over morphine because of their severe addictive liability. One example is dihydromorphinone (5).



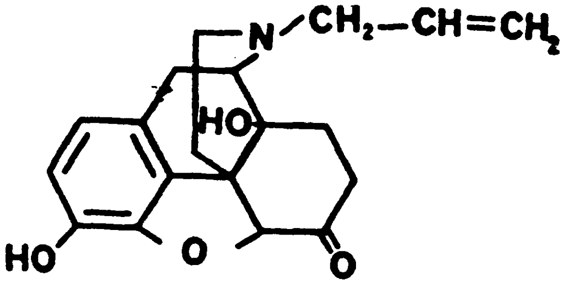
(5)

Substitution of morphine N-Me by certain other groups has led to the production of several compounds which antagonise a wide spectrum of morphine activities, with little or no analgesic potency in laboratory animals.[3] Thus, N-substituents such as allyl, dimethylallyl and cyclopropylmethyl (CPM) generally impart antagonist action in morphine and related substances. The N-allyl compound (Nalorphine, 6) was one of the first compounds recognised as a narcotic antagonist,[4] and has been used as an antidote in morphine poisoning.[3] Unfortunately, nalorphine has psychotomimetic effects which prevent its clinical use as an analgesic. This observation has led to the development of several clinically useful analgesics based on morphine antagonists.[5]



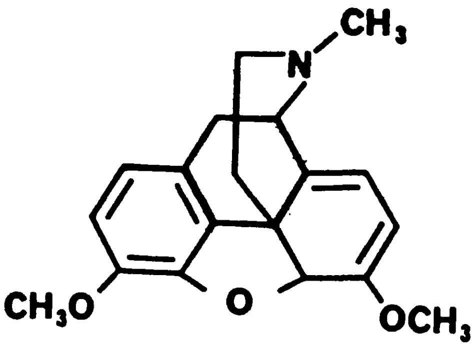
(6)

Naloxone, (7),the N-allylanalogue of oxymorphine,is a potent antagonist. It has seven times the potency of nalorphine in antagonising morphine, and is considered to be an almost pure antagonist, as it does not exhibit any analgesic activity.[6]



(7)

Utilization of the medically useless alkaloid thebaine (8) by Bentley and co-workers has produced a series of morphine analogues called the oripavines.[7] Thus, exploitation of the diene component of thebain via Diels Alder condensation with a variety of dienophiles, gave rise to ketonic adducts with activities comparable to those of morphine, while certain tertiary alcohols derived from Grignard reactions on these ketonic adducts were known to have very high levels of activity. One such compound, etorphine (9), has an activity 1,000-10,000 times that of morphine in a variety of animal species,[8] and has been used to capture large wild animals (as a consequence of its phenomenal potency).



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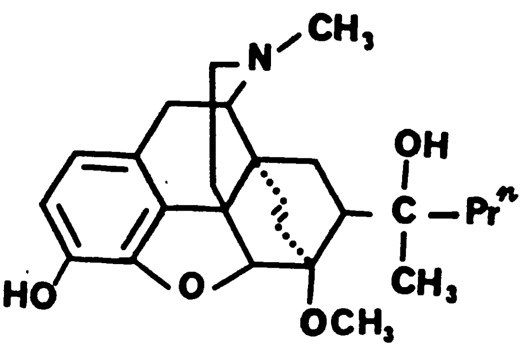


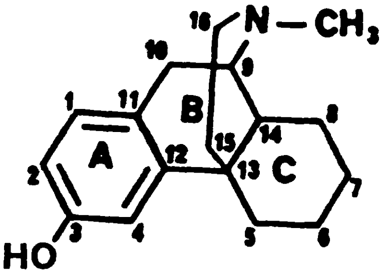
(9)

1.3 SYNTHETIC CENTRALLY-ACTING ANALGESICS

Research workers in the field of synthetic centrally-acting analgesics have concentrated on modification of the morphine structure in an effort to extract the pharmacophore necessary for activity. Although not in historical order of development, the following sections attempt to illustrate how a continual reduction in the size of the morphine structure has produced several groups of drugs with analgesic properties. Though these analgesics differ in structural characteristics, they can all be related to the standard morphine (see Fig. 1).

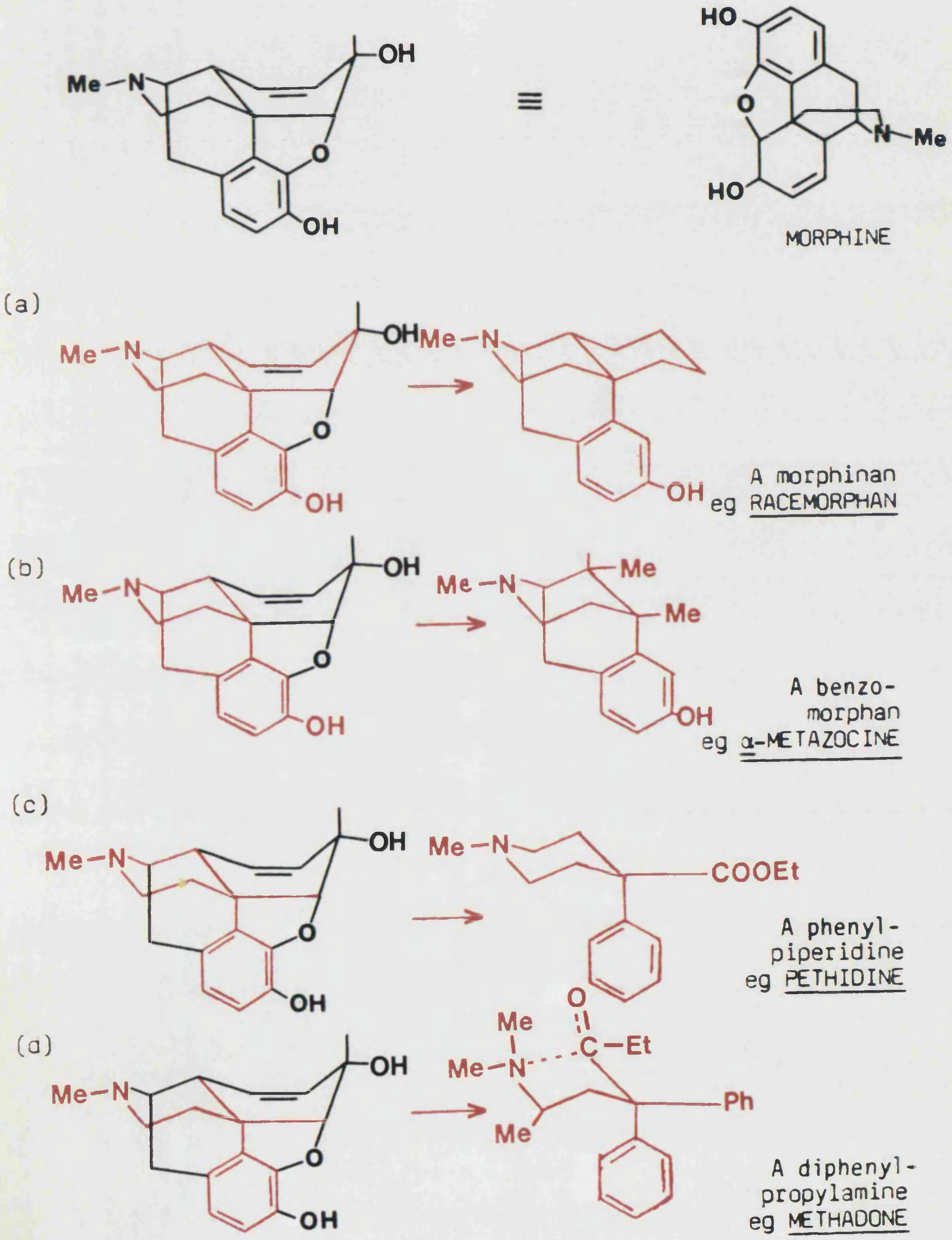
1.3.1 The Morphinans

The synthesis of the morphinan ring structure showed that the entire morphine nucleus is not essential for analgesic activity[9] (see Fig. 1a). Among the various derivatives within this group, racemorphan (10) was the first clinically valuable agent, with twice the activity of morphine,[10] and most of its activity resides in the levo-isomer, levorphanol.[11]

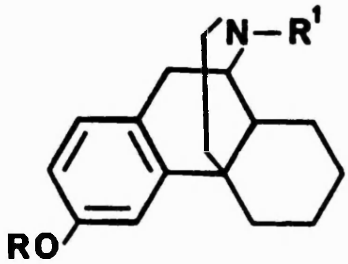


(10)

Fig. 1. Structural elements of (a) the morphinans, (b) the benzomorphans, (c) the phenylpiperidines and (d) the diphenylpropylamines as they may relate to morphine.



As with morphine, it has been found that methylation of the phenolic hydroxyl results in a significant decrease in potency, while replacement of the N-methyl group by N-allyl gives the potent morphine antagonist levallorphan (11), with about five times the potency of nalorphine.[12] Dextromethorphan (12), the O-methylether of the dextroisomer of racemorphan has found extensive use as a non-addictive antitussive agent.

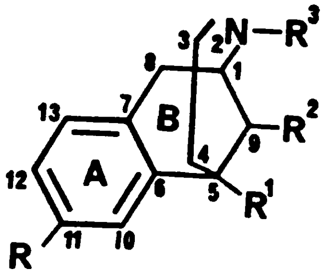


(11) **R = H ; R^1= $CH_2CH=CH_2$**

(12) **R = R^1 = CH_3**

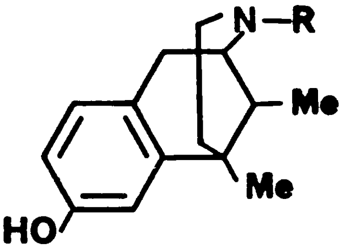
1.3.2 The 6,7-Benzomorphans

The synthesis of 6,7-benzomorphans of the type (13) was first carried out by May and Murphy in 1954.[13] In these compounds, the (C) ring has been replaced by methyl and other alkyl substituents at C-5 and C-9, a modification which confers additional cis/trans geometric isomerism on the derivative (see Fig. 1b). The isomer with the configuration in which (R^1) and (R^2) are cis in relation to ring (B) is designated the alpha (α-) isomer, while the trans orientation is the beta (β-) isomer. It has been found that greater analgesic activity, dependence liability and toxicity is associated with the β-series, and, additionally, agonist activity resides mainly in the levo-isomer.[14]



(13)

Clinically important 6,7-benzomorphan derivatives include phenazocine (14; N-phenethylnorbenzomorphan), with 3-5 times the activity of morphine in man but a lower dependence liability,[15] and pentazocine (15), the N-dimethylallylnorbenzomorphan derivative.[16,17] Although a weak antagonist of morphine, pentazocine is an effective analgesic in man and it is marketed as an analgesic with low addictive liability (as "Fortral"), but clinical experience has disproved this latter aspect. It is now classified as a controlled drug.

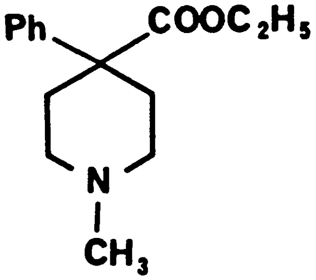


(14) $R=CH_2CH_2Ph$

(15) $R=CH_2CH=C(Me)_2$

1.3.3 The 4-Phenylpiperidines

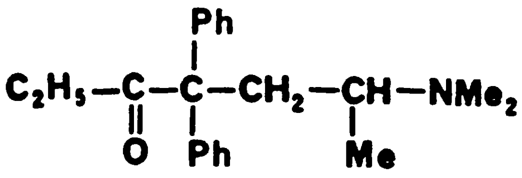
Pethidine (16), the parent compound of the 4-phenylpiperidine analgesics, was originally synthesised as a potential antispasmodic agent. Its analgesic properties were observed in the course of clinical trials.[18] After its analgesic properties became known, pethidine was recognised as bearing a similarity to part of the morphine molecule (see Fig. 1c). A full consideration of the chemistry and stereochemistry of the 4-phenylpiperidines and related compounds is given in Section 1.4.1.



(16)

1.3.4 Diphenylpropylamine Analgesics

Analgesics of this class have an open chain structure. The best known example employed in clinical practice is methadone (17)[19,20] This acyclic analgesic, a 3,3-diphenylpropylamine derivative, was one of the early non-fused ring analgesics recognised. A possible conformational relationship of methadone to morphine has been postulated (see Fig. 1d).

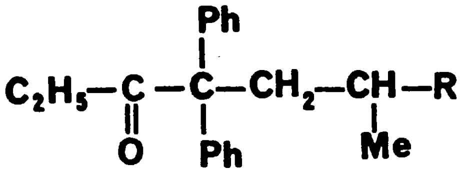


$$C_2H_5-\underset{\underset{O}{\|}}{C}-\overset{\overset{Ph}{|}}{\underset{\underset{Ph}{|}}{C}}-CH_2-\underset{\underset{Me}{|}}{CH}-NMe_2$$

(17)

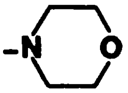
Advantages of methadone over morphine are that it sustains addiction at one quarter the dose of morphine, and withdrawal effects, both physical and emotional, are less severe.

Variations about the nitrogen atom of methadone produced other clinically used analgesics, such as the piperidino (19, dipipanone)[21] and morpholino (18, phenadoxone)[22] derivatives.

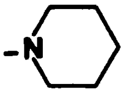


$C_2H_5-C(=O)-C(Ph)_2-CH_2-CH(Me)-R$

(18) R=



(19) R=



Many other analogues based on variation of the methadone structure have been prepared, some of which are used clinically, but none offers any real advantage over methadone itself.

1.4 ARYLPIPERIDINES

1.4.1 4-Phenylpiperidine Analgesics and Related Compounds

1.4.1.1 Introduction

The 4-phenylpiperidine type of analgesics is historically the oldest synthetic group (reports appeared in 1939). It has probably attracted the greatest amount of research towards related compounds of any of the synthetic analgesic classes. It is estimated that about 4,000 analogues of this type had been prepared by 1965.[23] Publications subsequent to that date suggest that phenylpiperidines are still not a dead issue, and the field continues to expand even today.

In 1939, Eisleb and Schaumann[18] prepared a large number of piperidine derivatives as potential antispasmotic agents on the basis of their chemical relationships to atropine. However, several of these compounds exhibited marked analgesic activity during the general screening tests. Pethidine (meperidine, 16) was the first clinically valuable derivative of this series, and it is remarkable how pethidine, the original nonopioid-derived analgesic, has maintained its popularity in the face of competition from other synthetic analgesics marketed over the past 47 years.

Pethidine has one fifth to one tenth the potency of morphine in man,[24] and is one of the most widely accepted substituents for morphine. It is useful for the suppression of mild to moderate pain, especially in patients intolerant to opioids. It has a lower level of toxicity and a shorter duration of action compared with morphine. Tolerance to pethidine develops slowly, and its dependence liability is lower than that of morphine in equivalent dosage. As with morphine, pethidine produces respiratory depression, nausea and vomiting. It is extensively used for the relief of labour pain,[25] where it has attracted some criticism.[26]

Extensive research into synthetic modifications of pethidine has been undertaken with the aim of producing an ideal analgesic, and also to investigate the structure-activity relationships that apply among the 4-phenylpiperidines.

1.4.1.2 Synthetic Modifications of Pethidine

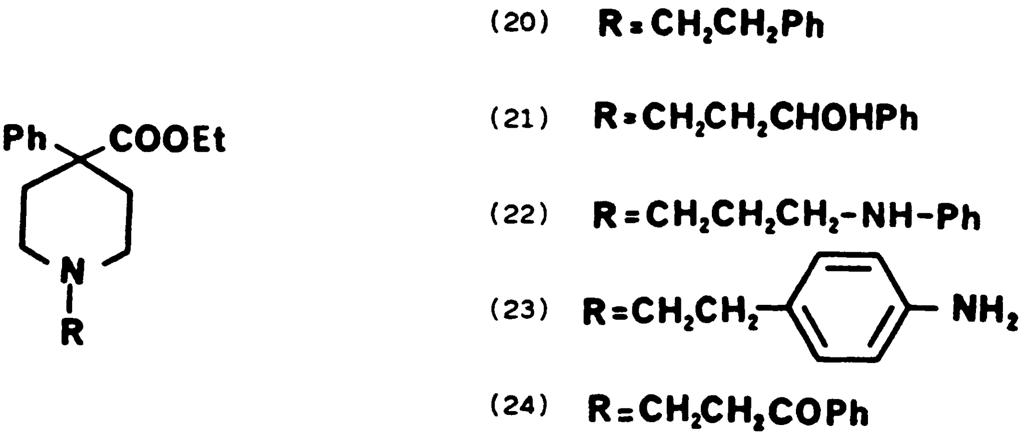
a. Variation of the Nitrogen Substituent

It has been found that the potency of analgesics in the 4-phenylpiperidine series depends critically on the nature of the substituent on the nitrogen, and substitution of pethidine N-methyl has led to the production of several compounds with greater potency than the parent drug, but it has also been found that the side effects, including addiction liability, have increased with the analgesic potency.

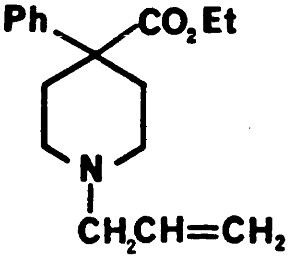
Perrine and Eddy[27] altered the character of the nitrogen substituent and related the length of the alkyl chain to potency. They found that N-phenethylnorpethidine (pheneridine, 20) had a potency twice that of pethidine in mice,[27] and they also found that the activity rises from N-benzyl (0.25 x pethidine) to N-phenylpropylnorpethidine (13 x pethidine), and decreases on further extension of the alkyl chain.[28] Replacement of the side chain aryl by pyridyl enhances activity,[29] whilst the dioxolane group in that position gives a compound with the same potency as the parent ester.[30] Substituents in the benzene ring of pheneridine, such as amino, nitro, methoxy and ring nitrogen (4-pyridyl), enhance activity in the N-phenethyl compounds but not always in other series. Chain branching severely reduces the potency.

N-substituted analogues of pethidine in clinical use include phenoperidine[26] (Operidine, 21), the secondary alcohol derived from the reduction of the Mannich base derived from norpethidine and acetophenone, with 150 times the potency of pethidine[31,32], anileridine (Leritine, 23) the N-*para* aminophenethyl analogue of pethidine, with 2-3 times the potency of pethidine[33,34], and piminodine (Alvodine, 22), which bears an *N*-substituent containing a secondary amino group between the alkyl and aryl function, is 100 times more potent than pethidine, and has been marketed in the United States.[35]

A variety of pethidine analogues with oxygen-containing *N*-substituents have been investigated by Janssen and co-workers, who reported that the highest activity was found in the propiophenone derivative (24), which was about 60 and 200 times more active than pethidine in mice and rats, respectively.[31,32]



Unlike the morphine and benzomorhan series, attempts to prepare antagonists in the 4-phenylpiperidine series by introducing appropriate *N*-substituents (such as allyl and CPM groups) was unsuccessful. Examples include the *N*-allyl derivative (25) of norpethidine, which is agonist with no power to block the opiate receptor.[36] However, a notable exception to this observation is compound (26), based on bemidone, which is reported to have one third the activity of nalorphine against morphine.[37]



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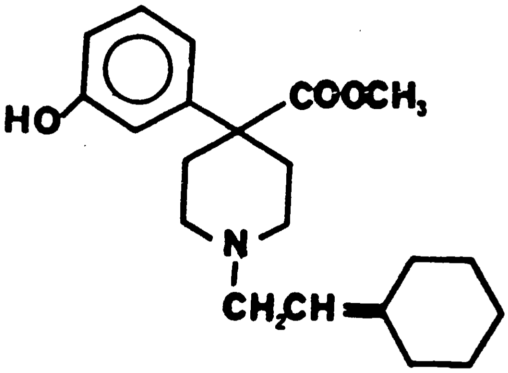
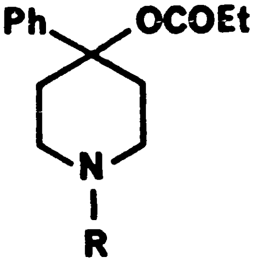


(26)

b. Variation of the C4-Oxygen Function

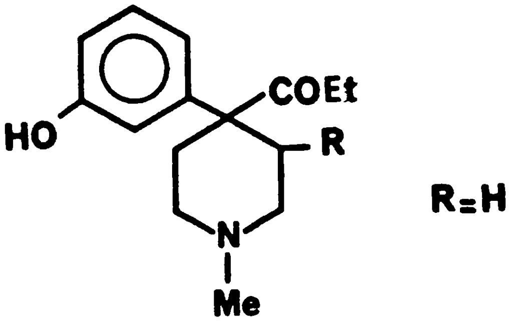
This was the second modification to the basic structure of pethidine, which was investigated soon after the drug was introduced into clinical practice. The carbethoxy group (CO_2Et) is considered to be of optimal size for analgesic activity,[38] and its replacement by carbomethoxy,[39] or a bulky ester function, decreases activity.[31,32] However, in 1943 it was reported that the replacement of 4-carbethoxy by 4-propionyloxy (OCOEt) enhanced potency by a factor of 20.[39,40] This group of analgesics, the so-called reversed esters of pethidine, showed high levels of potency, regardless of the nature of the N-substituent.[39] In 1960, Janssen and Eddy reported that remarkably potent 4-phenylpiperidine analgesics may be obtained by choosing the appropriate N-substituent,[39] and they also found that the reversed ester analogue of phenoperidine (27) is over 3000 times as active as pethidine in rats, while the precursor Mannich base (28) is about half as active as the secondary alcohol.[41]



(27) $R = (CH_2)_2CH(OH)Ph$

(28) $R = (CH_2)_2COPh$

The replacement of the carbethoxy (CO_2Et) group of pethidine with a ketone moiety gave the bemidone series. The best known example in this series is ketobemidone (29; R = H), made from the 4-cyano intermediate (30), which possesses a 4-propionyl group together with a 4-*m*-hydroxyphenyl group. It has 10 times the activity of pethidine,[42] with similar activity to *α*-prodine and morphine. It shows high PDC (physical dependence capacity) in monkeys and is at least as addictive as morphine in man.[33,43] The 4-ethoxy-4-(2'-furyl) analogue (31) of pethidine has 2.5 times the activity of the parent.[44]



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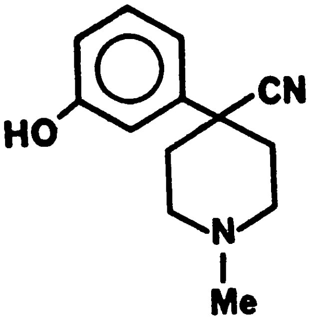

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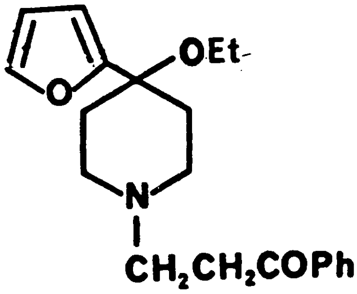
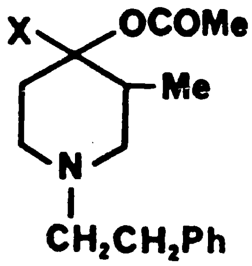


(31)

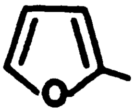
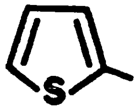
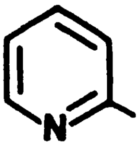
Since the replacement of C4-oxygen by various C-alkyl substituents is relevant to the present work, it will be discussed in more detail in section 1.4.2.

c. Variation of the 4-Aryl Group

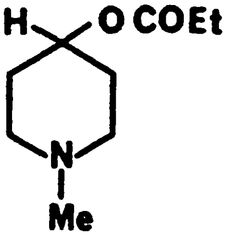
Most data concerning the effect of variation of 4-phenyl on potency in 4-arylpiperidine analgesics relate to reversed esters as a result of the versatility of 4-aryl-4-piperidinol syntheses. Bulk increase in the size of the aryl group, as in naphthyl derivatives, led to inactive compounds, while 4-tolyl analogues were reported to be less active than the parent compound.[45] Isosteric replacement of phenyl by other groups such as furyl, thienyl and pyridyl is also disadvantageous in terms of potency (see 32)[44,45,46], while its replacement by groups capable of donating π electrons, such as ethynyl, abolishes activity completely.[45]



(32)

X	Activity[44,45]
	Inactive
	63
	30
Morphine:	100

Complete removal of the 4-phenyl results in a severe fall in potency (see 33).[47,48]

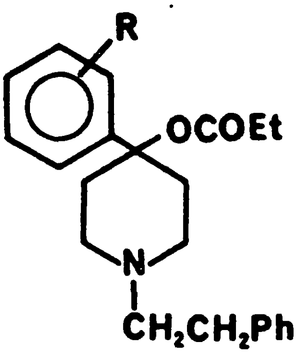


(33)

(33): ED_{50}: 20.2 mg/kg SC (MHP)

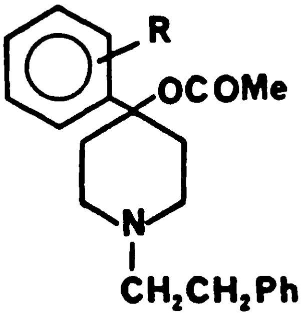
CODEINE ED_{50}: 7.5 mg/kg SC (MHP)

No consistent relationship between potency and position of substitution in the phenyl ring can be observed; however p-substitution usually results in the greatest, and ortho the least, fall in activity. The introduction of substituents into the aromatic ring, such as methyl (34) and methoxy (35) have been reported, although in most cases these analogues are less potent than the parent compound.



(34)

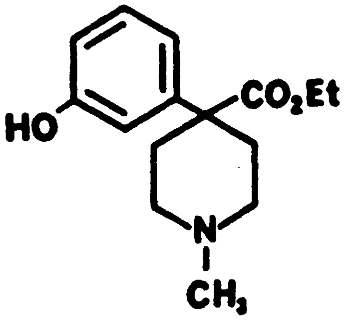
	Activity[49]
R=H	4.3
R=o-Me	2.6
R=m-Me	0.4
R=p-Me	0.2
Morphine	1.0



(35)

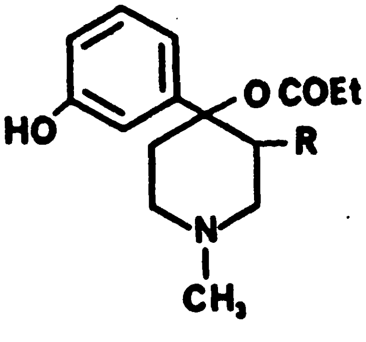
	Activity[50,51]
R=H	5.7
R=o-OMe	3.0
R=m-OMe	0.5
Morphine	1.0

In analgesics with a rigid skeleton like morphine and levorphanol, the presence of a free phenolic group is a prerequisite for high potency.[52] Such is not the case for most 4-arylpiperidines, although the introduction of a meta phenolic hydroxyl into pethidine, as in bemidone (36), elevates potency by a factor of 1.5.[33,43]



(36)

On the other hand, m-phenolic analogues (37), (38) and (39) of the reversed ester of pethidine, α- and β-prodine, and α- and β-allylprodine (see page 28) respectively, have been shown to be inactive in *in vitro* and in antinociceptive tests for analgesia.[53,54]



(37) **R=H**

(38)**R=CH_3**

(39) **R=$CH_2CH=CH_2$**

d. Alkylation of the Piperidine Ring

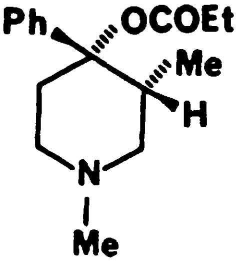
The effect of alkyl substitution in the piperidine ring of 4-phenylpiperidine analgesics has attracted much interest since the 3-methyl analogues of the reversed ester of pethidine were described by Roche workers in the late 1940s.[55] The ease of synthesis and high levels of activity associated with the reversed esters are probable reasons why most of the investigations have been associated with derivatives of the reversed ester of pethidine, rather than pethidine itself.

It has been found that further alkylation of the piperidine carbon atoms has a marked effect on the potency of the reversed ester of pethidine, and the potency of these derivatives depends not only on the nature of the C-alkyl substituent, but also on the stereochemical features associated with the molecules.[49]

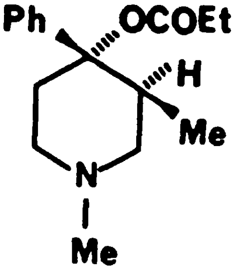
The 3-alkyl analogues of the reversed ester of pethidine, particularly the 3-methyl (*α*- and *β*-prodine) derivatives will be described in more detail in the following section. The mono and di-C-methyl analogues of the reversed ester of pethidine have been reviewed elsewhere.[56]

The isomeric 3-alkyl analogues of the reversed ester of pethidine

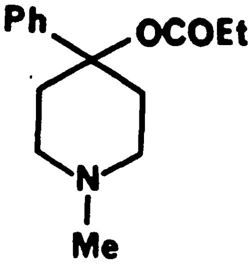
The 4-phenyl-4-acyloxy piperidines are "reversed ester" analogues of the pethidine series. This type of compound was first described in 1943 by Jensen *et al.*[40] who found that reversal of the ester function is generally correlated with increased analgesic potency. Extensive study of the isomeric nature of the 3-methyl derivative (and other alkyl derivatives) by Ziering *et al.*[57] has led to the synthesis of the isomeric derivative *α*-prodine (40) and *β*-prodine (41). The *α*-isomer was found to be the major synthetic product, with a potency equivalent to morphine. *β*-Prodine, the minor component, has been shown to have five times the activity of the parent desmethyl compound (42),[58] a potency level not shown by the corresponding *α*-isomer.



(40)



(41)



(42)

ED_{50} mg/kg	0.92	0.18	0.85

Definite stereochemical assignments of the prodines was a controversial area for some years until the relative configurations were established by X-ray crystallographic studies,[59] and substantiated by ^{1}H and ^{13}C NMR studies.[60,61] The assignments are *trans* 3-Me/4-Ph for *α*-prodine and *cis* 3-Me/4-Ph for *β*-prodine. The corresponding IUPAC nomenclature is *α*: *c*-3-Me; *r*-4-OCOEt;

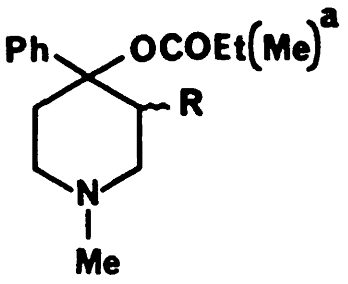
β: *t*-3-Me; *r*-4-OCOEt. It will be recalled that greater potency resides with the *β*-isomer. Both diastereoisomers are considered to exist in the equatorial 4-phenyl chair conformation.

However, it is now accepted that the case of the 3-methyl substituent is unique and in pairs with larger alkyl substituents, the *α*-isomer (*trans* 3-R/4-Ph) is more potent[62] (see Table 1). Hence, taking the unsubstituted ester (42) propionoxy and acetoxy as standards, the drug receptor interaction appears to be enhanced by *α*-ethyl and impeded by *α*-*n*-propyl (moderately) and *α*-*n*-butyl (severely), while all *β*-substituents except methyl have detrimental influences (see Table 1; the case of 3-allyl will be discussed later). Receptor affinities measured by determining the concentration of the 3-alkylated ester to displace 50% of specially bound [^{3}H]dihydromorphine from rat brain homogenates have confirmed the higher affinity of *β*- over *α*- (43; R = Me, Table 1) and *α*- over *β*- (43; R = Et, allyl and *n*-hexyl), and the results were found to be well correlated with analgesic potencies.[63]

Pharmacodynamic studies of 3-alkyl substituted reversed esters of pethidine, using analogues labelled with tritium in the aromatic moiety of the molecule,[64] have shown that the differences in the analgesic potency between the prodine isomers is also partly due to differences in brain level concentration, rather than other factors such as metabolism, distribution or plasma binding.

The influence of a *β*-3-methyl may be achieved directly through interaction with a binding site on the receptor specific for axial methyl. However, longer hydrocarbon groups of the same axial orientation are not accommodated at this site and act against

Table 1. Analgesic Activity (Hot Plate ED_{50} mg/kg SC in Mice) of Some Reversed Esters of Pethidine.[62]



(43)

R	α-(*t*-3R/4-Ph)	β-(*c*-3R/4-Ph)
Me	0.92 (6)	0.18 (0.98)
Et	0.4 (2.1)	3.5 (15.9)
Pr^n	2 (10.4)	14.7 (23.4)
allyl	0.09	11.7
Bu^n	54.7 (29.3)	12.8 (26.5)
$C_6H_{13}^n$	inactive at 80	54.4

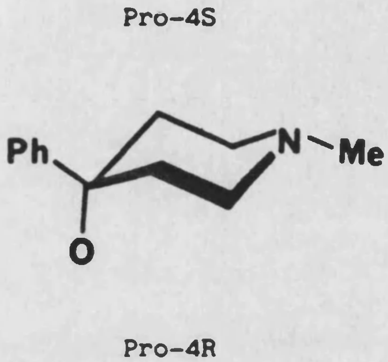
a. Acetate data in parentheses, pethidine reverse ester 0.85 (3.62) drug-receptor association. An alternative explanation, however, is that a β-3-methyl group has an indirect influence on ligand-receptor association by facilitating a rise in the population of reversed ester conformations that bind more effectively than the equatorial 4-phenyl chairs favoured for unsubstituted and 3 α-substituted derivatives.

Stereochemical studies of 3-allyl prodines been clarified by simultaneous results from two groups.[65,66] The configurations were established by ^{1}H NMR and X-ray crystallographic studies as trans 3-allyl/4-Ph for the α-isomer and cis 3-allyl/4-Ph for the β-isomer. α-Allyl prodine is about 13 times as active as morphine and the β-isomer about one-tenth as active as morphine, results which confirm the superiority of the α-form as an analgesic but give the β-compound a much lower potency than that originally reported.[67,68]

Comprehensive study of stereochemical structure-activity relationship of 4-phenylpiperidine analgesics has been carried out by Portoghese and co-workers,[69] who separated the two chiral diastereoisomers into antipodal forms, established the absolute configuration of each enantiomer, and determined each enantiomer's analgesic potency.

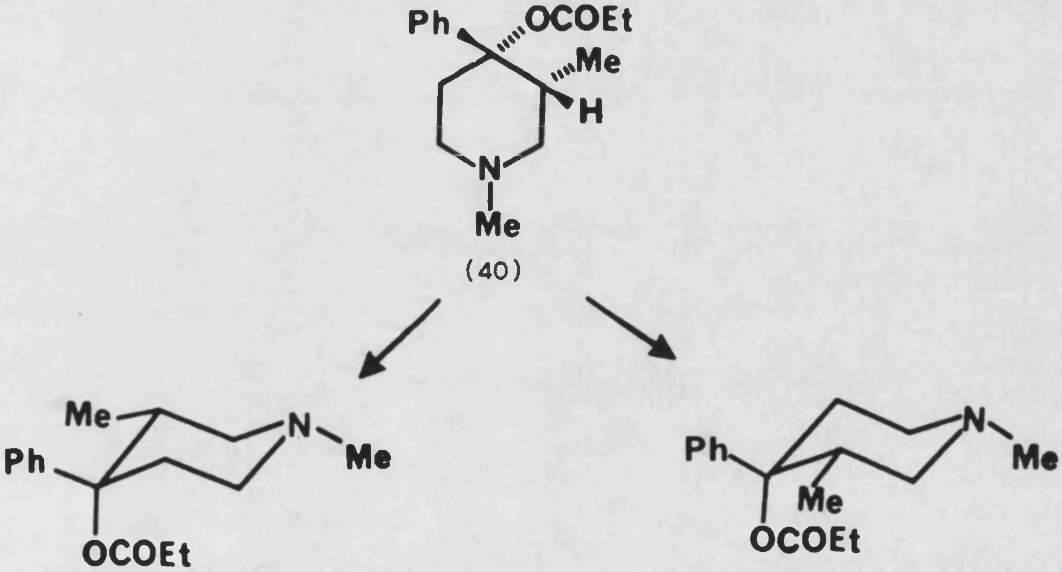
Considering the 4-phenylpiperidine reversed esters to exist in favourable 4-phenyl chair conformations, Portoghese and his workers used biochemical nomenclature[70] to differentiate between the two sides of the piperidine molecule. One side was termed pro-chiral-4S (Pro-4S) and the other pro-chiral-4R (Pro-4R; see 44). In the unsubstituted standard ester (42) C-4 is symmetrical, and insertion of an alkyl group on the Pro-4S side gives C-4 an S configuration by application of the Cahn Ingold-Prelog convention,[71] whilst substitution on the Pro-4R side gives C-4 an R configuration.

Partial formula



(44)

It has been found that greater activity resides in the 3R,4S enantiomer of <u>a</u>-prodine (40a) than the corresponding 3S,4R enantiomer (40b).[69]



(40)

(+)-3R, 4S

(40a)

(-)-3S, 4R

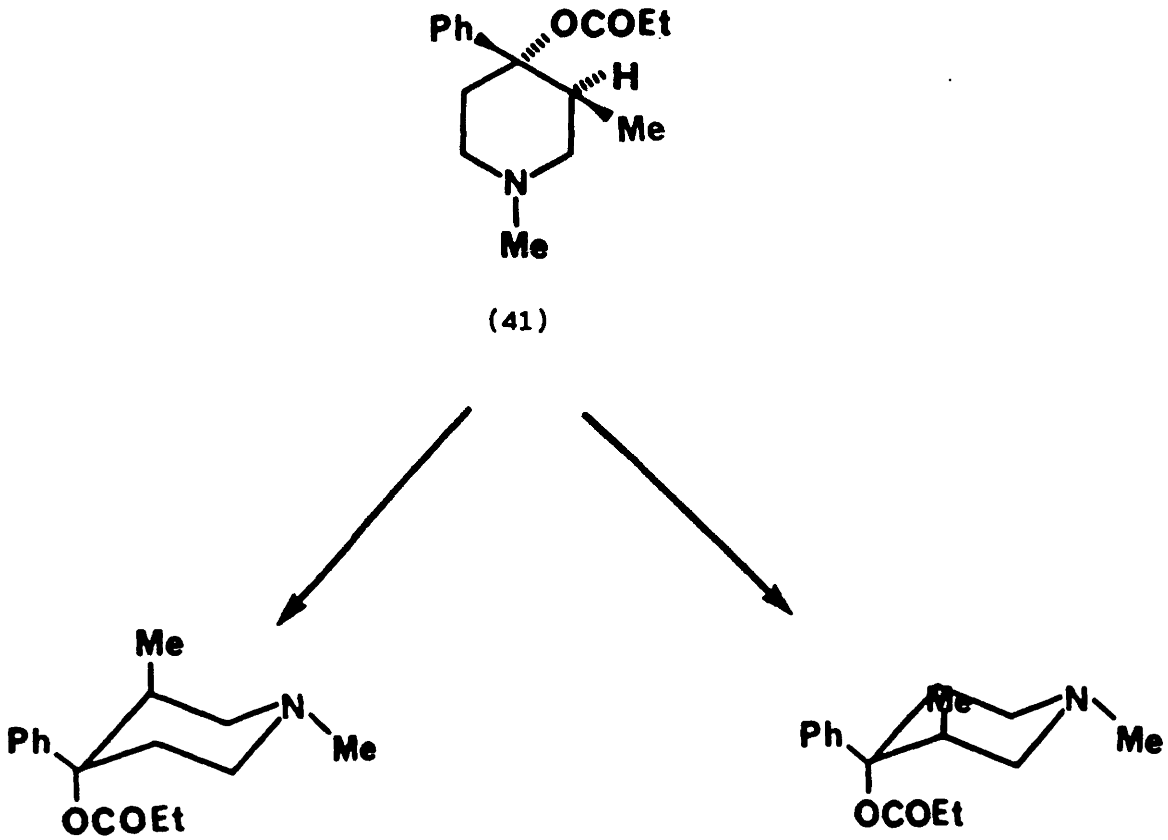
(40b)

ED$_{50}$ mg/kg	0.91	22.4

These results raised the question of whether the opiate receptor discriminates against the Pro-4S side of the molecule. Thus, if the Pro-4R side of the moledule is submitted to the opiate receptor, equatorial 3-Me substituents situated on this side hinder drug receptor binding, while equatorial 3-methyl groups on the Pro-4S side do not affect this binding.

This study has been proved by further investigations on other antipodal forms of 3-α-alkyl analogues. One example to demonstrate this is the 3-α-allyl derivative of the reversed ester of pethidine; the 3R,4S enantiomer (ED_{50} = 0.03 mg/kg) has a higher level of potency than the corresponding 3S,4R podal form (ED_{50} = 25.2 mg/kg) in mice (hot-plate test).[72,73]

A similar study of the two antipodal forms of β-prodine (41), in which the 3-methyl substituent has an axial orientation, revealed that greater analgesic potency resided with the 3S,4S antipode (41a) compared to the 3R,4R isomer (41b).[69]



(41)

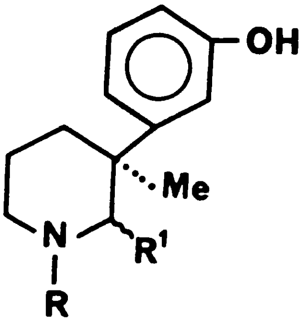
	(+)-3S, 4S	(-)-3R,4R
	(41a)	(41b)
ED_{50} mg/kg	0.25	3.3

Hence, with an equatorial 4-phenyl chair conformation, an axial 3-methyl substituent on the Pro-4S side is preferential for high levels of activity and, in addition, such axial 3-methyl substitution has an active role to play in opiate receptor interaction. This is illustrated by comparison of the analgesic activities of 3R,4S-$\underline{\alpha}$-3-methyl and 3S,4S-$\underline{\beta}$-3-methyl analogues of the reversed ester of pethidine.

1.4.2 3-Arylpiperidines

In 1965, certain 3-arylpiperidines with moderate analgesic activities were reported. Derivatives of this class are believed to be closely related to the 4,4-disubstituted piperidines, and also resemble morphine in their associations with opiate receptors.

N-methyl derivatives of this class are relatively weak analgesics, but high level of potency has been obtained by replacing the N-methyl by N-arylalkyl substituents. Examples include (45; R^1 = H; R = CH_2COPh), which was reported to have a potency equivalent to pethidine in mice (hot-plate test).[74]

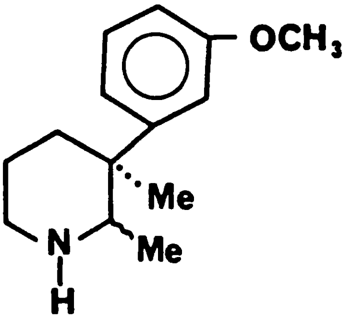


(45)

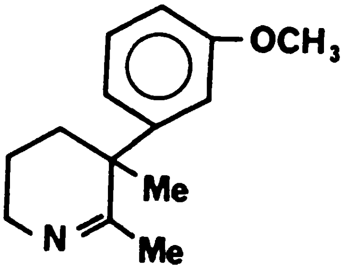
Insertion of a methyl substituent at C-2 of the piperidine ring has led to the production of compounds with higher potency, and a potency difference between the two diastereoisomers (examined as racemates) was reported. Stereochemical studies of this class have shown that single isomeric forms of the derivatives (45; R^1 = Me; R = CH_2CH_2Ph and $-CH_2COPh$) were about half as active as morphine in mice by the hot-plate test, while the corresponding

N-allyl derivative antagonises the analgesic effect of morphine in the same animal.[75,76] This contrasts with the action of 4-arylpiperidines bearing N-allyl functionalities (see page 17).

Stereochemical studies on 2,3-dimethyl-3-arylpiperidines have been clarified by further work,[77] which also provided pharmacological data that confirms the previous reports. Both isomeric forms of the parent secondary amine (46) were obtained by hydrogenation of the tetrahydropyridine (47), and then converted to N-substituted phenolic analogues by standard methods.[77]

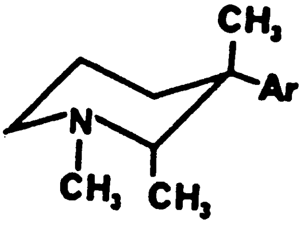


(46)

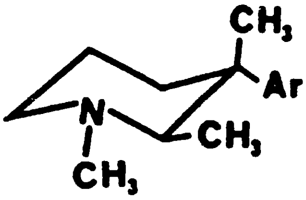


(47)

The configurations, termed c-2-Me, r-3-Ar for the α-isomer (48) and t-2-Me, r-3-Ar for the β-isomer (49), were established by analysis of differences in the ^{1}H NMR spectra of the N-benzyl and N-acetyl diastereoisomers, and also by ^{13}C NMR.[77]



(48)



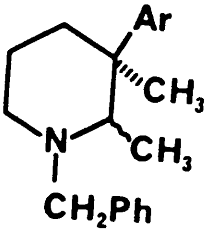
(49)

The N-methyl, N-allyl and N-CPM derivatives were found to be very weak or inactive as analgesics in mice, while the N-phenethyl isomers were active by tests on the guinea-pig ileum (α: 0.7; β: 0.3-0.4 x pethidine).[78] In rats the N-allyl and N-CPM derivatives were found to antagonise fentanyl-induced effects. The β-isomer was twice as active as nalorphine, and four times more effective than the α-isomer in both cases. Again, by comparing these results with the pharmacological properties of N-allyl and N-CPM derivatives of 4-phenylpiperidines, it seems likely that 3-arylpiperidines interact with the opiate receptor in a morphine-like manner.

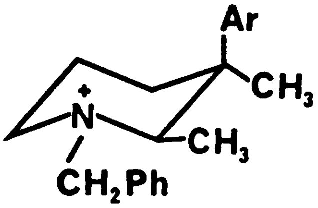
All active analogues of this class are phenols; the p-hydroxyphenyl derivatives [45; R^1 = Me; R = $CH_2CH{=}CH_2$, CPM and CH_2-$CH{=}C(Me_2)$] are much less potent antagonists than the corresponding m-hydroxyaryl isomers, a result which emphasises the importance of the m-hydroxyaryl moiety in binding with opiate receptors.

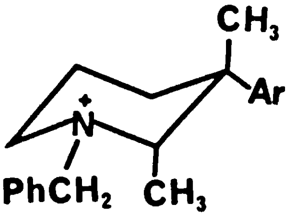
The original assignments of 2,3-dimethyl-3-arylpiperidines were later confirmed by ^{13}C NMR studies.[79]

^{1}H and ^{13}C NMR studies of the α-N-benzyl derivative (50, Ar = m.OH.C_6H_4) as the hydrochloride by Casy et al.[80] have shown that the preferred solute conformation is (52), and not the previously suggested one (51).[77] They also synthesised the 3,5- and 3,6-dimethyl derivatives and studied their stereochemical features, but no pharmacological data have been presented.



(50)

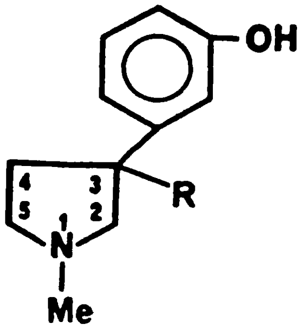




(51) (52)

Analgesically-active derivatives of 3-arylpyrrolidines (53; e.g. R = Me) were prepared, and converted to morphine antagonists by replacing N-Me by N-allyl or N-CPM.[81-83]

Profadol (53; R = n-Pr) was the first notable compound of this type. It shows twice the activity of codeine in rats by antinociceptive tests, and its action was antagonised by nalorphine.[84,85]



(53)

Replacement of the 3-alkyl substituent by CO_2Et or COEt results in a severe fall of potency. Derivatives with various 3-alkyl substituents have been reported.[81,82] Compound [53; R = $CH_2CH(Me)_2$] was found to be 2.7 times as active as codeine, while the corresponding N-CPM derivative was reported to have 3.5 times the activity of pentazocine against morphine.

1.4.3 4-Alkyl-4-ArylPiperidines

1.4.3.1 Introduction

The synthesis of these compounds was first described by McElvain and Clemens in 1958.[86] In these compounds, the C4-oxygen function has been replaced by various alkyl substituents, a modification which was initially intended to determine whether such a polar substituent as the former is essential for the analgesic activities of such compounds, or whether a non-polar alkyl substituent would be satisfactory.

To reiterate, narcotic antagonistic activity in morphine, 6,7-benzomorphans and the morphinans is usually associated with replacement of the N-Me by N-CPM, N-allyl (as in, for example, Naloxone) or other related groups.[5,87] On the other hand, such replacement in the 4-phenylpiperidine series has not produced narcotic antagonists.[36] Nevertheless, there are exceptions to this; levo-metazocine and profadol, both N-methyl compounds with agonist properties, show some antagonist activities, although this is relatively weak.

However, during pharmacological investigation of a series of 1,3,4-trialkyl-4-arylpiperidines (54), Zimmerman et al.[88] discovered that the presence of 3-methyl cis to 4-aryl, for example (54a; Table 3; p.41) resulted in analgesic-antagonist properties. Thus, they concluded that position 3 of the piperidine ring, rather than substitution at the nitrogen, is the area critical for determining antagonist activity in these compounds.

The following section attempts to illustrate the chemical and pharmacological aspects of this new series of phenylpiperidines.

1.4.3.2 Chemical and Pharmacological Aspects of 4-Aryl-4-alkylpiperidines and Related Compounds

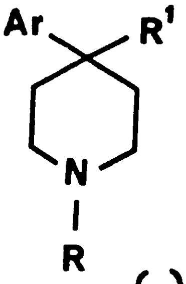
Structure-activity relationships of the 1,4-dialkyl derivatives[86] (55; see Table 2) have shown that the free m-phenolic hydroxyl is an essential feature of all active compounds, since introduction of a hydroxyl or a methoxyl substituent in the o- (see 55d and 55e) or p-position (see 55k) results in complete loss of analgesic activity.

Increasing the size of the C4-methyl substituent of (55h) to n-propyl (55ℓ) enhanced potency by a factor of 10-40, while its replacement by hydrogen results in compounds without any significant analgesic activity (for example, 55t).

Other changes include substitution of the N-methyl group in (55a) by N-butyl (as in 55r), which results in no significant change in analgesic properties, while its replacement by N-ethyl or N-propyl (as in 55m and 55n respectively) results in inactive compounds. Some activity returns when the N-substituent is isopropyl (as in 55p), but none of these compounds display any marked analgesic action.

No pharmacological data concerning compounds with a 3-methyl substituent have been presented in the series investigated by McElvain and Clemens.

Table 2. Analgesic Potencies of Some 1,4-Dialkyl-4-arylpiperidines and Other Related Compounds[86]



(55)

Compound	R^1	R	Ar	Dose (mg/kg	Analgesic Effect
a	CH_3	CH_3	C_6H_5	40-80	B
b	C_2H_5	CH_3	C_6H_5	10-12	B
c	n-C_3H_7	CH_3	C_6H_5	2-6	B
d	CH_3	CH_3	C_6H_4-OMe(*o*)	5-10	A
e	CH_3	CH_3	C_6H_4-OMe(*o*)	1-20	A
f	n-C_3H_7	CH_3	C_6H_4-OMe(*m*)	4; 8 and 16	C; D and E
g	CH_3	CH_3	C_6H_4-OH(*o*)	5-80	A
h	CH_3	CH_3	C_6H_4-OH(*m*)	10 and 20-80	C and D-E
k	CH_3	CH_5	C_6H_4-OH(*p*)	10-80	A
ℓ	n-C_3H_7	CH_3	C_6H_4-OH(*m*)	0.5; 1 and 2	C; D and E
m	CH_3	C_2H_5	C_6H_5	10-80	A
n	CH_3	n-C_3H_7	C_6H_5	5-40	A
p	CH_3	iso-C_3H_7	C_6H_5	10-80	B
r	CH_3	n-C_4H_9	C_6H_5	10-80	B
s	H	CH_3	C_6H_4-OMe(*m*)	10-80	A
t	H	CH_3	C_6H_4-OH(*m*)	5-80	B
Demerol				5 and 10-20	C and D-E
Morphine				1 and 2-40	C and D-E

A. No analgesia
B. Trace
C. Moderate
D. Marked
E. Profound

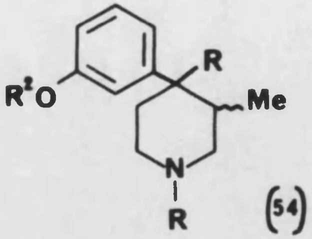
Interest in this series was revived in 1978 by a paper by Zimmerman et al.,[88] which confirmed the original structure-activity relationships, and also provided pharmacological data of some 1,4-dialkyl compounds and, of more interest, their corresponding 3-methyl derivatives. It has been found that the β-isomer (54a) is either half or twice as acive as nalorphine (depending on rodent species), and lacked agonist activity. The corresponding α-isomer (54b) was found to behave as a partial agonist.

Further investigation into the 4-propyldiastereoisomers gave less precise SAR data; the α-isomer (54d) was essentially an agonist, with less potency than the corresponding 3-desmethyl derivative, while the β-isomer (54c) was a significant antagonist in rats, and a weak agonist in mice.

It also has been found that replacement of the N-methyl of (54a) by N-allyl and N-CPM (substituents which produce antagonists in the morphine, morphinans and 6,7-benzomorphan series) resulted in a significant decrease in antagonist potency in rats, while its replacement by N-2-phenethyl (as in 54g) and N-2-benzoylethyl (54h), (substituents that usually increase agonist activity in the pethidine series), raised potency to the level of naloxone in the latter example. Resolution of (54h) into its antipodal forms provided only partial separating of activity, as both antipodes were antagonists, with the dextro-isomer being 2-6 times more potent than the levo-isomer in mice (see Table 3).

Antagonist properties were also alleged for β-3-methylketobemidone (29; R = Me) and the phenolic analogue (38) of β-prodine (see Table 3).

Table 3. **Agonist and Antagonist Activities of Some 4-m-Hydroxyphenyl -4-alkylpiperidines**[89-91]



(54)

R² = H
α: t-3-Me/4-Ar
β: c-3-Me/4-Ar

Compound	R	R^1	Isomer	Antagonist measure $(AD_{50})^A$		Agonist measure	
				Rats	Mice	Rats	Mice
						$(ED_{25})^B$	$(ED_{50})^C$
a	Me	Me	β	0.24	1.0	50	50
b	Me	Me	α	13.0	45.0	33.0	15.0
c	Me	Pr	β	4.6	43.0	50	13.0
d	Me	Pr	α	Addictive	45.0	2.0	2.4
e	C_3H_5	Me	β	0.47	0.98	–	–
f	CPM	Me	β	0.72	0.72	–	–
g	$(CH_2)_2Ph$	Me	β	0.11	0.14	–	–
h	$(CH_2)_2COPh$	Me	β-(±)-	0.056	0.049	–	–
			β-(–)-	0.05	0.14	–	–
			β-(+)-	0.023	0.025	–	–
Pentazocine				20.0	14	–	–
Nalorphine				0.45	0.045	–	–
Naloxone				0.022	0.079	–	–
Morphine				–	–	1.8	0.97
54ℓ				Addictive	–	0.89	0.85
29(R = Me)			β	21	38	–	–
38			β	6.2	9.9	–	–

Footnotes to Table 3.

A. Dose (mg/kg, S.C.) required for a 50% reduction in the response to morphine in rats (tail heat) and mice (Straub tail and locomotion).

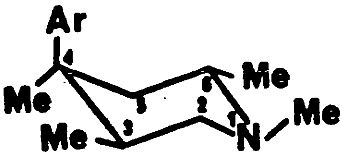
B. Dose required for a 2 second increase in reaction time in rat tail heat test.

C. Dose required for 50% reduction in the frequency of writhing.

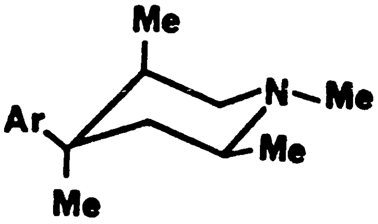
Separation of the two optical forms of the α-4-n-propyl derivative (54d; Picenadrol) and subsequent analgesic testing indicated that most of the activity resided in the dextro-isomer, while the levo-isomer, which is a weak agonist in mice, exhibited marked antagonist properties in rats (tail flick test), with a potency between that of nalorphine and pentazocine.[89-91] Since all 4-propyl derivatives differed little in their IC_{50} binding values, their different pharmacological profiles were accredited to changes in intrinsic activity rather than receptor affinity.

The view that the β-derivatives of this series were pure antagonists was backed by the following test; they were without measurable agonist activity at 100 mg/kg, SC in the mouse writhing analgesic test, a test procedure in which compounds with mixed agonist-antagonist activity (such as nalorphine) exhibit analgesic effects, and this was supported by in vitro tests.[92]

In an attempt to determine the active conformational mode of (54; axial or equatorial-4-chair), some 3,6-dimethyl analogues were synthesised and tested, and evidence that the axial 4-aryl conformation leads to an agonist response, while equatorial 4-aryl conformation causes receptor blockade, was obtained.[89-91] Thus, the trans-3,6-dimethyl isomer (56) was an agonist with a potency half that of morphine, while the cis isomer (57) was an antagonist, with a potency similar to that of nalorphine.



(56)



(57)

These ideas require that the agonist (55ℓ, Table 2;p.39)binds in the axial 4-aryl conformation, and there is computational evidence that such a conformer is preferred in this derivative.[93]

If axial 4-arylpiperidine chairs are in fact the active conformational species in those members of this series with agonist properties, then the close relationship of their binding mode to that of morphine becomes an attractive possibility and accounts for their need of a phenolic substituent.

1.5 PHENCYCLIDINE

1.5.1 Introduction

Phencyclidine (58a; PCP) was initially introduced as a surgical anaesthetic in 1958,[94] but a few years later emerged as a drug of abuse in street use. Adverse psychotic reactions, such as agitation, disorientation, delirium, hallucination and many other undesired side effects, developed in many post surgical patients and it was later abandoned, though it is still used legally in veterinary medicine. The remarkably high potency of PCP, and its ease of synthesis, made it one of the widely abused psychotomimetic drugs.

The precise classification of PCP is presently unsettled. PCP has stimulant,[95] depressant,[96] hallucinogenic,[97] and analgesic properties,[98] some of which are dose-dependent.

In all actuality, PCP probably falls into a class of its own, given the unique spectrum of properties that it displays. However, a report suggested that PCP, and a variety of its analogues, interfere with cholinergic processes.[99]

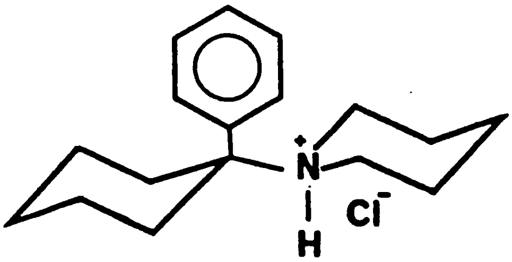
Evidence on whether or not the analgesic property of PCP is mediated through the σ-receptor, which is known to be the third of the original three sub-species of opioid receptor,[100] was first obtained by Vaupel and Jasinski.[101] They reported that N-allylnormetazocine, already known to bind with the σ-receptor,[100] and PCP have similar effects on the dog with transected spinal cord, a result which suggests that a common receptor is involved in their actions, and this was later supported by further tests.[102,103]

1.5.2 Some Derivatives of Phencyclidine

Variation of the PCP structure in an attempt to produce a safe general anaesthetic has led to the production of several analogues (see Table 4), some of which have similar psychic effects. Compounds 58e-58p represent the most active members of the series.[104]

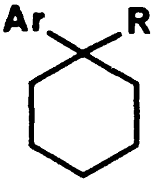
Variations in the amine and aromatic functional moieties of PCP produced other active compounds (Table 5), but none offers any real advantage over PCP.[105]

NMR and X-ray crystallographic studies[106,107] of PCP hydrochloride have established that the preferred solute conformation of PCP hydrochloride is (60) in which both the cyclohexane and piperidine rings are in the chair form, and the phenyl ring assumes an axial position relative to the cyclohexyl and piperidine rings. This was later confirmed by variable temperature NMR, X-ray crystallographic and molecular mechanics studies.[108]



(60)

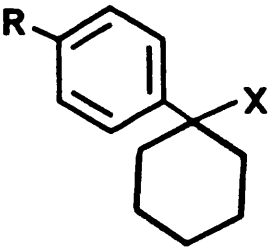
Table 4. Some Phencyclidine Derivatives[104]



(58)

Compound	R	Ar
a	NC_5H_{10}	C_6H_5
b	NC_5H_{10}	$C_6H_4.CH_3$(m)
c	NC_5H_{10}	$C_6H_4.Cl$(m)
d	NC_5H_{10}	$C_6H_4.OCH_3$(o)
e	NC_5H_{10}	$C_6H_4-OCH_3$(p)
f	$3-CH_3.NC_5H_9$	C_6H_5
g	NC_4H_8	C_6H_5
h	$3-(CH_3)_2-NC_4H_6$	C_6H_5
k	NHC_2H_5	C_6H_5
ℓ	$NHn-C_3H_7$	C_6H_5
m	$NHCH_2CH_2OCH_3$	C_6H_5
n	$NHCH_2CH_2CH_2OCH_3$	C_6H_5
p	NHC_2H_5	$C_6H_4.CH_3$(m)

Table 5. Relative Systemic Potencies of PCP Derivatives as the Hydrochlorides in Mice, as Measured by the Rotarod Test[105]

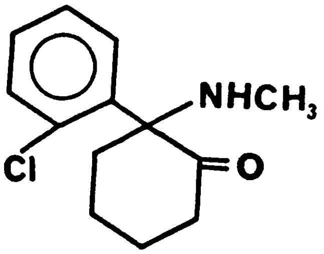


(59)

Compound	R	X	ED$_{50}$ mg/kg
a	H	$-NH_2$	9.50
b	H	$CH_3NC_5H_{10}.I^-$	not active up to 6.5 mg/kg
c	OH	NC_5H_{10}	1.24
d	NH_2	NC_5H_{10}	9.8
e	NO_2	NC_5H_{10}	not active up to 10 mg/kg
58k			1.25
58a			3
58e			11.8

1.5.3 New Analgesic Drugs Derived From PCP

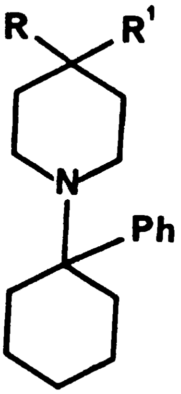
Despite its undesirable side effects, PCP is unique in its lack of depressant effect on the heart and respiration.[94,109] PCP has been accredited with the exertion of analgesia,[110,111], but no precise data are available. It has thus been assumed that a proper manipulation of the PCP structure might change the balance between its antinociceptive and psychotomimetic properties in favour of the former. This is not unreasonable in view of the successful precedence offered by ketamine (61), which has retained the anaesthetic profile of the parent structure, but lost much of its psychotomimetic activity.[112]



(61)

The introduction of new substituents at position 4 of the piperidine ring of PCP has led to the production of several compounds which are structurally similar to the well known 4-phenylpiperidine narcotic analgesics, some of which were reported to possess analgesic properties in the usual animal tests (see Table 6).[113,114]

Table 6. Analgesic Activity[A] of 4-Substituted 1-(1-Phenylcyclohexyl) piperidines[113]



(62)

Compound	R	R^1	ED_{50} mg/kg SC	
			Hot-Plate Test	Writhing Test
a	H	OH	C	11.2
b	H	$3,4\text{-}(OCH_3)_2C_6H_3CO_2$	7.5	5.2
c	H	$C_6H_5CO_2$	15	24.5
d	H	$3\text{-}CO_2NC_5H_4$	45	16.5
e	H	$4\text{-}NH_2C_6H_4CO_2$	40	9.3
f	H	CH_3CO_2	40	14.5
g	OH	C_6H_5	1.3	0.27
h	$C_2H_5CO_2$	C_6H_5	12.1	5.8
k	H	C_6H_5	56	42
Morphine			2.5	0.42
58a			B	2.8

A. Tested as water soluble hydrochloride salts

B. Not active up to 9 mg/kg SC; higher doses produced ataxia

C. Not active up to 25 mg/kg SC; higher doses produced ataxia.

It has been presumed that different mechanisms are involved in the antinociceptive effect of PCP and the new compounds, particularly (62g), (62h) and (62k); (Table 6) . The fact that there is a good correlation between the relative potencies found in the hot-plate test and the mouse vas-deferens bioassay, that the effects are reversed by naloxone, and that the new compounds are structurally similar to the 4-phenylpiperidine analgesics, imply that the analgesic effect is mediated by the opiate receptors. This view is supported by preliminary results of the radioreceptor assay using [^{3}H]morphine.[104]

So, the introduction of a second phenyl moiety at position 4- of the piperidine ring of PCP (Table 6) significantly enhanced the affinity of these molecules to specific opiate receptors, both _in vivo_ and _in vitro_. In contrast, PCP-4-OH (no. 62a, which lacks the additional phenyl moiety) is devoid of any opiate-like activity and is about 50-70 times less active than PCP-4-Ph-4-OH (62g). Also, esterification (i.e. PCP-4-Ph-4-OCOEt)of the alcohol (as in compound 62h) significantly reduced the potency of the substance.

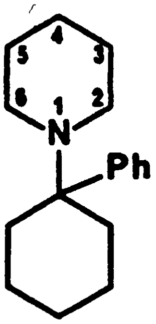
In summary, the structural modification of the PCP "skeleton" gives rise to two different analgesic groups. It is proposed[113] that certain substituents direct the molecule preferably towards the μ-receptor of morphine, but other substances (i.e., 62a) exert their antinociceptive effect differently.

2. DISCUSSION

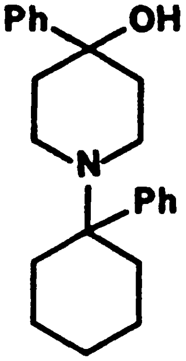
2.1 INTRODUCTION

As pointed out in the introduction of this thesis, early modification of phencyclidine (58a; PCP or "Angel dust"), in an effort to produce a safer general anaesthetic and analgesic, devoid of hallucinogenic effects, was unsuccessful.[104,105]

However, recent structural modification of PCP which borrowed elements from the well known 4-phenylpiperidine analgesics proved more successful.[113,114] Thus, introduction of a phenyl and hydroxyl moiety at position 4 of the piperidine ring of PCP significantly enhanced the affinity of this molecule (62g) towards the stereospecific receptor postulated for analgesic activity (see p. 51).

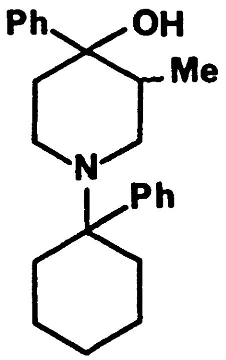


(58a)



(62g)

Following the successful chemical manipulation of the PCP structure, which altered the balance between its antinociceptive and psychotomimetic properties in favour of the former, it was considered of interest to study the effect of 3-methyl substitution in the piperidine ring since such substitution in piperidine reverse ester significantly enhances analgesic potency.[55,57] Thus, a portion of the research undertaken by the author involved the synthesis of the α- and β- forms of compound (70), and, because of interesting pharmacological data, the resolution of the α- isomer (which is much more readily available) into its antipodal species.



(70)

One other major aim of the present work is to re-examine the stereochemical structure-activity relationships that apply among the 4-alkyl-4-aryl-3-methylpiperidines and their corresponding

3-desmethyl analogues, with a view to establishing the relative configuration and the preferred solute conformation of the isomers.

The detailed aims and objectives of this thesis thus entail:

1. The synthesis of required compounds.
2. Separation of isomers.
3. Resolution of α-prodinol.
4. Configurational and conformational assignments using spectroscopic techniques (particularly high field ^1H and ^{13}C NMR).
5. Pharmacological evaluation.

2.2 PHENCYCLIDINE DERIVATIVES DERIVED FROM $\underline{\alpha}$-and $\underline{\beta}$-PRODINE

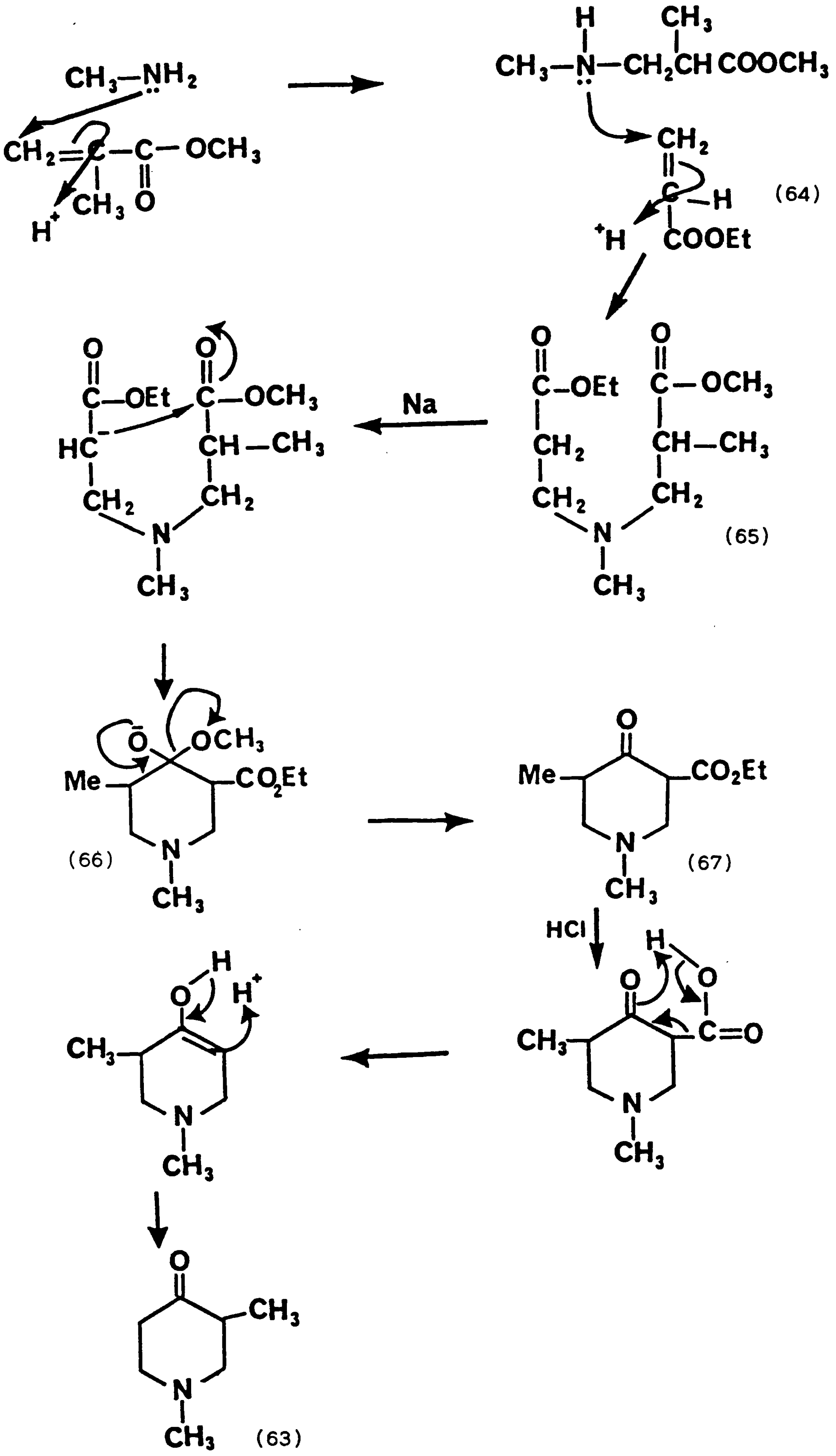
The proposed route of synthesis for these analogues is as outlined in Schemes 1, 2, 3, 4 and 7.

2.2.1 Synthesis and Separation of $\underline{\alpha}$- and $\underline{\beta}$-Prodine

1,3-Dimethyl -4-piperidone (63; Scheme 1), the key intermediate in the synthesis of $\underline{\alpha}$- and $\underline{\beta}$-prodine, (40) and (41) respectively, was prepared as outlined in Scheme 1.

The synthesis of this compound (63) involved the stepwise Michael condensation[115-117] of methylmethacrylate with methylamine, then the addition of the resulting secondary amino ester (64) to ethylacrylate, to yield the diester (65).

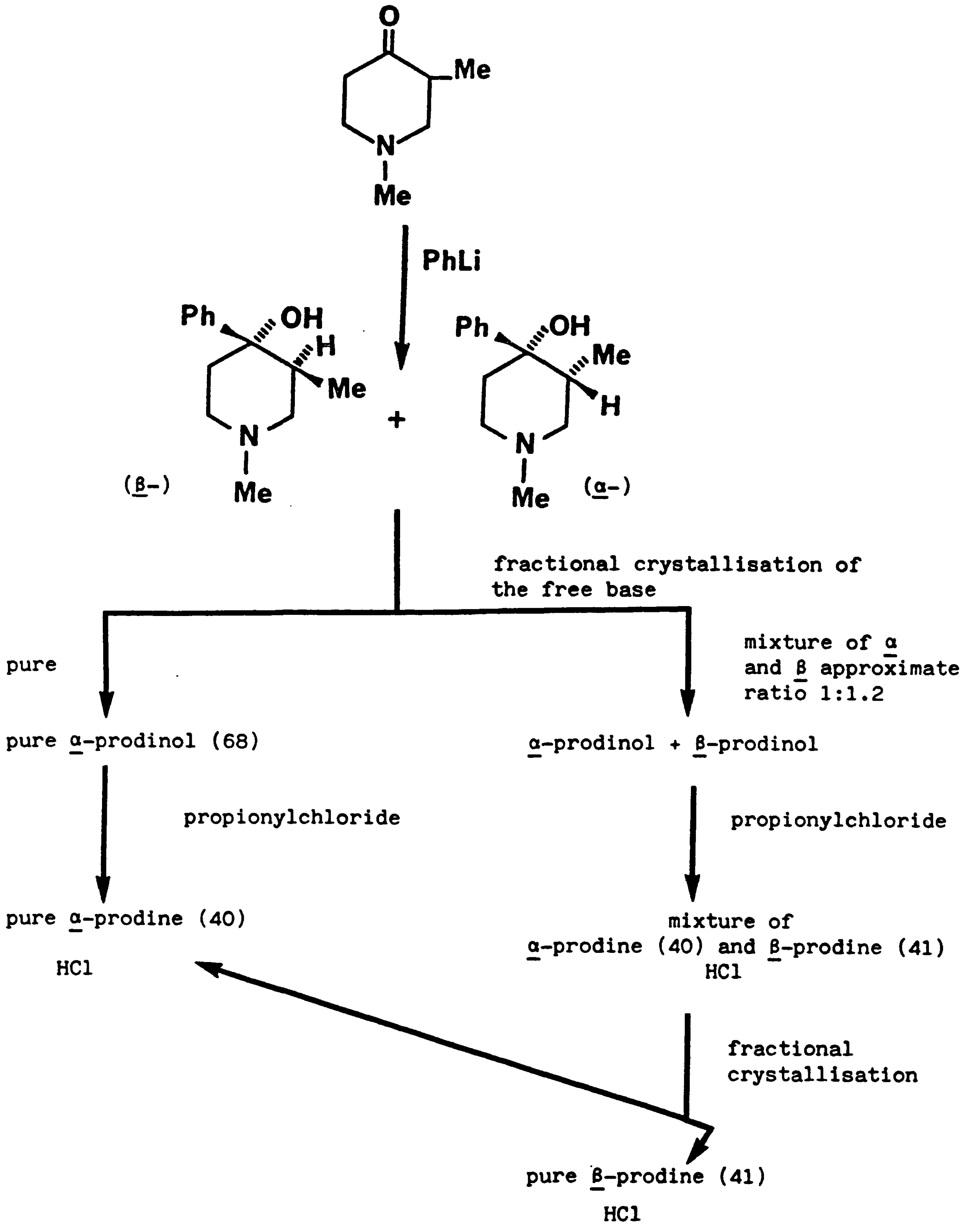
Dieckmann cyclization[118] of the diester using the shot-bird sodium method yielded compound (67). Hydrolysis followed by decarboxylation of (67) afforded the desired 1,3-dimethyl-4-piperidone.



Scheme 1

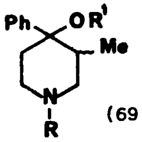
Reaction of phenyl lithium with the ketone (63), afforded a mixture of α-and β-prodinol in the approximate ratio 9:1 as judged by N- and C3-methyl ^1H NMR signals. Separation of the α-isomer was achieved by fractional crystallisation of the free base, while the β-isomer was separated as the hydrochloride salt of the corresponding propionate ester after most of the α-isomer had been collected (see Scheme 2).

Acylation of α-prodinol with propionyl chloride afforded (40) as the hydrochloride salt. The IR spectrum of this compound displayed a strong absorption at 1750 cm^{-1}, characteristic of ester carbonyl. Propionoxy carbonyl was also observed at 171.34 ppm in the ^{13}C NMR spectrum. Another important feature confirming esterification was the downfield chemical shift (approximately 9-10 ppm) of the C-4 quaternary carbon in the ^{13}C NMR spectrum, due to a stronger deshielding effect of OCO group over the OH group of the alcohol. [C-4 in alcohol (68) at 72.38 ppm; C-4 in ester (40) at 82.16 ppm].


O
Me
N
Me
PhLi
Ph
OH
H
Me
N
Me
(β-)
+
Ph
OH
Me
H
N
Me
(α-)
fractional crystallisation of the free base
pure
mixture of α and β approximate ratio 1:1.2
pure α-prodinol (68)
α-prodinol + β-prodinol
propionylchloride
propionylchloride
pure α-prodine (40) HCl
mixture of α-prodine (40) and β-prodine (41) HCl
fractional crystallisation
pure β-prodine (41) HCl

Scheme 2

Table 7. ^{13}C Chemical shifts of some α- and β- Diastereoisomeric Analogues of Piperidine^{A}



(69)

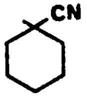
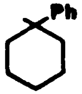
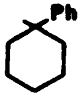
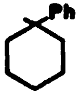
Compound	R	R^1	Isomer design.	C-2	C-3	C3-Me	C-4	C-5	C-6	4Ph-Cq	Cq-1^{C}	Cq-1'^{D}	Other carbons
				^{13}C Chemical shifts (ppm, TMS as internal standard)									
40	Me	COC_2H_5	$\underline{\alpha}$	58.26	41.91	11.69	82.16	31.77	50.38	141.02	-	-	$\underline{N}$-$\underline{C}H_3$; 45.15; $\underline{C}O$: 171.31; $\underline{C}H_2$: 27.68; $\underline{C}H_3$: 8.58; Ar-$\underline{C}$: 124.15-127.01
41	Me	COC_2H_5	$\underline{\beta}$	57.60	40.07	14.68	82.20	25.41	51.35	143.04	-	-	$\underline{N}$-$\underline{C}H_3$: 46.14; $\underline{C}O$: 172.10; $\underline{C}H_2$-ester 28.27; $\underline{C}H_3$: 8.85; Ar-$\underline{C}$: 124.57-127.88
69a, in DMSO-d_6	COC_2H_5	H	$\underline{\alpha}$	47.56 (43.75)^{B}	40.05	12.18 (12.03)	74.71	40.14 (39.41)	41.24 (37.44)	148.31	-	-	$\underline{C}O$: 174.58; $\underline{C}$H2: 25.73; $\underline{C}H_3$: 9.68 Ar-$\underline{C}$: 125.20-127.88
69b, in CD_3OD	COC_2H_5	H	$\underline{\beta}$	48.71 (44.86)	41.84 (42.04)	15.02 (14.95)	74.40	31.14 (32.1)	43.3 (39.27)	148.25	-	-	$\underline{C}O$: 175.60; $\underline{C}H_2$: 27.28 (27.60); $\underline{C}H_3$: 10.51 (10.35); Ar-$\underline{C}$: 126.91-129.44
69c	H	H	$\underline{\alpha}$	49.30	39.89	12.65	74.12	39.70	42.29	148.31	-	-	Ar-$\underline{C}$: 126.21-129.44
69d	H	H	$\underline{\beta}$	48.01	39.51	14.83	73.40	31.89	41.88	147.73	-	-	Ar-$\underline{C}$: 125.29-128.05
69e		H	$\underline{\alpha}$	49.65	39.54	12.36	73.33	40.59	42.59	146.74	-	60.01	$\underline{C}N$: 119.35, cyclohexyl-$\underline{C}$: C-2/6: 33.96; $\overline{C}$-3/5:22.24; C-4: 24.86; Ar-$\underline{C}$: 124.66-128.05
69f		H	$\underline{\beta}$	48.66	39.48	15.89	73.01	31.40	40.19	146.53	-	60.17	$\underline{C}N$: 119.61; cyclohexyl-$\underline{C}$: C-2/6: 33.86; C-3/5: 21.73; C-4:24.91; Ar-$\underline{C}$: 124.61-128.01

Table 7. Continued

				^{13}C Chemical shifts (ppm, TMS as internal standard)									
Compound	R	R^1	Isomer design.	C-2	C-3	C3-Me	C-4	C-5	C-6	4Ph-Cq	Cq-1^C	Cq-1'^{D}	Other carbons
69g		H	*α*	48.52	40.22	12.45	74.09	40.25	41.58	147.20	139.91	60.04	Cyclohexyl-C: C-2/6: 33.64; C-3/5: 22.64; C-4: 24.56; Ar-C: 124.73-128.04
69h		H	*β*	47.71	40.91	16.38	73.88	33.44	41.45	147.26	141.45	60.65	Cyclohexyl-C: C-2/6: 33.60; C-3/5: 22.28; C-4: 26.8; Ar-C: 124.88-127.96
69j		$-COCH_3$	*α*	48.36	42.61	12.81	84.00	33.51	40.81	142.00	138.1	61.21	CO: 169.10; CH_3: 21.58; Cyclohexyl-C: C-2/6: 33.32; C-3/5: 22.48; C-4: 26.31; Ar-C: 124.80-127.87

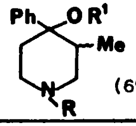
A. Spectra recorded as base in $CDCl_3$, unless otherwise stated.

B. Data in parentheses refer to distinct spectra resonances noted from the other form.

C. The quaternary carbon of the phenyl group attached to cyclohexane.

D. The quaternary carbon of cyclohexane.

Table 8. ^{1}H NMR (δ scale) Characteristics of Some α- and β- Diastereoisomeric Analogues of Piperidine^{A}



(69)

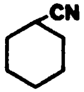
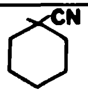
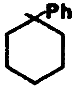
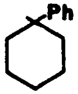
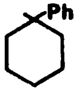
Compound	R	R^1	Isomeric designation	C2-H		C6-H		C5-H		C3-H	C3-Me	Other protons
				ax	eq	ax	eq	ax	eq			
40	Me	COC_2H_5	$\underline{\alpha}$	2.52dd	2.58brt	2.01brt	2.88brd	1.74brt	2.22d	1.78m	0.54d	Ar-$\underline{H}$: 7.01-7.34m; $\underline{N}$-C$\underline{H}_3$: 2.13s CH_3 (Ester): 1.04t; OC$\underline{H}_2$: 2.28q
41	Me	COC_2H_5	$\underline{\beta}$	2.78m	2.52brd	2.57dt	2.88brd	2.13dt	2.32m	2.15brq	0.73d	Ar-$\underline{H}$: 7.19-7.30m; $\underline{N}$-C$\underline{H}_3$: 2.26s C$\underline{H}_3$ (ester): 1.08t; OC$\underline{H}_2$: 2.30q
69a, in DMSO-d_6	COC_2H_5	H	$\underline{\alpha}$	2.62brt (3.11brt)	3.75brd (4.38brd)	2.91dt (3.41dt)	3.61dd (4.28dd)	1.62m	1.97m	1.84m	0.52t	Ar-$\underline{H}$: 7.15-7.50m; OC$\underline{H}_2$: 2.35 dq; C$\underline{H}_3$ (amide): 1.20t
69b, in CD_3OD	COC_2H_5	H	$\underline{\beta}$	3.11dt (3.52dd)^{G}	3.84dd (3.29dd)	3.35brd (3.64brd)	3.94m (4.56)	1.72brt	F	2.02m	0.59dd	Ar-$\underline{H}$: 7.22-7.47;)C$\underline{H}_2$: F C$\underline{H}_3$ (amide): 1.14dt
69c	H	H	$\underline{\alpha}$	2.90m	3.05m	2.52m	3.10brd	1.68dt	2.75m	1.95m	0.60d	Ar-$\underline{H}$: 7.21-7.47m; $\underline{N}$-$\underline{H}$: 2.3^{B}
69d	H	H	$\underline{\beta}$	3.33dd	3.0m	2.54brt	2.85brd	1.53dt	2.31m	2.22m	0.64d	Ar-$\underline{H}$: 7.21-7.43m; $\underline{N}$-$\underline{H}$: 2.32^{C}
69e		H	$\underline{\alpha}$	2.62m	2.85brd	2.38t	3.15brd	1.38m	1.84^{B}	1.84^{B}	0.65d	Ar-$\underline{H}$: 7.23-7.48m; cycl. $\underline{H}^{E}$: 1.74^{D}

Table 8 (continued)

Compound	R	R^1	Isomeric designation	C2-H ax	C2-H eq	C6-H ax	C6-H eq	C5-H ax	C5-H eq	C3-H	C3-Me	Other protons
69f		H	β	3.12m	2.94dd	2.62^{B}	2.64^{B}	1.35m	2.10^{B}	2.15m	0.73d	Ar-H: 7.25-7.45; cycl. H: 1.65
69g		H	α	2.18m	2.88^{D}	2.08m	2.88^{D}	1.60m	1.32m	1.76^{D}	0.52d	Ar-H: 7.11-7.31m; cycl. H: 1.76
69h		H	β	2.89m	2.58brd	2.37^{D}	2.76m	1.42m	2.12^{D}	2.08^{D}	0.68d	Ar-H: 7.13-7.43m; cycl. H: 1.77
69j		$COCH_3$	α	2.27^{D}	2.88^{D}	2.27^{D}	2.88^{D}	1.36	2.10^{D}	1.78m	0.58d	Ar-H: 7.10-7.37m; cycl. H: 1.64 CH_3(ester): 1.81s

A. Spectra recorded as base in CDCl3 with TMS as internal standard. Values refer to centres of resonance signal and hence represent only approximate chemical shift in most cases.

B. Overlapping multiplet (4H)

C. Overlapping multiplet (8H)

D. Overlapping multiplet (10H)

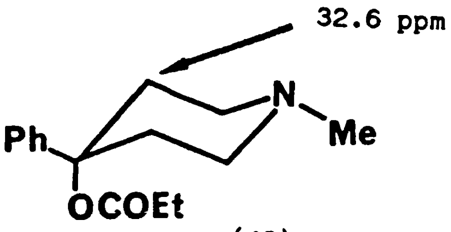
E. Cyclohexane ring protons

F. Overlapping multiplet 2.28-2.61 (3H)

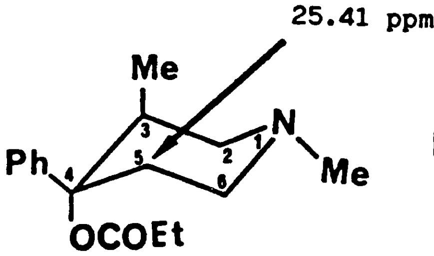
G. Data in parenthesis refer to distinct spectra resonances noted from the other form.

Spectral data obtained for *β*-prodine were consistent with the assigned structure (41). The stereochemistry of *α*- and *β*-prodine has been the subject of previous investigation and is well established.[59,60,61,78] Present assignments of the isomeric esters correlated well with the stereochemical assignments made.

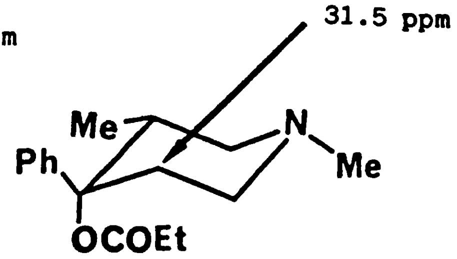
Analysis of ^{13}C NMR spectra provides two characteristic features that can be used to distinguish the two isomers. Firstly, the C3-methyl chemical shift (at 11.69 and 14.68 ppm) is assigned respectively as equatorial C3-methyl for the *α*-isomer and axial C3-methyl for the *β*-isomer. Secondly, the high field chemical shift of the C-5 (25.41 ppm) of the *β*-isomer, compared with C-5 of the *α*-isomer (31.77 ppm), is due to the *γ*-gauche effect of the axial C3-methyl causing steric compression on C-5. This *γ*-effect is of particular stereochemical significance in conformational studies of 6-membered alicyclic compounds. It is based on the fact that insertion of an equatorial substituent such as methyl in position 3 of compound (42), for example, causes very little change about (0.5 ppm) in the chemical shift of C-5, while insertion of an axial C3-methyl in the same compound resulted in large upfield shift (approximately 7 ppm, see 42, 41 and 40).



(42)



(41)

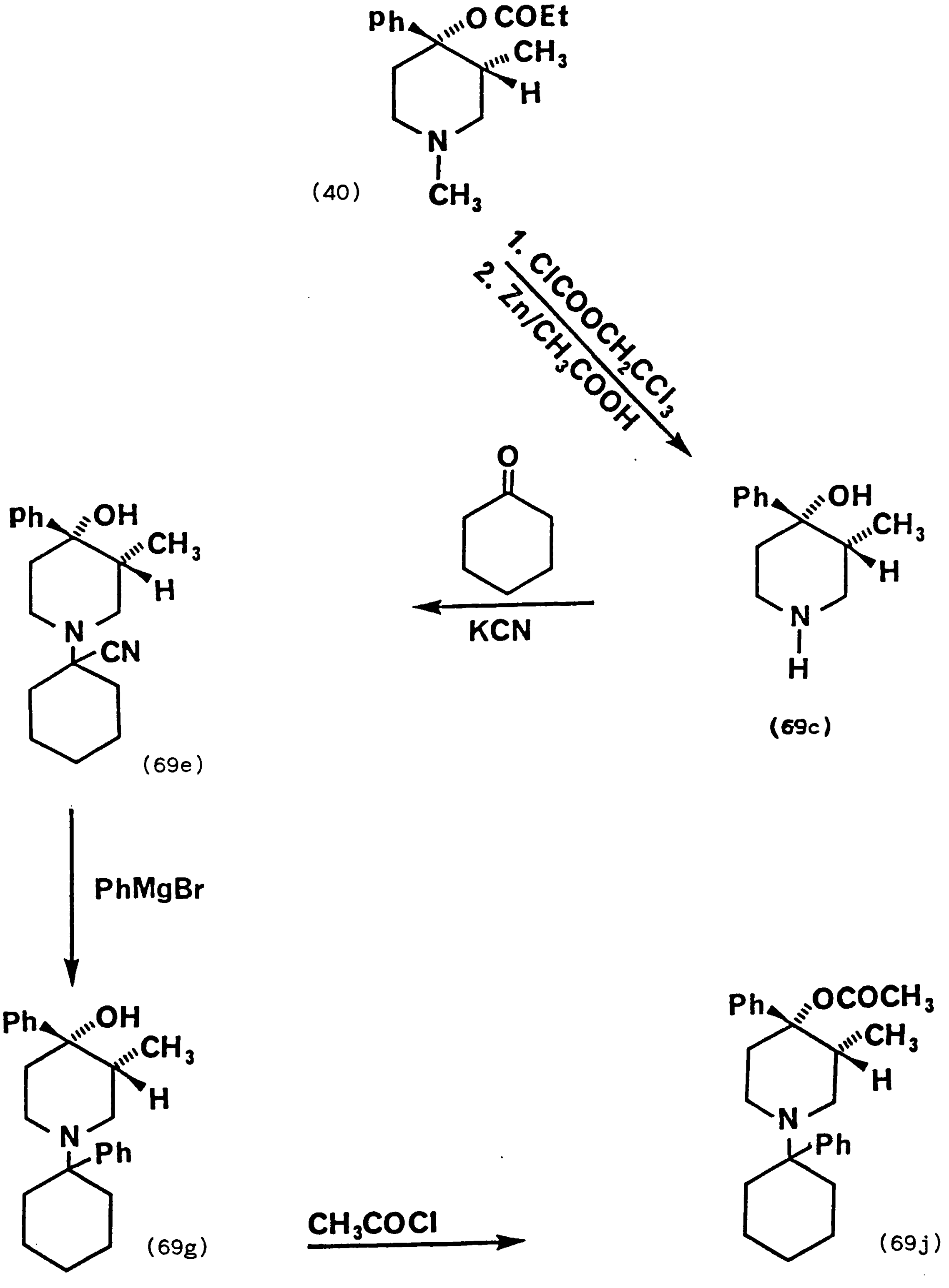


(40)

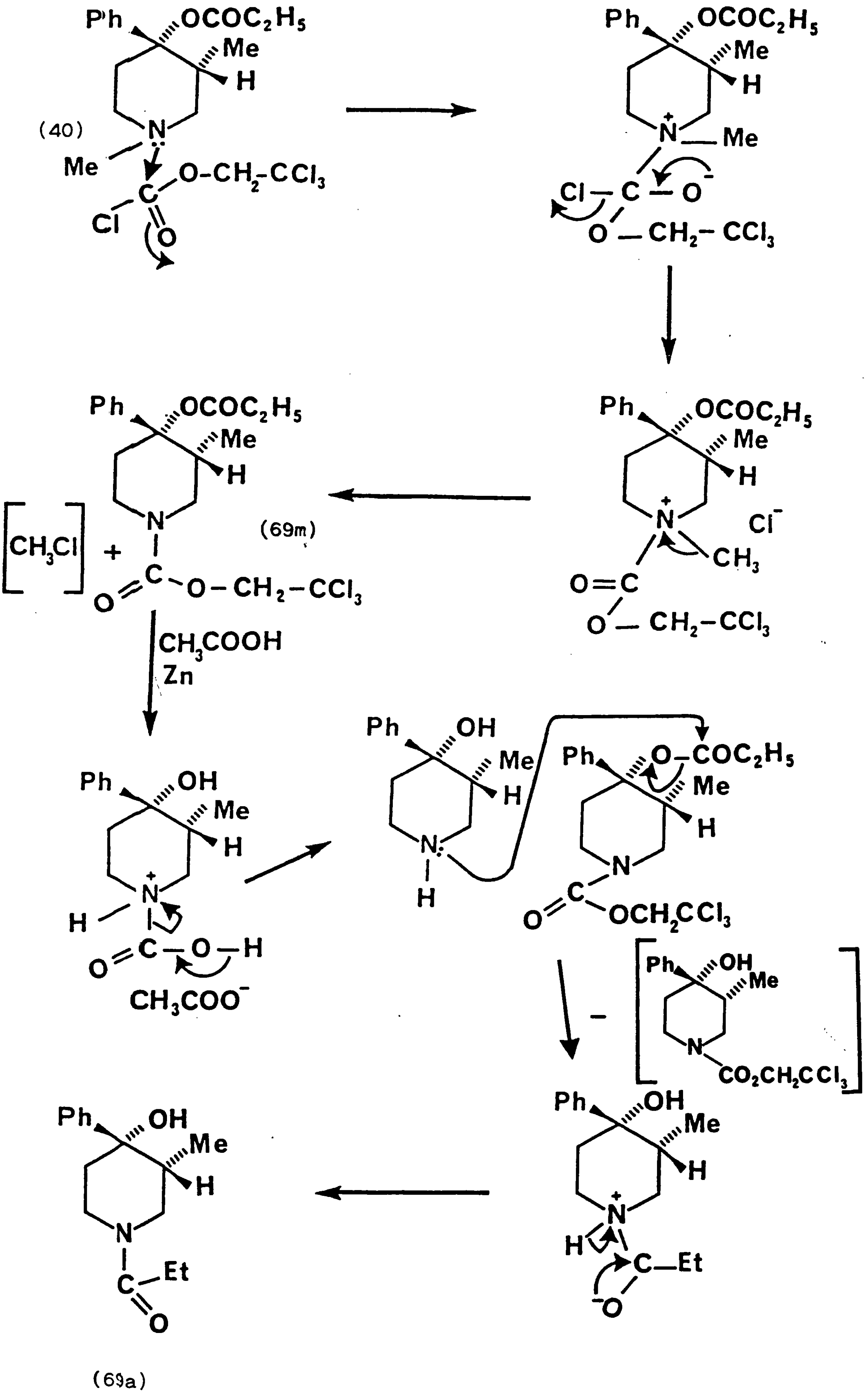
2.2.2 The Synthesis of α-4-hydroxy-3-methyl-4-phenylpiperidine (69c; Scheme 3) by N-demethylation of α-prodine

The synthesis of this compound was effected by N-demethylation of α-prodine (40) with 2,2,2-trichloroethylchloroformate[121] via the intermediate carbamate (69m; Scheme 4). Ordinarily such carbamates are hydrolysed to secondary amines using Zn and acetic acid. However, hydrolysis of the carbamate (69m) with zinc and glacial acetic acid in an effort to secure the secondary amine (69c) afforded the amide (69a) instead. Formation of this compound is believed to proceed as outlined in Scheme 4.

Characterisation of this amide was based on the spectral data obtained. The IR spectrum displayed a strong carbonyl absorption at 1640 cm^{-1}, characteristic of amide carbonyl functionality. The ^{13}C NMR spectrum was consistent with the assigned structure (69a), with characteristic amide carbonyl carbon resonance (at 174.88 ppm). Additonally, ^{1}H NMR signals for C-2; C3-$C\underline{H}_3$; C-5 and C-6 of the piperidine ring were duplicated, in accord with the amide resonance expressed in Scheme 5 (see Fig. 2; p. 70).

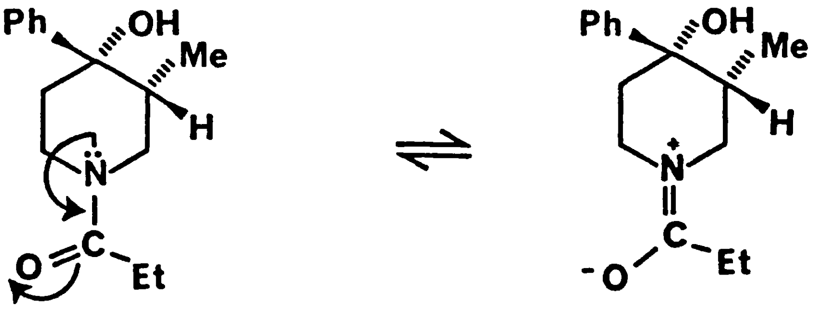

Ph
O COEt
CH$_3$
H
N
CH$_3$
(40)
1. ClCOOCH$_2$CCl$_3$
2. Zn/CH$_3$COOH
Ph
OH
CH$_3$
H
N
H
(69c)
O
KCN
Ph
OH
CH$_3$
H
N
CN
(69e)
PhMgBr
Ph
OH
CH$_3$
H
N
Ph
(69g)
CH$_3$COCl
Ph
OCOCH$_3$
CH$_3$
H
N
Ph
(69j)

Scheme 3



Scheme 4

Duplication of signals observed in the ^{13}C and ^{1}H NMR spectra is thought to be the result of a cis/trans relation between the piperidine ring and the N-substituent.

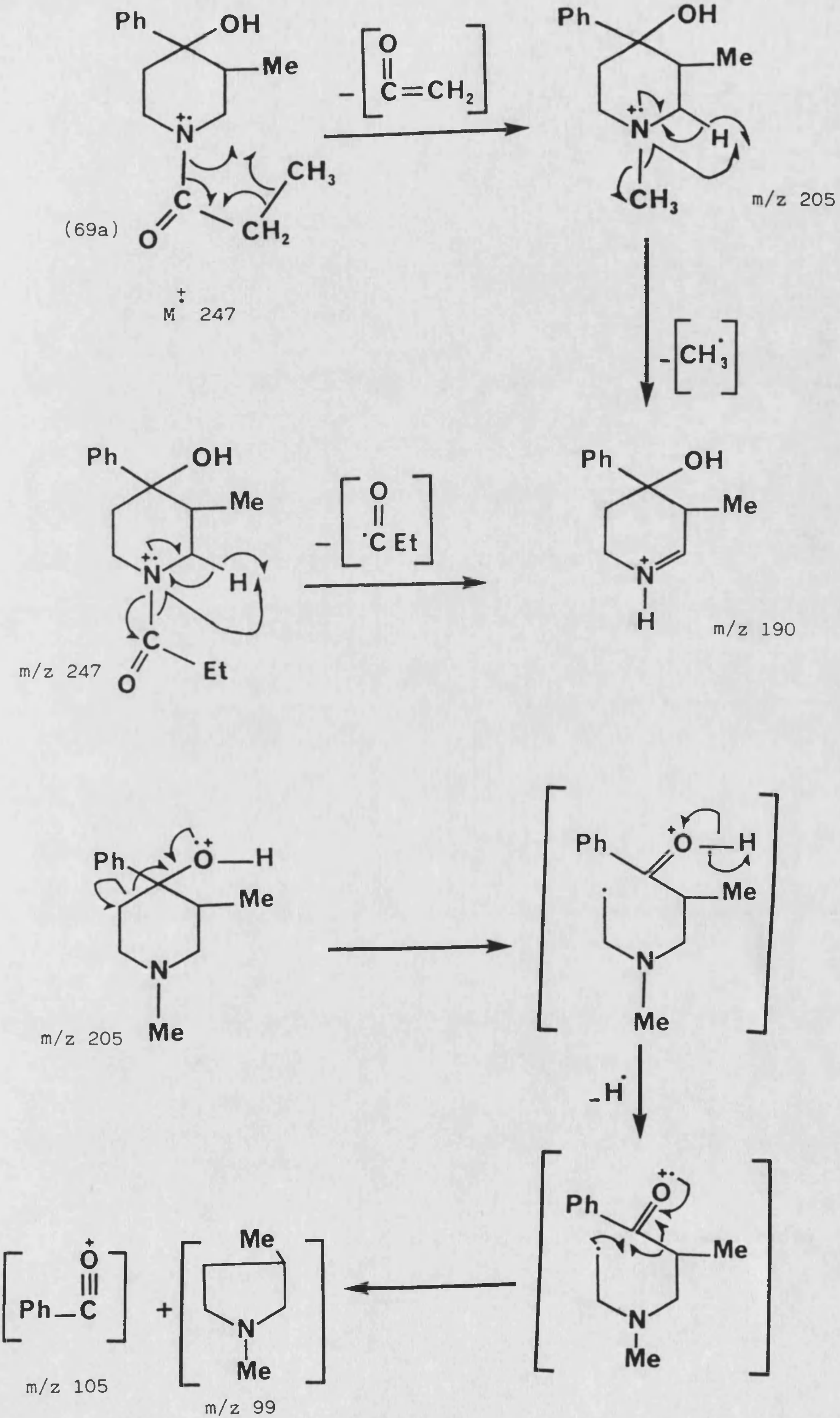


(69a)

Scheme 5

^{1}H and ^{13}C NMR analysis of the β-amide (69b) also indicated duplication of resonances, and it was noticeably more pronounced for the C3-CH_3(dd) and OCH_2CH_3 (dt), presumably due to a 1,3-interaction involving axially placed methyl (see Fig. 3; p.71). Duplicated signal chemical shift differences for the piperidine ring protons, particularly C2-H and C6-H, were narrower compared with those in the α-isomer (69a).

This compound (69a) was analysed by mass spectroscopy, and the possible routes of fragmentations are shown in Scheme 6.


(69a)
M⁺· 247
$-[O=C=CH_2]$
m/z 205
$-[CH_3^{\cdot}]$
m/z 247
$-[\cdot C(=O)Et]$
m/z 190
m/z 205
$-H^{\cdot}$
m/z 105
m/z 99

Scheme 6

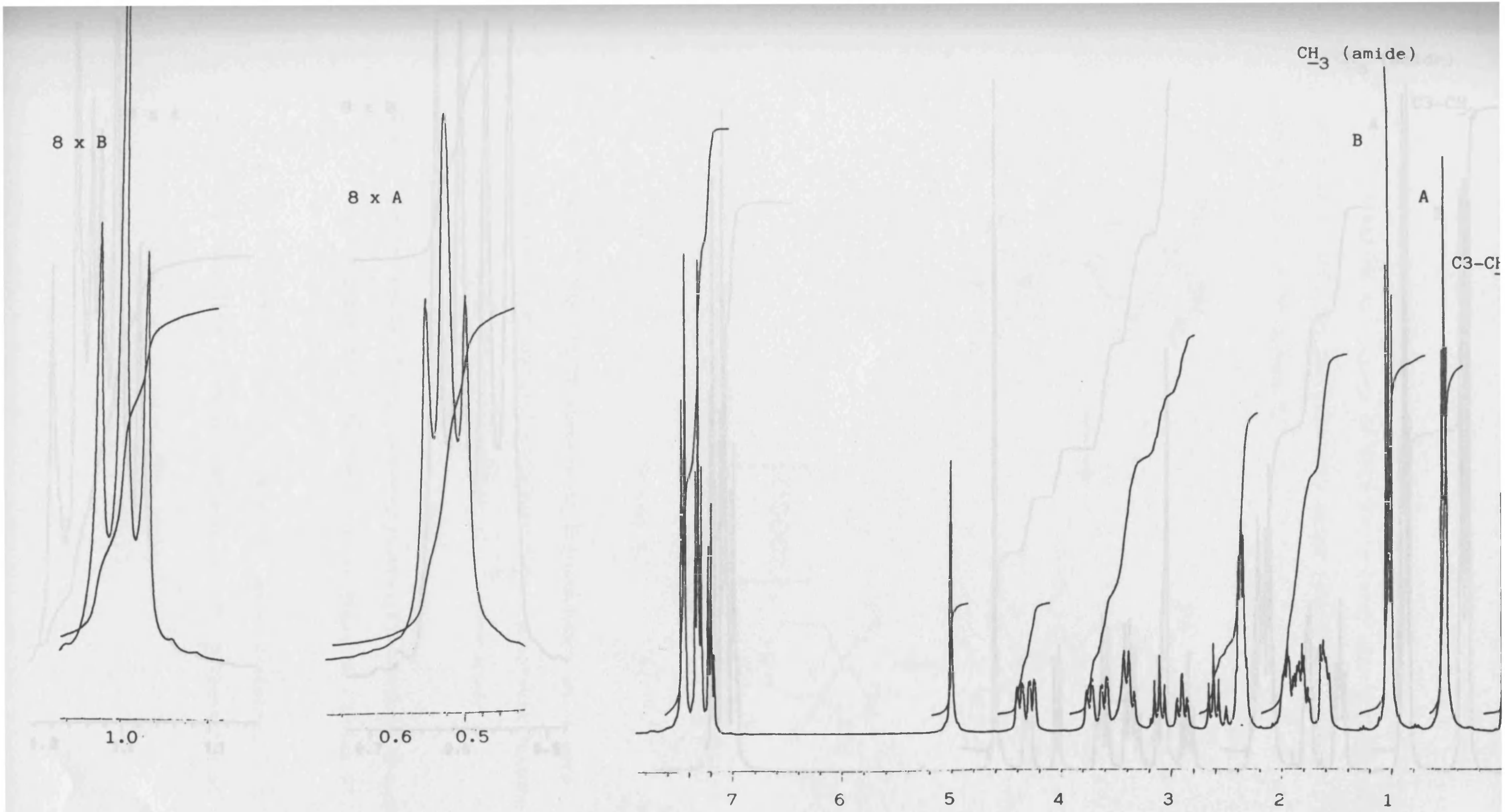


Fig. 2. ^{1}H NMR spectrum of $\underline{\alpha}$-4-hydroxy-3-methyl-4-phenyl-1-propanoylpiperidine, recorded at 270 MHz in DMSO-d$_6$ to illustrate duplication of signals.

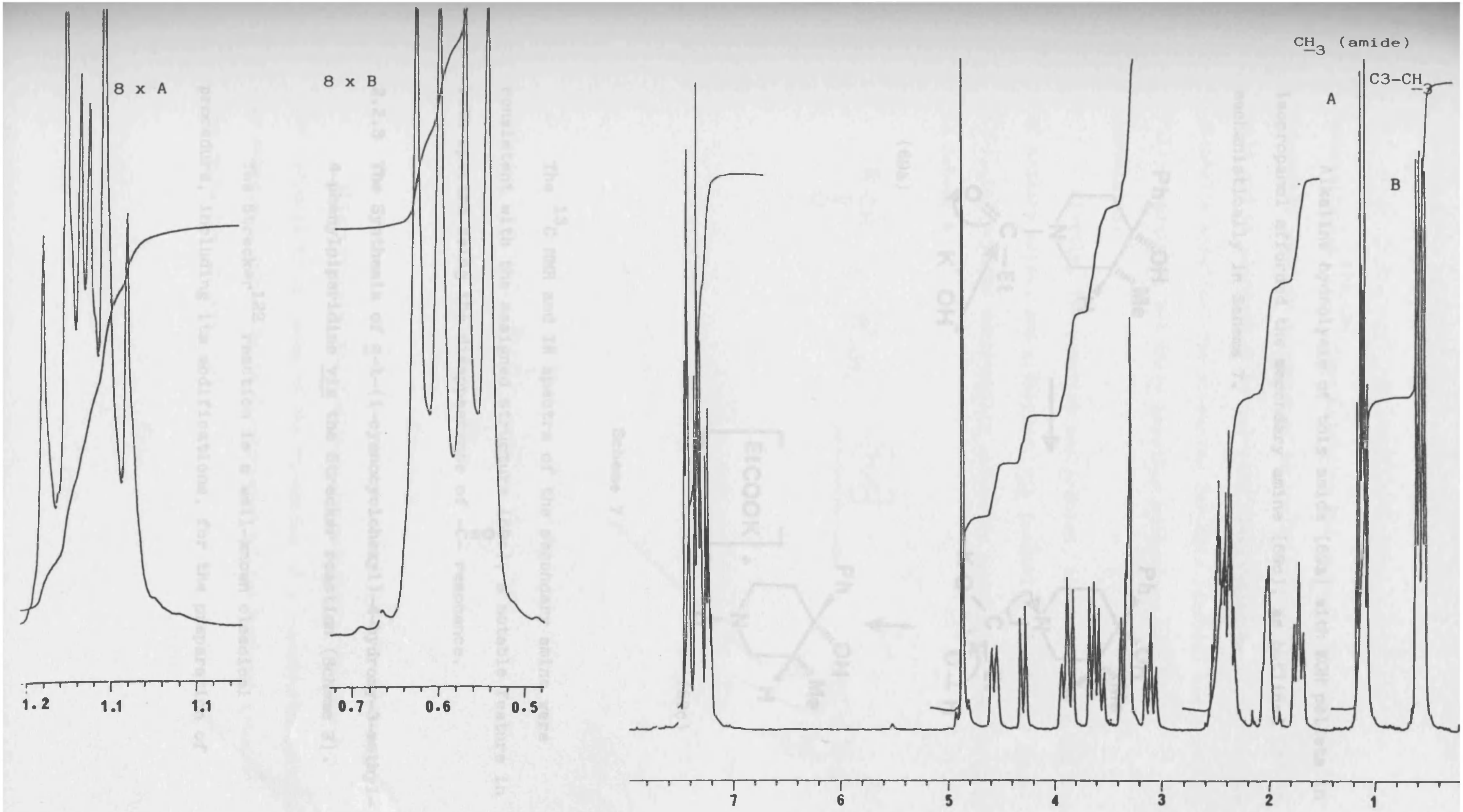
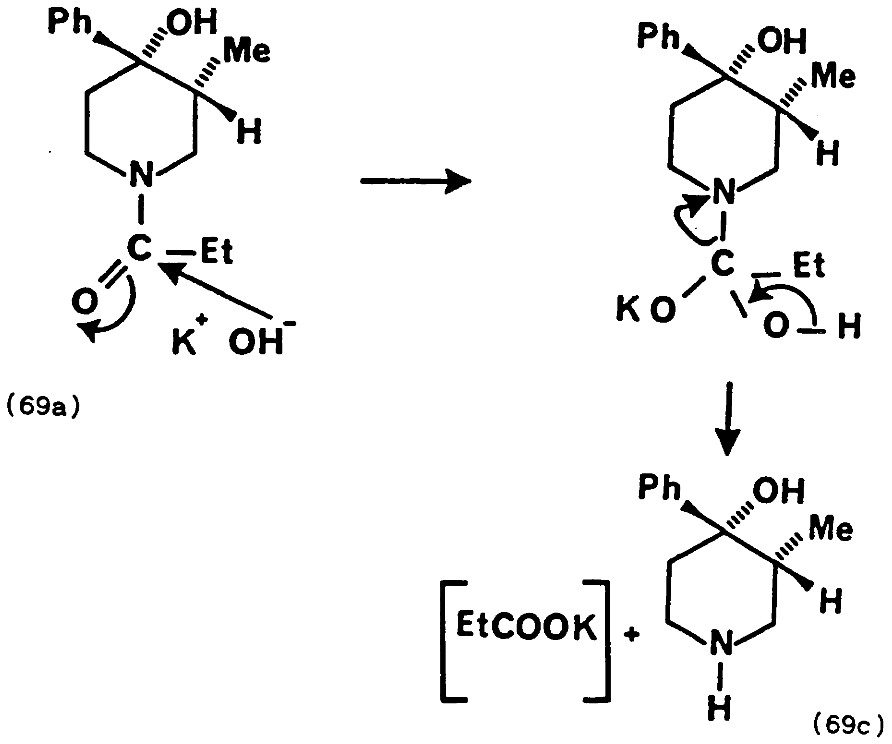


Fig. 3. ^{1}H NMR spectrum of $\underline{\beta}$-4-hydroxy-3-methyl-4-phenyl-1-propanoylpiperidine, recorded at 270 MHz in CD_3OD to illustrate duplication of signals.

Alkaline hydrolysis of this amide (69a) with KOH pellets in isopropanol afforded the secondary amine (69c), as outlined mechanistically in Scheme 7.



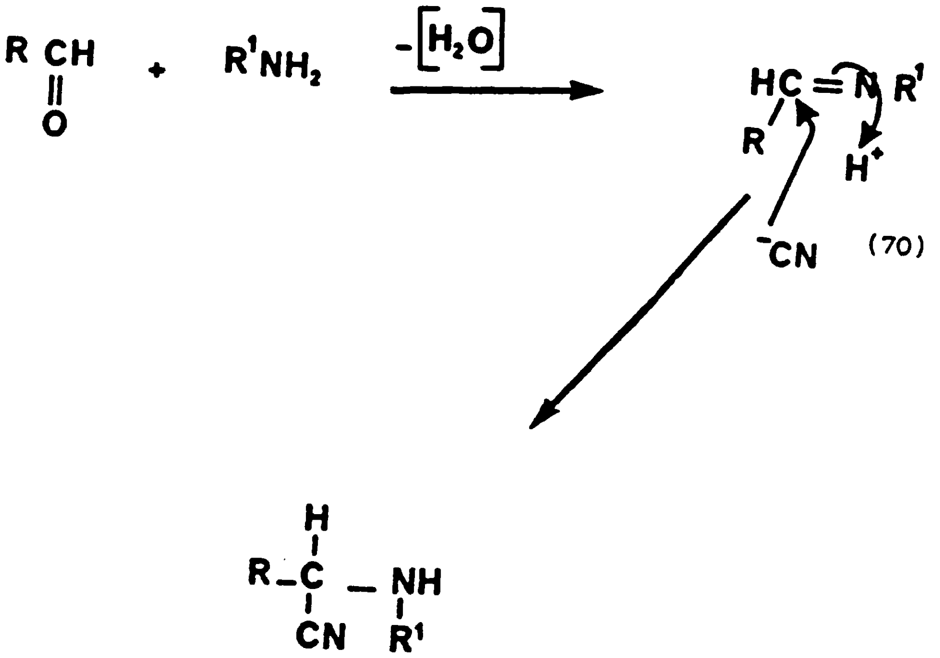
Scheme 7

The ^{13}C NMR and IR spectra of the secondary amine were consistent with the assigned structure (69c), a notable feature in both spectra being the disappearance of -$\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}$- resonance.

2.2.3 The Synthesis of α-1-(1-cyanocyclohexyl)-4-hydroxy-3-methyl-4-phenylpiperidine *via* the Strecker reaction (Scheme 3).

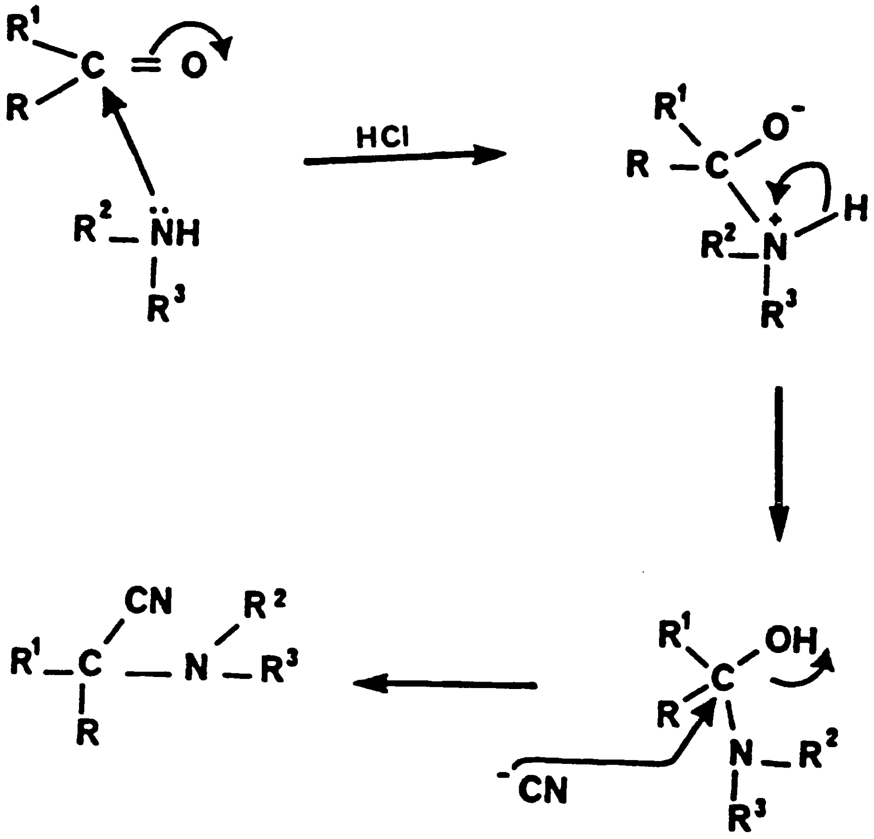
The Strecker[122] reaction is a well-known classical procedure, including its modifications, for the preparation of aminonitriles[123,124] from aldehydes and ketones. In general, the procedure involves reaction of equimolar proportions of an amine salt and an aldehyde or ketone with alkali cyanide in aqueous or alcoholic solution. The mechanism for this reaction has not been fully explained, but three possible mechanisms have been postulated.

Firstly, the reaction may proceed, particularly in the case of primary amines and aldehydes, via formation of a Schiff base (70), followed by nucleophilic attack by cyanide ion, as outlined in Scheme 8.



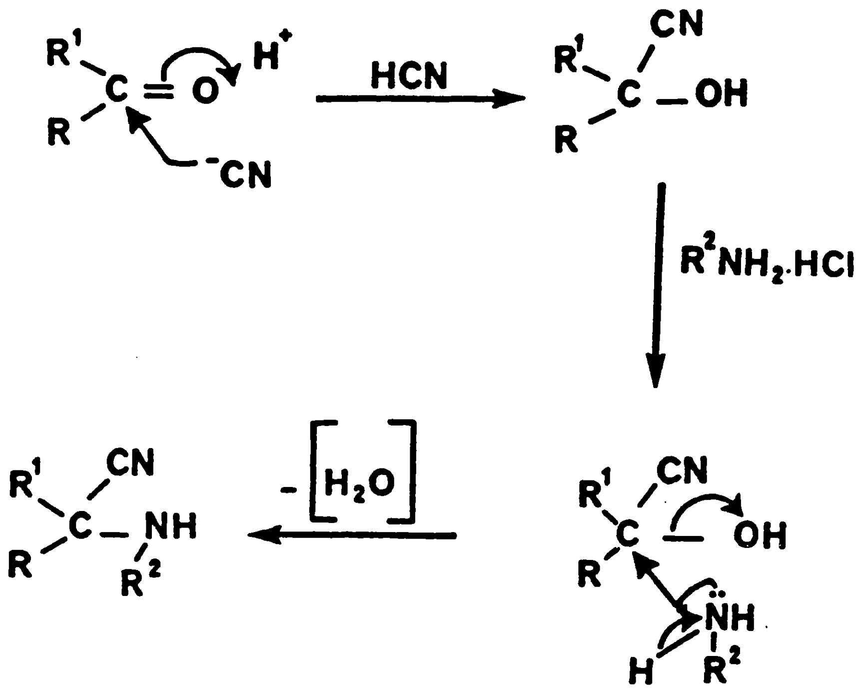
Scheme 8

Alternatively, the nucleophilic addition of cyanide ion to the carbonyl group leads to the formation of a cyanohydrin followed by subsequent nucleophilic displacement of the hydroxyl group by the amine (see Scheme 10).



Scheme 9

Another possibility is the formation of an amino alcohol intermediate, which could undergo nucleophilic attack by cyanide ion, as shown in Scheme 9 .

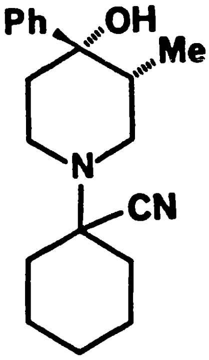


Scheme 10

However, it is possible that formation of amino nitriles may well be due to a combination of all three mechanisms.

This general synthetic reaction was successfully employed in the present work for the synthesis of (69e), using the secondary amine (69c) as the hydrochloride salt, cyclohexanone and potassium cyanide in aqueous solution, as shown in Scheme 3.

The ^{13}C NMR spectrum of this compound was consistent with the assigned structure (69e), with characteristic $\underline{C}{\equiv}N$ resonance (at 119.35 ppm). Also, the spectrum displayed six $-CH_2$ lines in addition to two quaternary carbons in the aliphatic region, compared with only three $-CH_2$ lines and one quaternary carbon in the starting material, due to C-1 (quaternary); C-3/5; C-2/6 and C4 $-\underline{C}H_2$ carbons of the N-cyclohexyl ring.



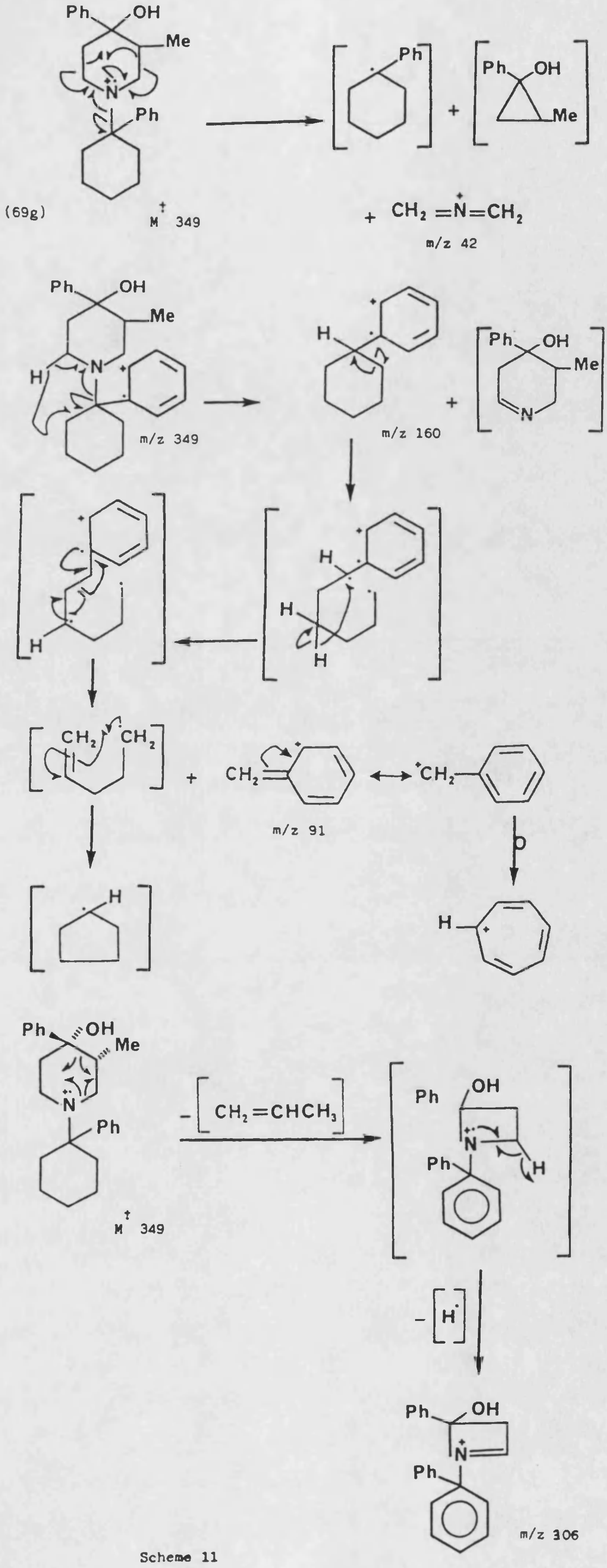
(69e)

2.2.4 The Synthesis of α-4-hydroxy-3-methyl-4-phenyl-1-(1-phenylcyclohexyl)piperidine and the corresponding acetoxy ester.

The synthesis of (69g; Scheme 3), one of the main aims of the present work, was achieved by reaction of (69e) with phenyl magnesium bromide.

The spectral data obtained for this compound were consistent with its assigned structure. Thus, the ^{13}C NMR spectrum showed absence of $\underline{C}\equiv N$ resonance (characteristic of starting material). The spectrum also displayed the appropriate aromatic signals in accord with the assigned structure.

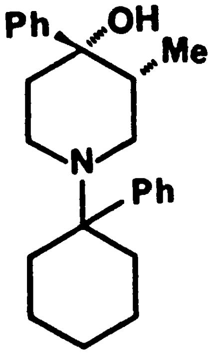
This compound was analysed by mass spectroscopy, and the possible routes of fragmentation are shown in Scheme 11.


(69g)
M⁺ 349
CH₂ =N̈=CH₂
m/z 42
m/z 349
m/z 160
m/z 91
CH₂=CHCH₃
M⁺ 349
H·
m/z 306

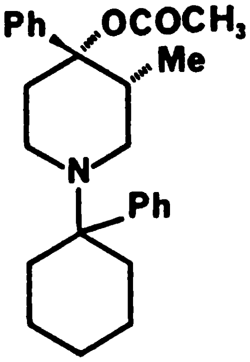
Scheme 11

Esterification of (69g) with acetyl chloride afforded 69j; see Scheme 3) as the hydrochloride salt.

The IR spectrum of this compound displayed a strong absorption at 1760 cm^{-1}, characteristic of an ester carbonyl group. The characteristic feature of the ^{1}H NMR spectrum was the methyl ester protons, which appeared as a singlet at 1.81 ppm. Acetoxy carbonyl carbon chemical shift (at 169.10 ppm) was observed in the ^{13}C NMR spectrum. Another important feature confirming esterification was the down field chemical shift of the C4-quaternary (at 84.00 ppm).



(69g)

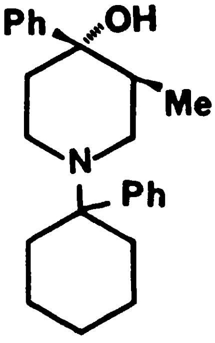


(69j)

2.2.5 The Synthesis of β-4-hydroxy-3-methyl-4-phenyl-1-(1-phenylcyclohexyl)piperidine

β-Prodine was subjected to the same synthetic procedures previously described in Schemes 3, 4 and 7 for the synthesis of the α-isomeric analogue (69g), in order to secure the β-isomeric analogue (69h).

There were no distinctive differences in the experimental results obtained for the α- and β-isomers. However, for full details of the experimental results see Table 25, p. 216. For ^{1}H NMR results, see Table 8, p. 61 and for ^{13}C NMR results, see Table 7, p. 59 .



(69h)

2.2.6 Resolution Studies

2.2.6.1 α-Prodinol

Pharmacological evaluation of compound (69g) showed that it had about 3 times the activity of morphine (see p. 199 for pharmacological results). Thus, resolution of α-prodinol was undertaken to establish the analgesic activity of the two optical forms of compound (69g).

The term resolution is generally defined as a procedure through which both optical isomers (enantiomers) are separated in the purified state from a racemic mixture.

Resolution of α-prodine was achieved by diastereoisomeric salt formation.[125] This general procedure involves the interaction of racemic bases (B) with optically active acids (A) or racemic acids with optically active bases. Thus, enantiomers are transformed to diastereoisomeric salts which may then be separated by differential solubility (Scheme 12)

(+) A + (±) B	**(+) A (+) B + (+) A (−) B**
(+) B + (±) A	**(+) B (+) A + (+) B (−) A**

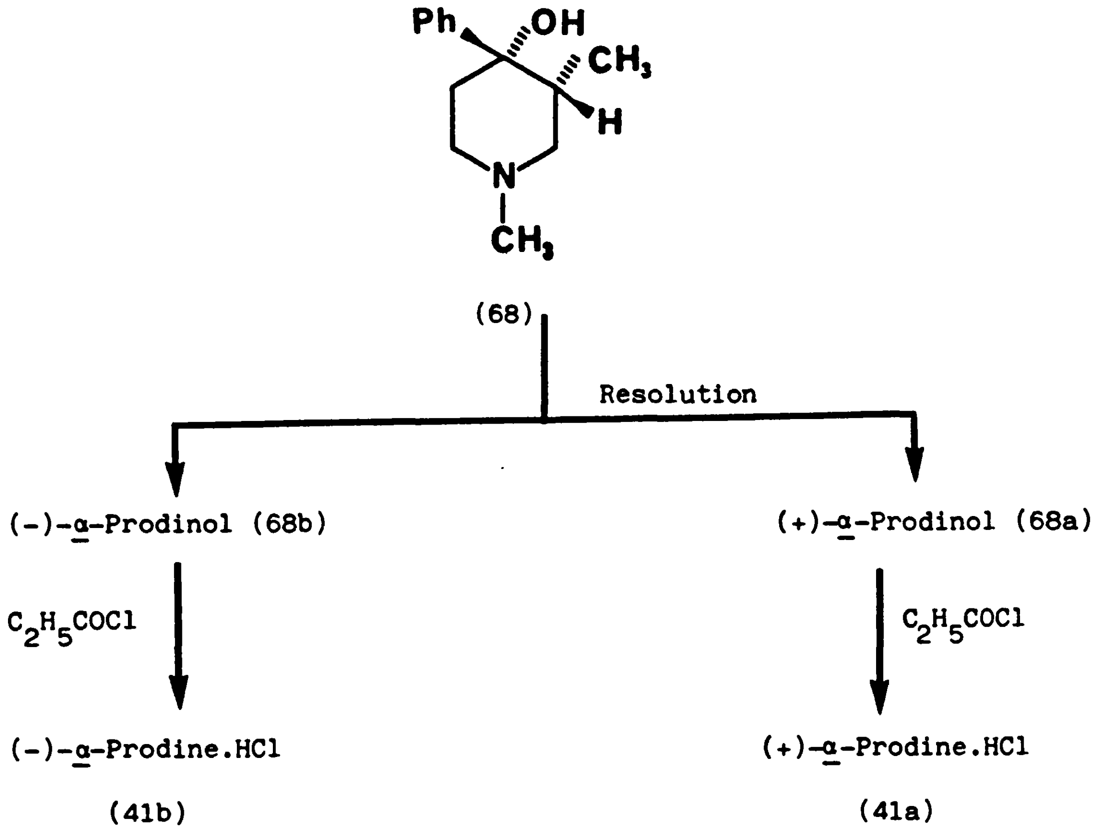
Scheme 12

The diastereoisomeric salts cropped after fractional crystallisation can then be hydrolysed with inorganic alkalis or acids to give the enantiomers. This procedure usually involves many recrystallisations, monitored by polarimetry.

Common optically active acids used for the resolution of racemic bases include tartaric acid, mandelic acid, camphoric acid and camphor-10-sulphonic acid. Optically active bases such as morphine, ephedrine and menthylamine are used for resolving racemic acids. The conditions necessary to effect resolution cannot be generalised, although the choice of optically active resolving agent and the solvent are important considerations.

Optical resolution of (±)-α-prodinol was achieved by utilizing the same procedure described by Portoghese *et al.*[69] which employed fractional crystallisation of the tartarate salts. Basification of the two salts generated (+)-α- and (-)-α-4-hydroxy-1,3-dimethyl-4-phenylpiperidine (see Table 26, p.217 for specific optical rotation results).

Esterification of (+)- and (-)-α-4-hydroxy-1,3-dimethyl-4-phenylpiperidine with propionyl chloride afforded the corresponding (+)- and (-)-α-1,3-dimethyl-4-phenyl-4-propionoxypiperidine respectively, as the hydrochloride salts (see Scheme 13).



Scheme 13

2.2.6.2 Qualitative determination of enantiomeric purity of resolved α-prodinol by ^{1}H NMR using β-cyclodextrin

Optical purity of (+)-α -prodine was judged by the application of the ^{1}H NMR spectroscopic technique described by Casy and Mercer.[126] This procedure involves the use of β-cyclodextrin which has been reported to form inclusion complexes with chiral medicinal agents (chiefly antihistamines and central analgesics to date).

The ^{1}H NMR spectrum of a 1:1 mixture of(±)α-prodine and β-cyclodextrin has indicated the formation of an inclusion complex between the two compounds. Thus, analysis of this spectrum indicated duplication of ligand resonances, which was clear for the 3-methyl (doublet becomes a triplet) and ester (methyl triplet becomes a double triplet) signals (see Fig. 4). On the other hand, the symmetrical appearance of the 3-methyl doublet signal of (+)-α-prodine (see Fig. 4.) in the presence of β-cyclodextrin is clear evidence of its high degree of optical purity.

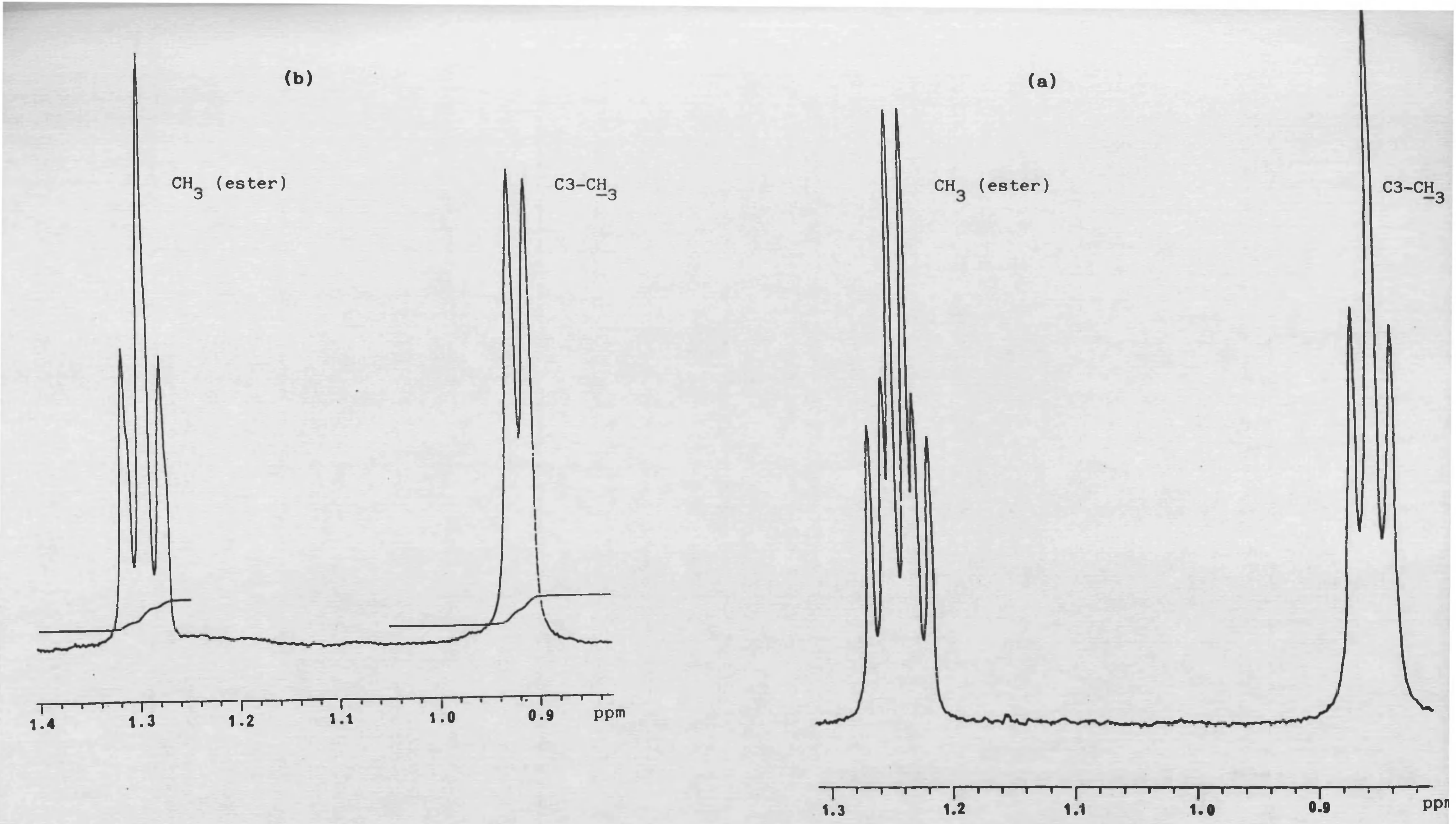


Fig. 4. Partial ^{1}H NMR spectra (at 400 MHz, in D_2O) of: **a)** A 1:1 mixture of (±)-α-prodine hydrochloride and β-cyclodextrin, which clearly illustrates duplication of C3-CH_3 and CH_3 (ester) signals; **b)** A 1:1 mixture of (+)-α-prodine hydrochloride and β-cyclodextrin, which shows the symmetrical appearance of both signals.

2.2.6.3 Synthesis of (-)- and (+)-$\underline{\alpha}$-4-hydroxy-3-methyl-4-phenyl-1-(1-phenylcyclohexyl)piperidine

The synthesis of the two optical forms of (69g) was carried out by the same synthetic procedures previously described for the synthesis of the racemate (69g; Schemes 3, 4 and 7), by using the appropriate resolved $\underline{\alpha}$-prodinol. For experimental results see Tables 27, 28, p. 218-219.

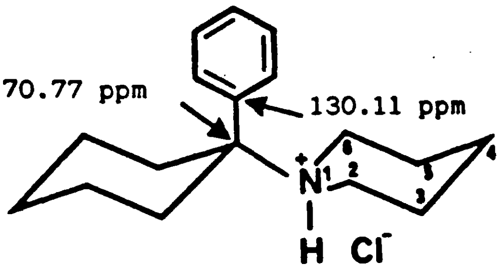
Attention will now be given to the stereochemical features associated with (69g) and (69h).

Stereochemical assignments of both isomers were based on ^{13}C NMR chemical shift parameters following similar assignments of α- and β- prodinol and phencyclidine, compounds of established stereochemistry, and evidence supporting the relative configuration trans 3-Me/4-Ph for (69g) and cis 3-Me/4-Ph for (69h) with an axially oriented phenyl chain [of 1-(1-phenylcyclohexyl] in both isomers was obtained. Thus, the two isomers have retained the original stereochemistry of α- and β-prodinol, and phencyclidine.

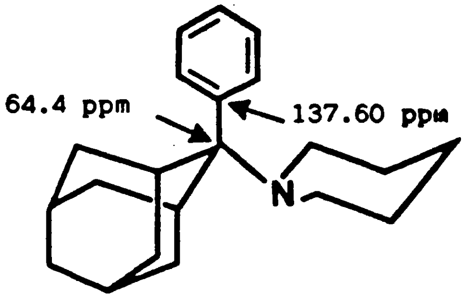
^{13}C NMR data of the α-isomer (69g) indicated that both C3-Me (12.45 ppm) and C4-Ph (Cq at 147.20 ppm) have an equatorial orientation. The C-5 chemical shift at 40.25 ppm (similar to that of the des 3-Me analogue) is further evidence that the C3-Me has an equatorial orientation.[119,120] The upfield chemical shift of Ar-Cq (of the phenyl attached to cyclohexyl) relative to Ar-Cq of the piperidine moiety suggests the preferred axial phenyl-chair conformation of the cyclohexyl moiety.

On the other hand, the downfield chemical shift of C3-CH_3 of (69h, at 16.38 ppm), characteristic of axial C3-Me, with a corresponding upfield chemical shift of the C-5 by about 7 ppm, due to the steric compression produced by the axial C3-Me,is evidence that the compound retains the stereochemistry of β-prodinol. C4-Ar-Cq and Ar-Cq (of the phenyl attached to cyclohexyl) chemical shifts at 147.26 ppm and 141.45 ppm (at higher field because it subjects to greater steric polarization at Cq),[119,120] respectively, suggested that the C4-Ar has an equatorial orientation, while the second phenyl is axially orientated.

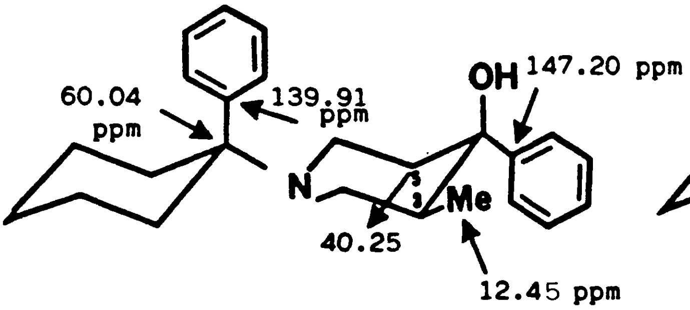
In the case of phencyclidine, the adamantyl analogue (PAP) provides a good model for the Cq-1' ^{13}C chemical shift of an axially placed phenyl substituent.[108] The conformation of the PAP of the rigid adamantyl derivative has been established unequivocally by X-ray analysis.[108]



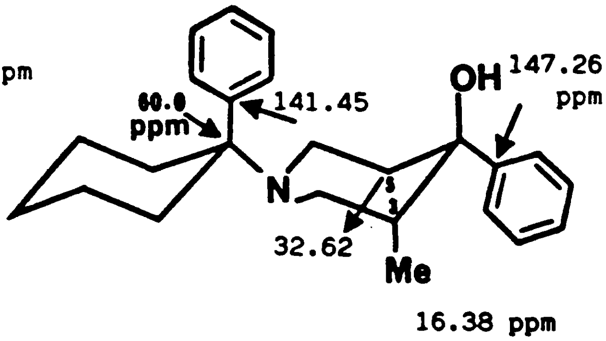
(PCP in D_2O)



(PAP in $CDCl_3$)



(69g in $CDCl_3$)



(69h in $CDCl_3$)

2.3 THE 4-ALKYL-4-ARYLPIPERIDINES

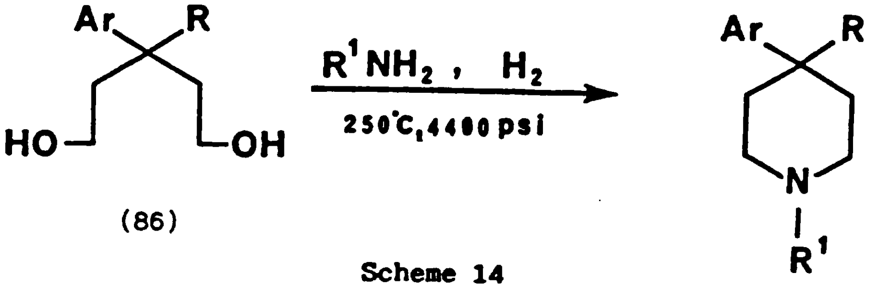
2.3.1 Introduction

The marked mixed agonist/antagonist activity of some analogues in the 4-alkyl-4-aryl series has resulted in intensive investigation of the chemical and stereochemical aspects of these analogues.

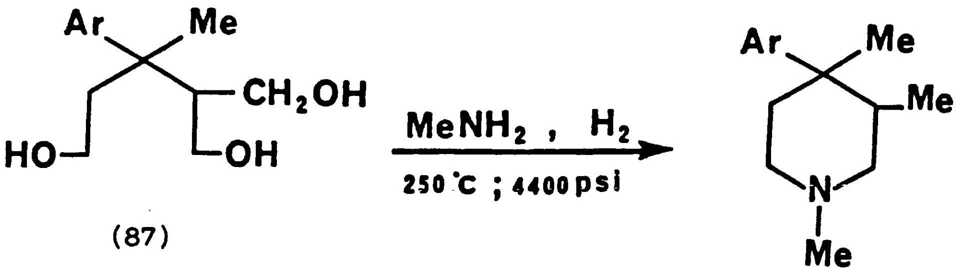
A brief discussion is presented here on some of the synthetic procedures employed to secure these analogues.

The original 4-alkyl-4-arylpiperidines[86] (Table 2, p. 39) were prepared by cyclization of 3-alkyl-3-arylpentane-1,5-diol (86; Scheme 14) with the appropriate primary amine, in the presence of hydrogen at 250°C and 4400 p.s.i. On the other hand, 2-hydroxymethylpentane-3-(o-methoxyphenyl)-3-methyl-1,5-diols and methylamine (87; Scheme 15), under similar conditions, was utilised to secure the 1,3,4-trimethyl analogues.[86]

However, this procedure required a multistep reaction scheme with vigorous reaction conditions at certain stages.

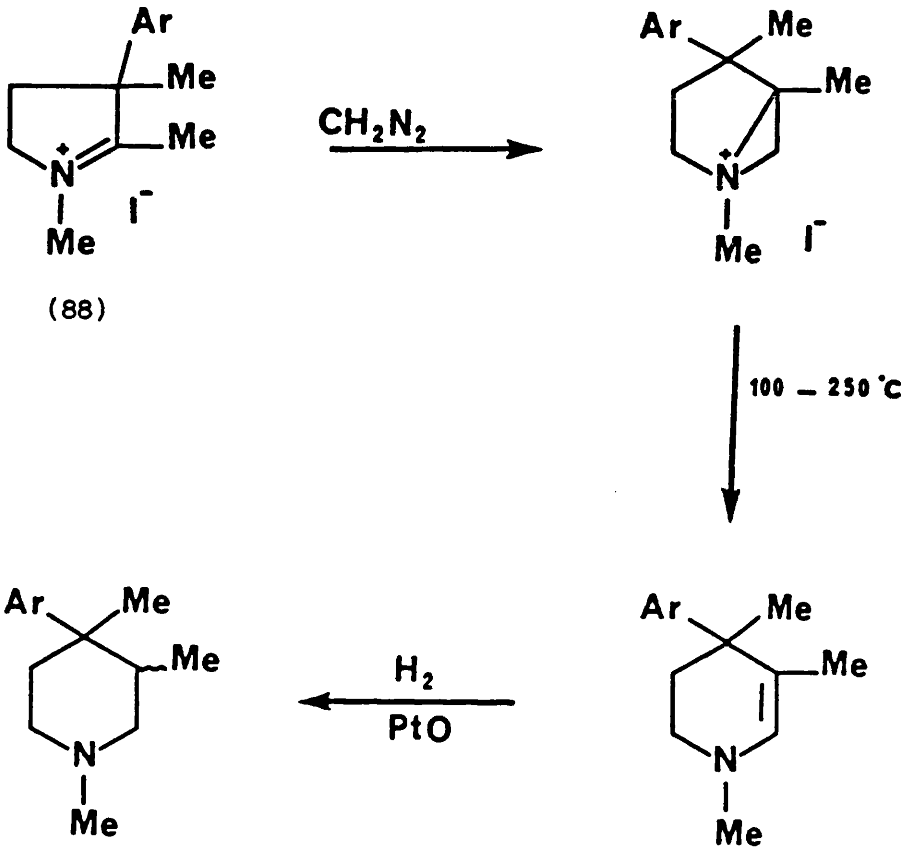


Scheme 14



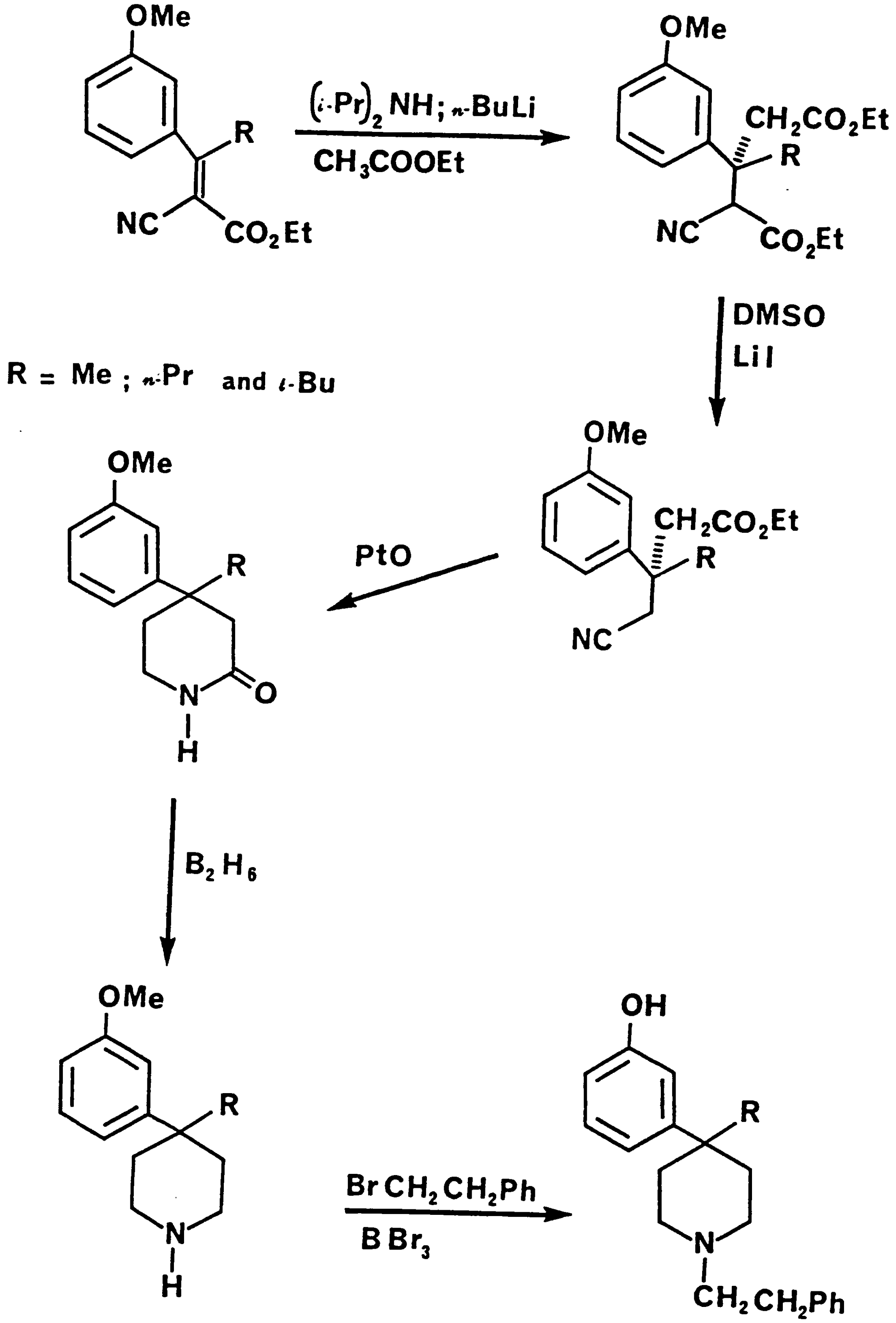
Scheme 15

Compounds of this type were later prepared by ring expansion of 3-arylpyrrolinium iodide using diazomethane[127] (88; Scheme 16), a method which demands great caution. The relevant patent relating to this approach gave no details of the precursor pyrrolinium salt, nor evidence of the stereochemistry.



Scheme 16

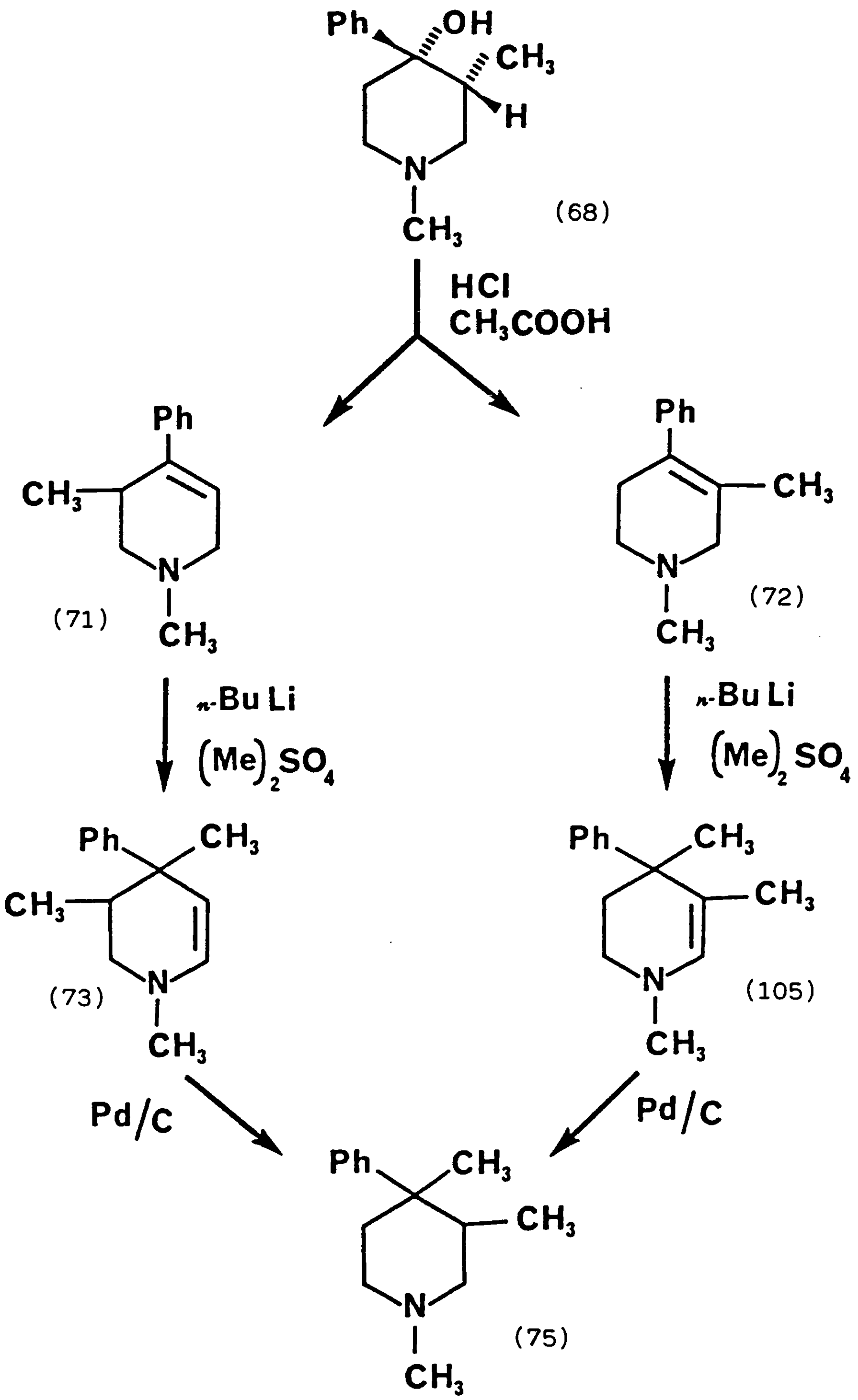
At the time of writing this thesis, an SRI international group has reported[128] the synthesis of 4-alkyl-4-arylpiperidines by a slight modification of the method described by these authors in their original report (Scheme 17).[129] Although preparation of the corresponding 3-methyl analogues was not reported, in this author's opinion the use of ethylpropionate in the first step of the reaction instead of ethylacetate could constitute a route to the synthesis of the 3-methyl analogues.


OMe
R
NC
CO2Et
(i-Pr)2NH; n-BuLi
CH3COOEt
OMe
CH2CO2Et
R
NC
CO2Et
DMSO
LiI
R = Me ; n-Pr and i-Bu
OMe
R
N
O
H
PtO
OMe
CH2CO2Et
R
NC
B2H6
OMe
R
N
H
BrCH2CH2Ph
BBr3
OH
R
N
CH2CH2Ph

Scheme 17

In 1980, Zimmerman et al. demonstrated an important general synthetic approach for the synthesis of morphinan-based analgesics.[130] This approach was later utilized for the synthesis of the 4-alkyl-4-arylpiperidines.[131] The method consists of treating the tetrahydropyridine (89) with n-butyllithium and the appropriate alkylhalide, followed by catalytic hydrogenation of the resultant enamine (90) to yield the desired 4-alkyl analogue (Scheme 18; p.108).

This procedure was employed in the present work to secure the 4-alkyl analogues, for a number of reasons. Firstly, the ease of synthesis of the precursor tetrahydropyridine (89); secondly, it avoids the use of diazomethane which is central to the pyrrolinium salt route;[127] and, lastly, it is sufficiently flexible to be applicable for the synthesis of 3-methyl analogues through use of a Mannich condensation between the enamine (90), formaldehyde and dimethylamine, followed by catalytic hydrogenation of the Mannich base (91; see Scheme 18). Work by this author on such compounds commenced with attempted 4-methylation of the two dehydrated products of α-prodinol in an effort to secure (75; Scheme 19).


(68)
HCl
CH₃COOH
(71)
(72)
n-Bu Li
(Me)₂SO₄
n-Bu Li
(Me)₂SO₄
(73)
(105)
Pd/C
Pd/C
(75)

Scheme 19

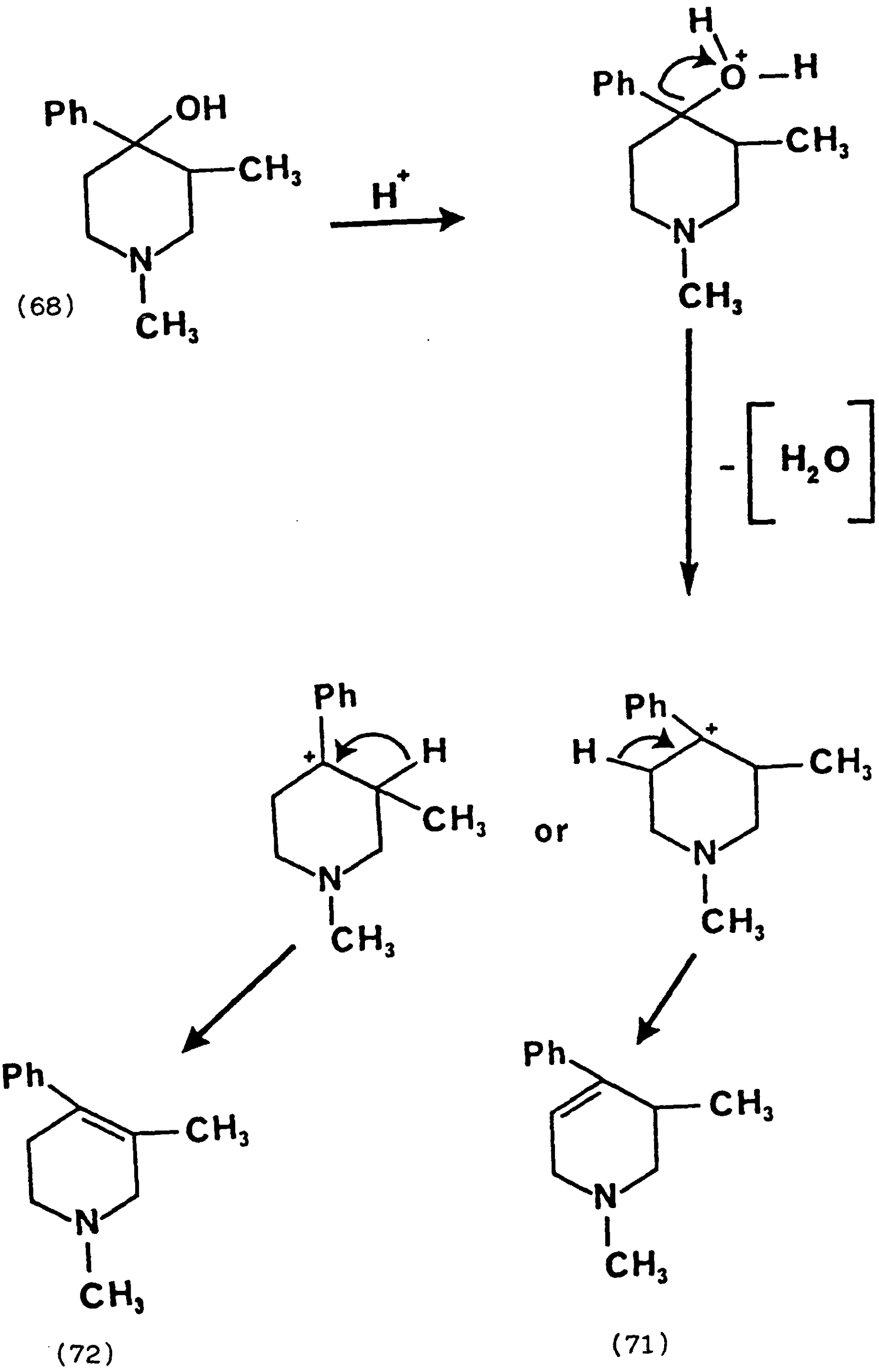
2.3.2 Synthesis

2.3.2.1 The Synthesis of 1,3,4-trimethyl-4-phenylpiperidine

Original attempts to secure this compound concentrated on the chemical reactions expressed in Scheme 19.

A. Dehydration of α-prodinol

Acid catalysed dehydration of α-prodinol (68) was accomplished using concentrated HCl and glacial acetic acid,[132] and yielded a mixture of the two isomers (71) and (72). This dehydration is considered to proceed *via* a two step E_1 mechanism as outlined in Scheme 20. Isomer separation was achieved by fractional crystallisation of the corresponding hydrochloride salts.

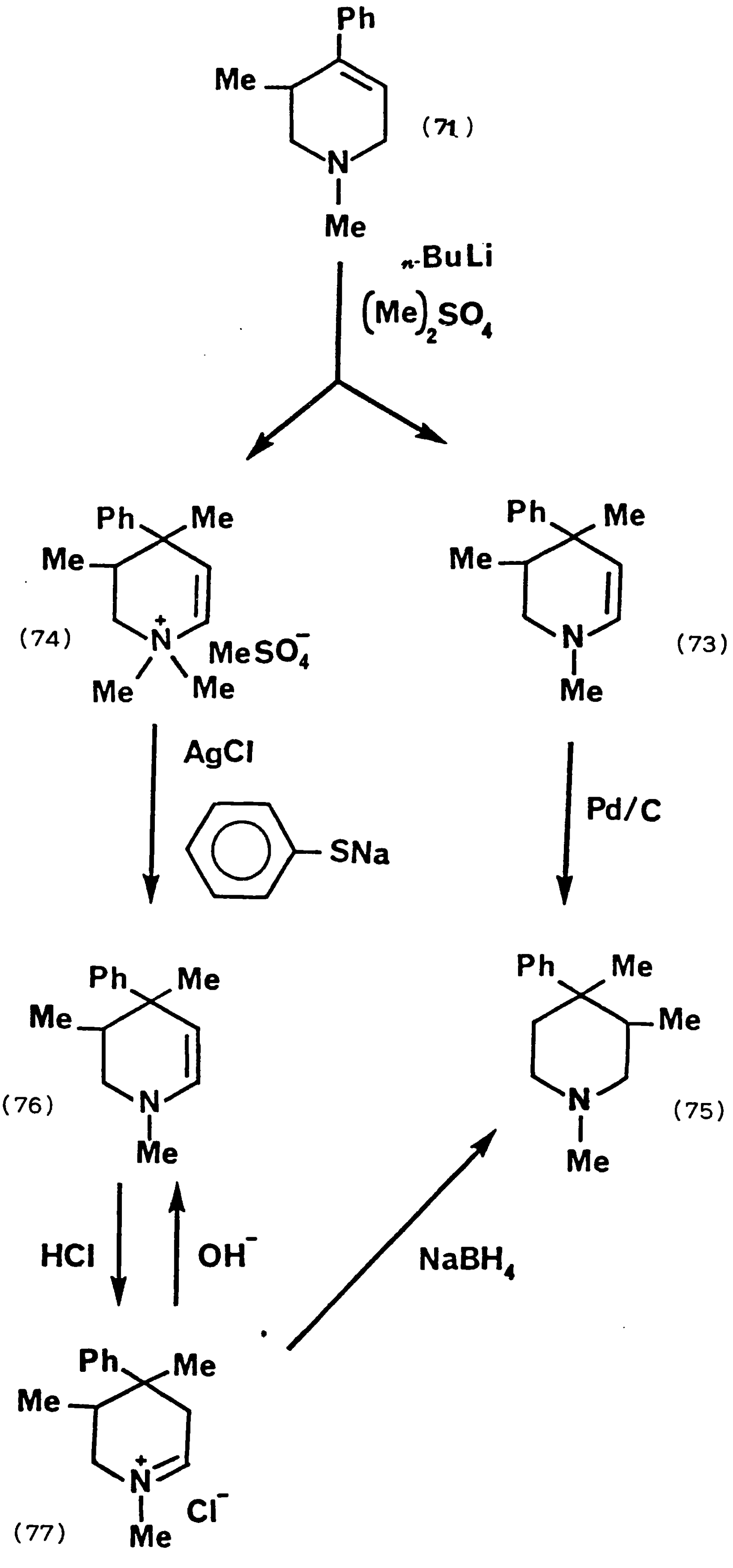

Ph
OH
CH3
N
CH3
(68)
H+
H
O+
H
Ph
CH3
N
CH3
- [H2O]
Ph
+
H
CH3
N
CH3
or
Ph
+
H
CH3
N
CH3
Ph
CH3
N
CH3
(72)
Ph
CH3
N
CH3
(71)

Scheme 20

Spectral data obtained for the two dehydrated compounds were consistent with the assigned structures, and differentiation was readily achieved by means of ^{1}H NMR spectroscopy. Thus, the spectrum of (71) displayed an olefinic multiplet at 5.80 ppm due to C5-H and a doublet at 0.77 ppm due to C3-CH_3, while the spectrum of (72) displayed a singlet at 1.62 ppm due to C3-CH_3 and was devoid of olefinic proton resonance.

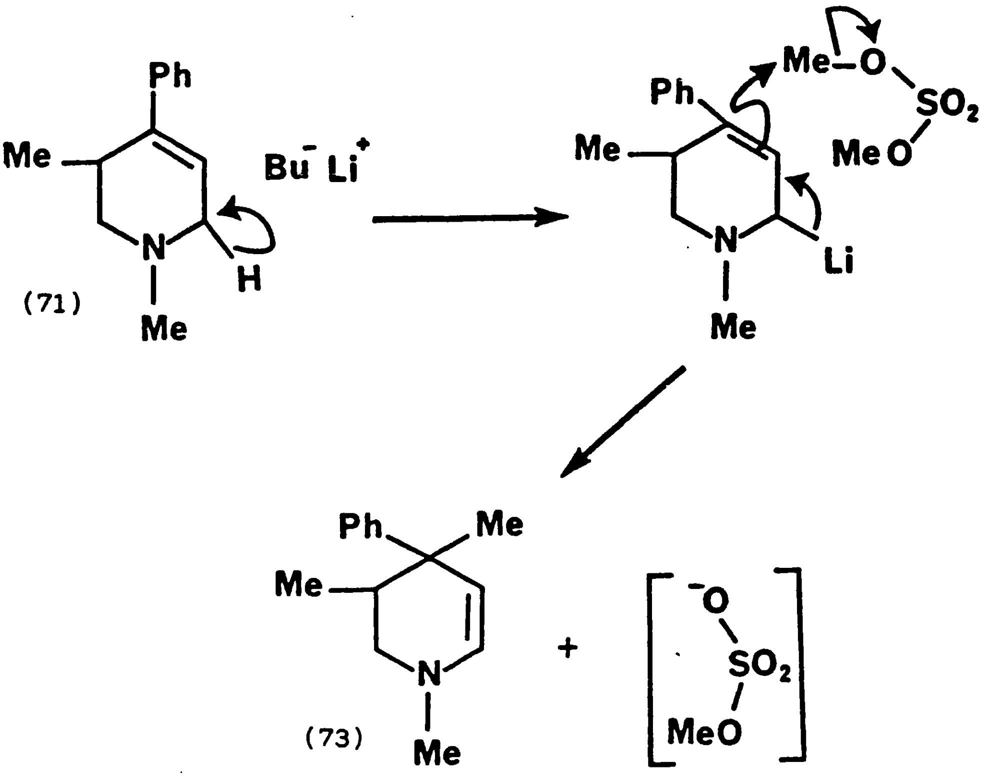
B. Metaloalkylation of (71)

Alkylation of (71) with n-butyllithium and dimethylsulphate was expected to proceed as outlined in Scheme 19, p 92 . However, this reaction afforded a mixture of (73; in about 2% yield) and the corresponding quaternary ammonium salt (74; in about 8% yield; see p.221). Separation of the two compounds was achieved by trituration of the mixture with ether, the salt separating as a colourless solid.


(71)
n-BuLi
(Me)2SO4
(74)
MeSO4-
(73)
AgCl
SNa
Pd/C
(76)
(75)
HCl
OH-
NaBH4
(77)
Cl-

Scheme 21

A probable mechanism for this alkylation is outlined in Scheme 22.



Scheme 22

Characterisation of compound (73) was based on ^{1}H and ^{13}C NMR spectral data, both of which were consistent with structure. A notable feature of the ^{1}H NMR spectrum was the two olefinic doublets centred at 4.34 and 5.98 ppm due to C3-$\underline{H}$ and C2-$\underline{H}$ respectively. Also of significance was the C4-C$\underline{H}_3$ singlet at 1.46 ppm.

The characteristic feature of the ^{1}H NMR spectrum of the quaternary ammonium salt (74) was the down field chemical shifts of $\overset{+}{N}$-Me$_2$, which appeared as two sharp signals at 3.78 and 3.81 ppm, which are assigned, respectively, as axial $C\underline{H}_3$ and equatorial $C\underline{H}_3$.[133] Two olefinic signals at 5.83 and 6.46 ppm were also observed due to C3-$\underline{H}$ and C2-$\underline{H}$ respectively, as well as a C4-$C\underline{H}_3$ singlet at 1.58 ppm. $\overset{+}{\underline{N}}$-$Me_2$ ^{13}C chemical shifts at 42.27 and 42.91 ppm, due to axial $C\underline{H}_3$ and equatorial $C\underline{H}_3$ respectively, were noted.[133]

C. Catalytic hydrogenation of the enamine (73)

Catalytic hydrogenation of (73; Scheme 21) using palladium on charcoal, in ethanol as solvent, yielded one single isomer (75) as judged by ^1H and ^{13}C NMR data.

The ^1H NMR spectrum of the reduced product (75) clearly demonstrated the disappearance of the olefinic doublet. A full discussion of the stereochemical features of this compound is presented in Section 2.3.3; p. 156 .

The mechanism of catalytic hydrogenation is complex and still controversial. The generally accepted current theory suggests the adsorption of the substrate to the metallic catalyst surface, forming a chemisorption complex.[134-136] Willstätter[137] and Ingold[138] envisaged that electrons are being transferred from the surface of the chemisorption complex to the substrate.

D. The synthesis of 1,3,4-trimethyl-4-phenylpiperidine by N-demethylation of the quaternary ammonium salt (74)

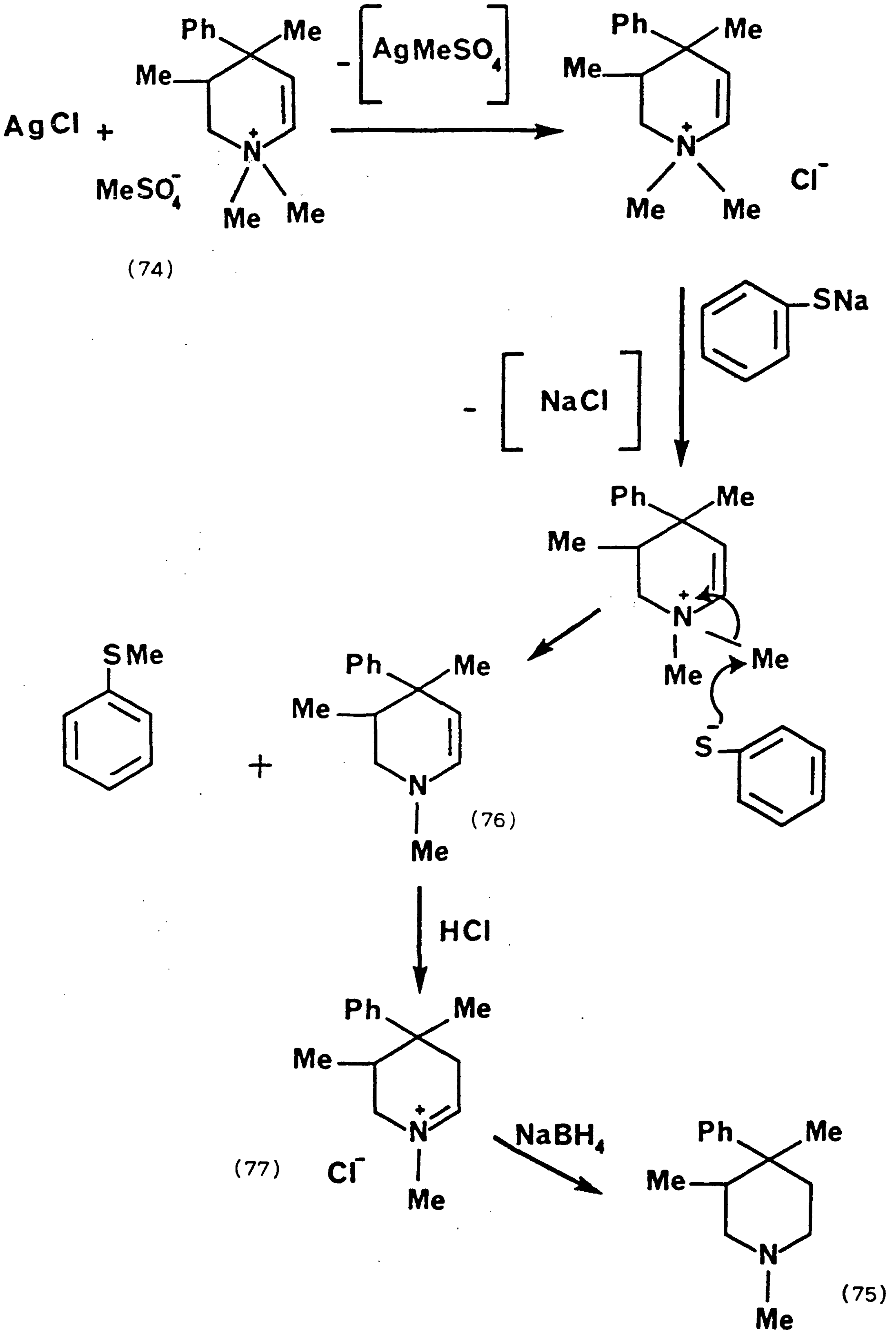
$\underline{N}$-Demethylation of compound (74) was achieved by treatment with AgCl ($MeSO_4^- \rightarrow Cl^-$; the quaternary chloride generated subsequently displays more favourable solubility characteristics), and then refluxing with sodium thiophenate in 2-butanone.[139] This reaction is of the simple S_N2 type, and consists of attack by the thiophenoxide anion on the $\underline{N}$-methyl group, as outlined in Scheme 23.

The ^{1}H and ^{13}C NMR spectra of enamine (76) were consistent with structure. Thus, the ^{1}H NMR spectrum displayed only one $\underline{N}$-$C\underline{H}_3$ signal at the upfield position of 2.70 ppm, compared with two more deshielded $\overset{+}{\underline{N}}$-$C\underline{H}_3$ signals in the starting material. Olefinic resonances at 4.35 and 6.00 ppm, assigned respectively to C3-$\underline{H}$ and C2-$\underline{H}$, were also observed in the ^{1}H NMR spectrum.

Treatment of compound (76) with ethereal-HCl afforded the corresponding enamine salt (77; Scheme 23). The characteristic feature of the ^{1}N HMR spectrum of this compound was the down field chemical shift of C2-$\underline{H}$ at 8.95 ppm, typical of the $\overset{\overset{N}{\|}}{C\underline{H}}$ function. The low field chemical shift for $\overset{+}{\underline{N}}$-$C\underline{H}_3$ at 3.80 ppm, compared with the corresponding group in starting material at 2.70 ppm, was also observed.

Reduction of the enamine salt (77) with $NaBH_4$ afforded compound (75; Scheme 23).

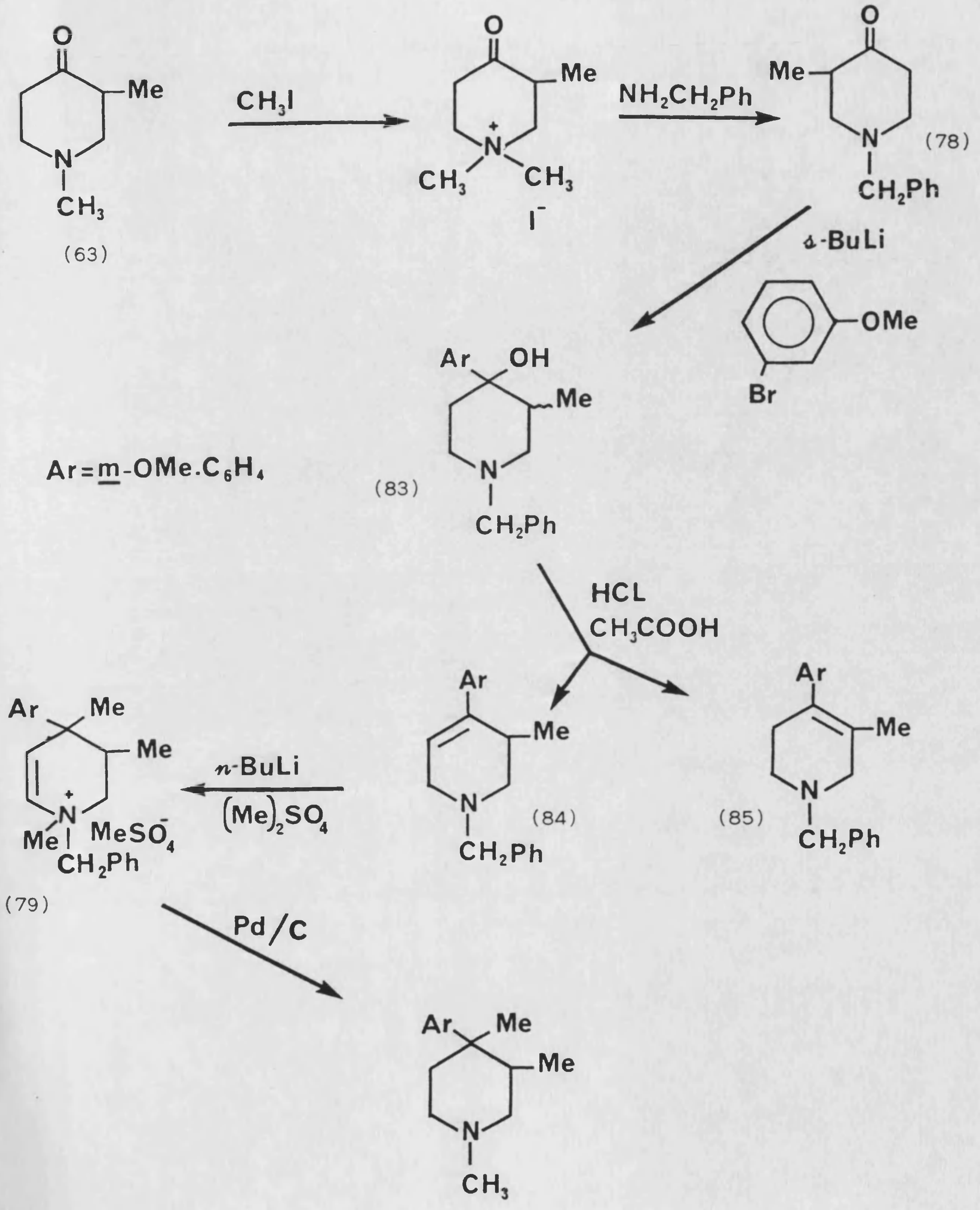
Spectral analysis of the reduced product indicated disappearance of the olefinic signal. This compound was identical with the material obtained from the base (73) described in Scheme 21.



Scheme 23

Following the successful synthesis of (75) using the 5-Me isomer, the attempted synthesis of (73) in an effort to secure this distereoisomer by utilizing the 3-Me compound (72) was unsuccessful, mainly because the reaction is associated with steric hindrance, and returned unconverted starting material, in addition to the corresponding quaternary methosulphate salt, at the alkylation stage.

The synthesis of compound (75) by the route described was unsatisfactory in that the overall yields were very low, due to quaternisation of the key intermediate (73). Therefore, in an effort to increase the yield of the 4-methyl derivative, the use of 1-benzyl-3-methyl-4-piperidone (78), instead of the N-methyl derivative, was undertaken, as the quaternary ammonium salt (79), likely to be formed, should readily undergo catalytic N-debenzylation to give the desired 4-aryl-1,3,4-trimethylpiperidine, as shown in Scheme 24.


Me
N
CH3
(63)
CH3I
Me
N
CH3
CH3
I⁻
NH2CH2Ph
Me
N
(78)
CH2Ph
s-BuLi
OMe
Br
Ar
OH
Me
Ar=m-OMe.C6H4
(83)
N
CH2Ph
HCL
CH3COOH
Ar
Me
Me
N
Me
MeSO4⁻
CH2Ph
(79)
n-BuLi
(Me)2SO4
Ar
Me
N
(84)
CH2Ph
Ar
Me
(85)
N
CH2Ph
Pd/C
Ar
Me
Me
N
CH3

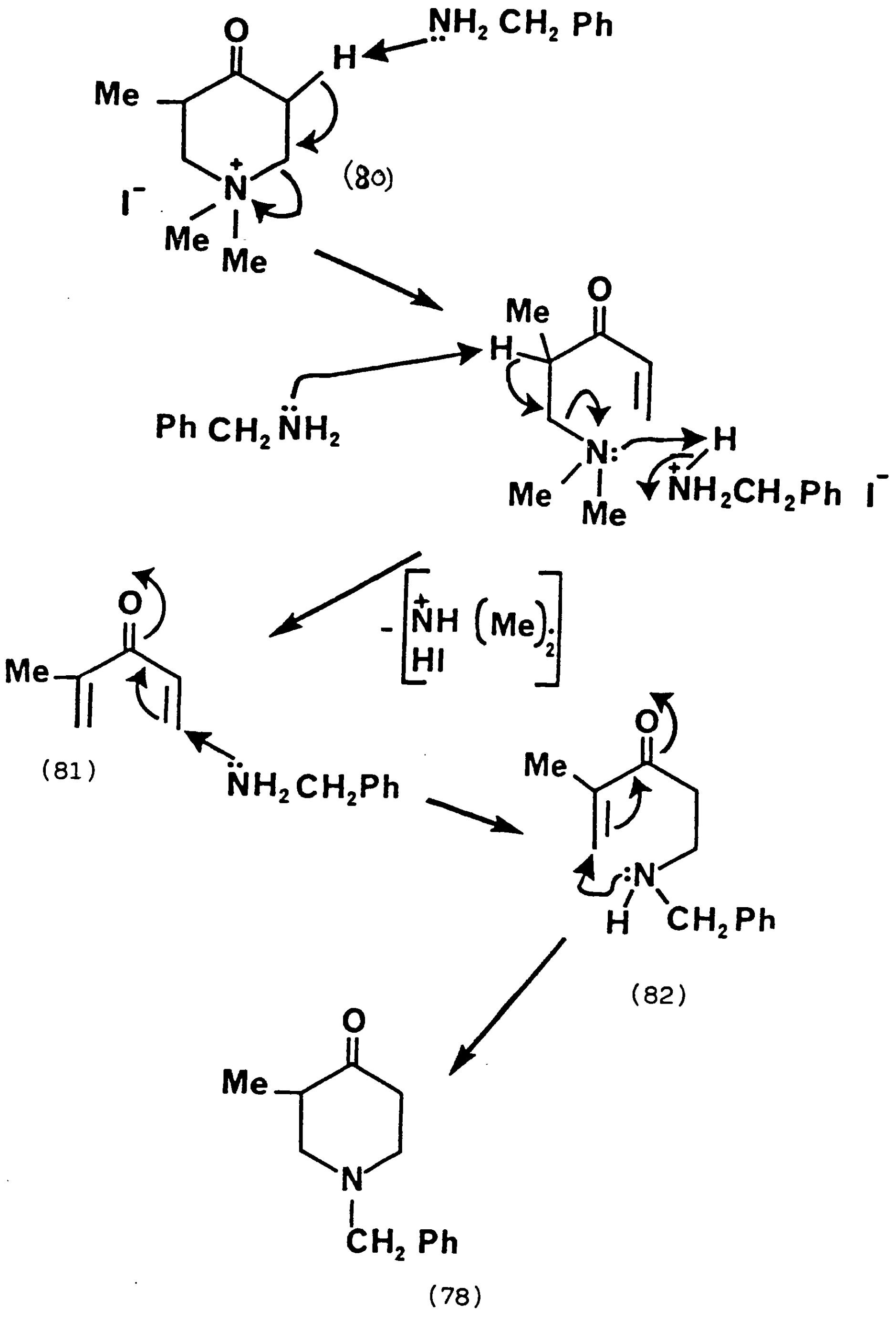
Scheme 24

2.3.2.2 The attempted synthesis of 4-(3-methoxyphenyl)-1,3,4-trimethylpiperidine using 1-benzyl-3-methyl-4-piperidone

The proposed route of synthesis for this compound by this particular method is outlined in Scheme 24.

In view of the difficulties generally experienced in preparing 1-benzyl-3-methylpiperidone (78) by the acrylate condensation method,[41] application of the synthetic procedure described by Mistryukove *et al.*[140] for the synthesis of *N*-alkylpiperidines was undertaken. This procedure is based on an exchange reaction between the methiodide of an *N*-alkylpiperidone and a primary amine.

The probable mechanism is shown in Scheme 25 and it may be viewed as a facile "double Hofmann elimination reaction," facilitated by the *β*-placed carbonyl group, followed by Michael addition reactions of benzylamine and amine (82) to the activated alkenes (81) and (82).


NH2 CH2 Ph
H
O
Me
I⁻
N
Me
Me
(80)
Me
O
H
Ph CH2 NH2
N:
H
Me
Me
NH2CH2Ph I⁻
- [NH (Me)2 / HI]
O
Me
(81)
NH2CH2Ph
O
Me
:N
H
CH2Ph
(82)
O
Me
N
CH2 Ph
(78)

Scheme 25

The ^{13}C NMR spectrum of compound (78) displayed four $\underline{C}H_2$ lines in the aliphatic region, compared with three $\underline{C}H_2$ lines in the starting material. The spectrum also displayed the appropriate aromatic signals in accord with the assigned structure.

The characteristic feature of the ^1H NMR spectrum was the Ar-$C\underline{H}_2$ protons which appeared as a singlet at 3.58 ppm, and the absence of $\overset{+}{\underline{N}}$-$(C\underline{H}_3)_2$ resonances at 3.27 ppm and 3.53 ppm.

Condensation of the ketone (78; Scheme 24) with 3-anisyl lithium (derived from 3-bromoanisole and sec. butyl lithium) afforded an oil which, by t.l.c. analysis, was seen to be a mixture of two compounds, neither of which corresponded to the starting ketone. Sec. butyl lithium was employed in this synthesis, as a lower yield was obtained when n-butyl lithium was used as the metalating agent. The IR spectrum of this oil indicated disappearance of carbonyl absorption and the appearance of OH absorption.

Purification of this isomeric mixture (83) was not attempted, since acid-catalysed dehydration using concentrated HCl and glacial acetic acid affords the desired 5-Me isomer (84) as the major product, as well as the minor 3-Me isomer (85; see Scheme 24). Separation of the 5-Me isomer was achieved by fractional crystallisation of the hydrochloride salts.

Spectral data obtained for this alkenic isomer were consistent with its structure. A characteristic feature of the ^1H NMR spectrum was the olefinic multiplet at 5.85 ppm due to C3-$\underline{H}$.

An attempted synthesis of (79) by treatment of (84) with n-butyl lithium and 2.5 mole equivalents of dimethylsulphate resulted in the formation of a mixture of the quaternary methosulphate salts of starting material and the desired product. All attempts to separate this mixture were unsuccessful. Spectroscopic data relating to these salts are presented on p.253 .

At this stage in the work, the synthetic approach expressed in Schemes 19 and 24 was abandoned.

2.3.2.3 The synthesis of 4-alkyl-4-arylpiperidines using 4-aryl-1,2,5,6-tetrahydro-1-methylpyridine as a precursor

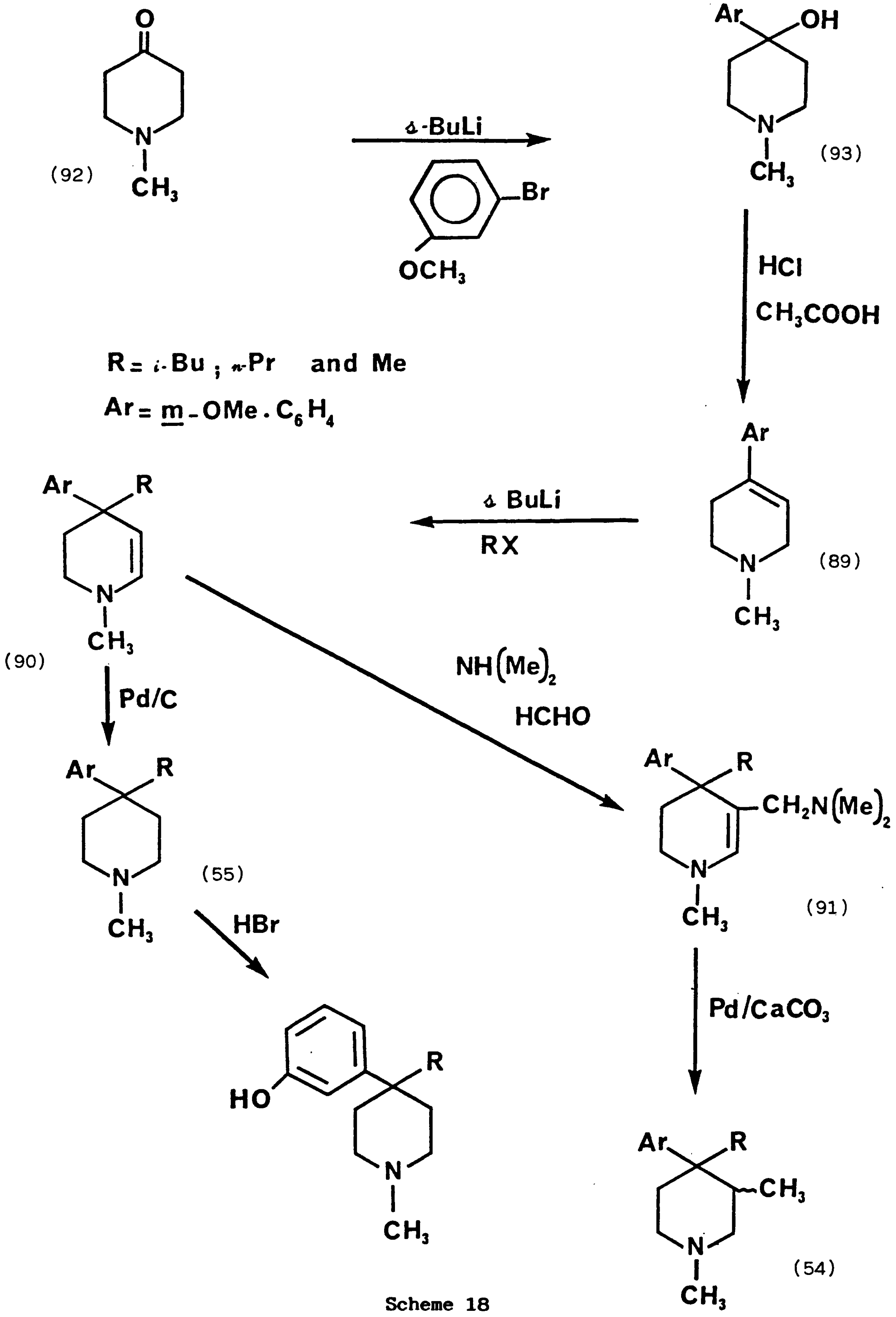
In view of the difficulties reported in the last section, application of the synthetic procedure described by Zimmerman *et al.*[130,131] for the synthesis of 4-alkyl-4-aryl-1-methylpiperidine (Scheme 18; R = Me, *n*-Pr and *iso*-Bu; p.108) was therefore undertaken, using 4-aryl-1,2,5,6-tetrahydro-1-methylpiperidine (89; Scheme 18) as a precursor.

A. The synthesis of 4-hydroxy-4-(3-methoxyphenyl)-1-methylpiperidine

Treatment of the ketone (92; p.108) with the Grignard reagent derived from 3-bromoanisole and *sec*-butyllithium afforded the alcohol (93). Characterisation of this alcohol was achieved by ^{13}C NMR and IR spectra, one notable feature being the absence of carbonyl absorption (a characteristic of starting ketone).

B. The synthesis of 1,2,5,6-tetrahydro-4-(3-methoxyphenyl)-1-methylpyridine

In this work compound (89), a key intermediate in the synthesis of the whole series of 4-alkyl analogues, was prepared by acid-catalyzed dehydration of the alcohol (93) using concentrated HCl and glacial acetic acid.


(92)
s-BuLi
Br
OCH$_3$
(93)
Ar
OH
N
CH$_3$
HCl
CH$_3$COOH
R = i-Bu ; n-Pr and Me
Ar = m-OMe . C$_6$H$_4$
(89)
s BuLi
RX
(90)
Pd/C
NH(Me)$_2$
HCHO
(91)
CH$_2$N(Me)$_2$
(55)
HBr
HO
R
Pd/CaCO$_3$
(54)
CH$_3$

Scheme 18

Confirmation of this olefinic product was provided by the detection of additional resonances at 111.54 and 144.0 ppm, due to C3 and C4 respectively, in the ^{13}C NMR spectrum. The C3-H olefinic multiplet at 6.01 ppm was also observed in the ^{1}H NMR spectrum.

Because the 4-isobutyl, 4-n-propyl and 4-methyl analogues were produced by a similar procedure, only the synthesis of the 4-isobutyl analogues will be described in detail and remarks concerning derivatives of the other two analogues, particularly the 4-methyl derivatives, will be made when necessary.

C. The synthesis of 1,4,5,6-tetrahydro-4-(3-methoxyphenyl)-1-methyl-4-(2-methylprop-1-yl)pyridine

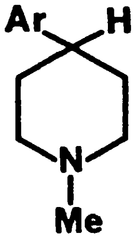
This compound (90a) was prepared by metalloenamine alkylation of the dehydrated derivative (89) using n-butyl lithium and 1-bromo-2-methylpropane. Purification of the crude product was achieved by slurrying it in a mixture of hexane : ethyl acetate and silica gel.

n-Propylbromide and dimethylsulphate respectively were utilized as alkylating agents for the synthesis of the 4-n-propyl and the 4-methyl analogues.

This reaction proceeded smoothly to yield (90a) and (90b) in good yields. However, the yield of the C4-methyl analogue was low (39%) due to the formation of the by-product (94). This arises from partial C4-methylation; but the piperidine basic centre seems to show a preference for the highly reactive dimethylsulphate, forming the quaternary ammonium salt, a finding experienced in the

C4-methylation of (71; p. 95).

Attempts to increase the yield of the C4-methyl analogue by using only a slight excess of dimethylsulphate or utilizing methyl iodide as alkylating agent proved unsuccessful, generating a mixture of the desired product and more of the corresponding quaternary ammonium salt. This result was expected as methyl alkylating agents are much more reactive than their higher homologues.[141]



Ar=m.OMe.C_6H_4

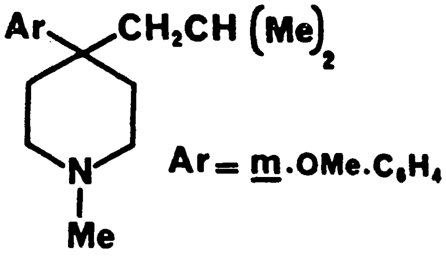
(94)

The ^{13}C and ^{1}H NMR spectra of the C4-isobutyl compound (90a) were consistent with the assigned structure. Thus, the ^{13}C NMR spectrum displayed carbon signals for the 4-isobutyl group, and C2 and C3 chemical shifts at 136.32 and 111.80 ppm, respectively, were noted.

The characteristic feature of the ^{1}H NMR spectrum was the two olefinic signals at 5.40 and 4.81 ppm, which are assigned, respectively, to C2-H and C3-H.

D. The synthesis of 4-(3-methoxyphenyl)-1-methyl-4-(2-methylprop-1-yl)piperidine and its corresponding free phenol

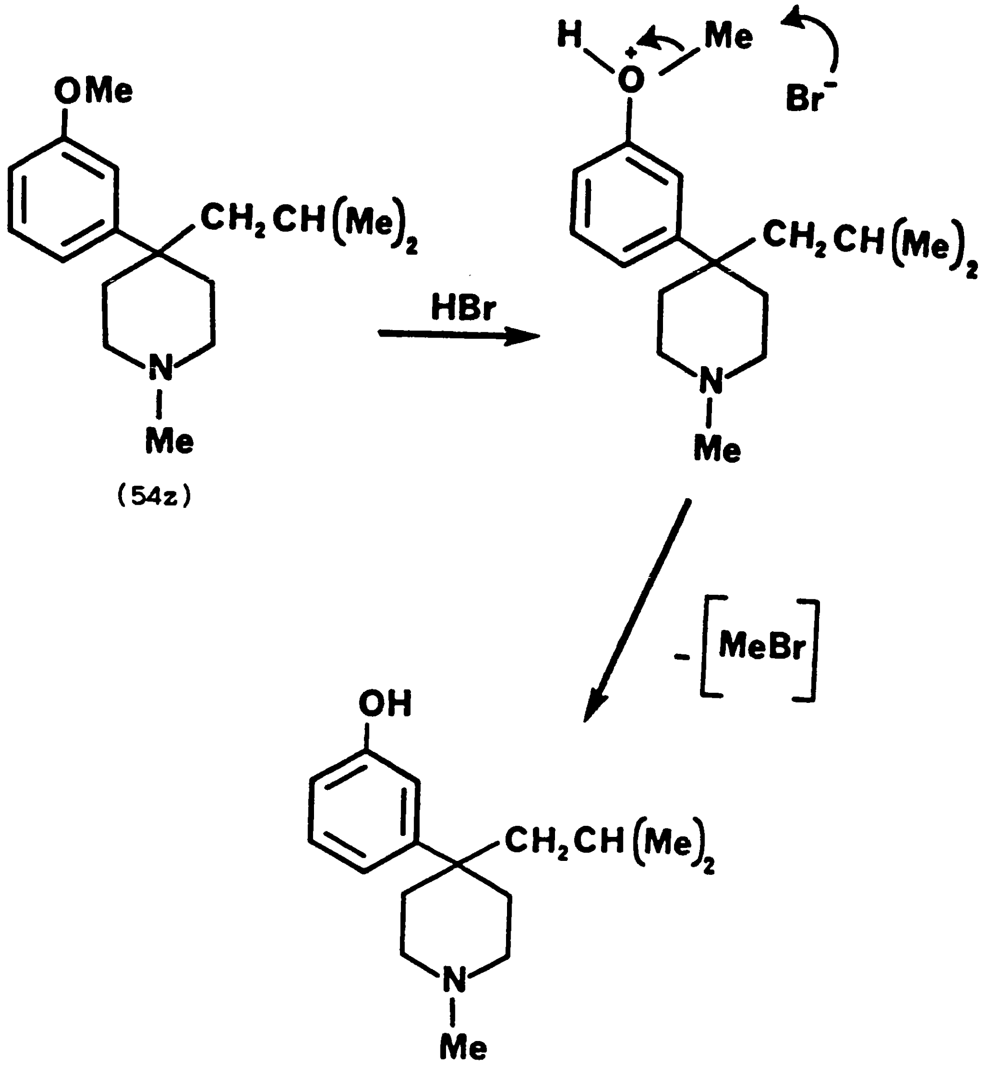
Catalytic hydrogenation of the enamine (90a) with palladium on charcoal, in ethanol as solvent, yielded compound (55z).



(55z)

The ^{1}H NMR spectrum of the reduced product (55z) indicated the disappearance of the olefinic signals.

O-Demethylation of the reduced product (55z) with HBr (48%) yielded the corresponding phenolic analogue. This O-demethylation is of the nucleophilic category and it is considered to proceed as shown in Scheme 26.



Scheme 26

The ^{13}C and ^{1}H NMR spectra of this compound were consistent with structure, the notable feature being absence of the signal for $\underline{O}$-CH$_3$.

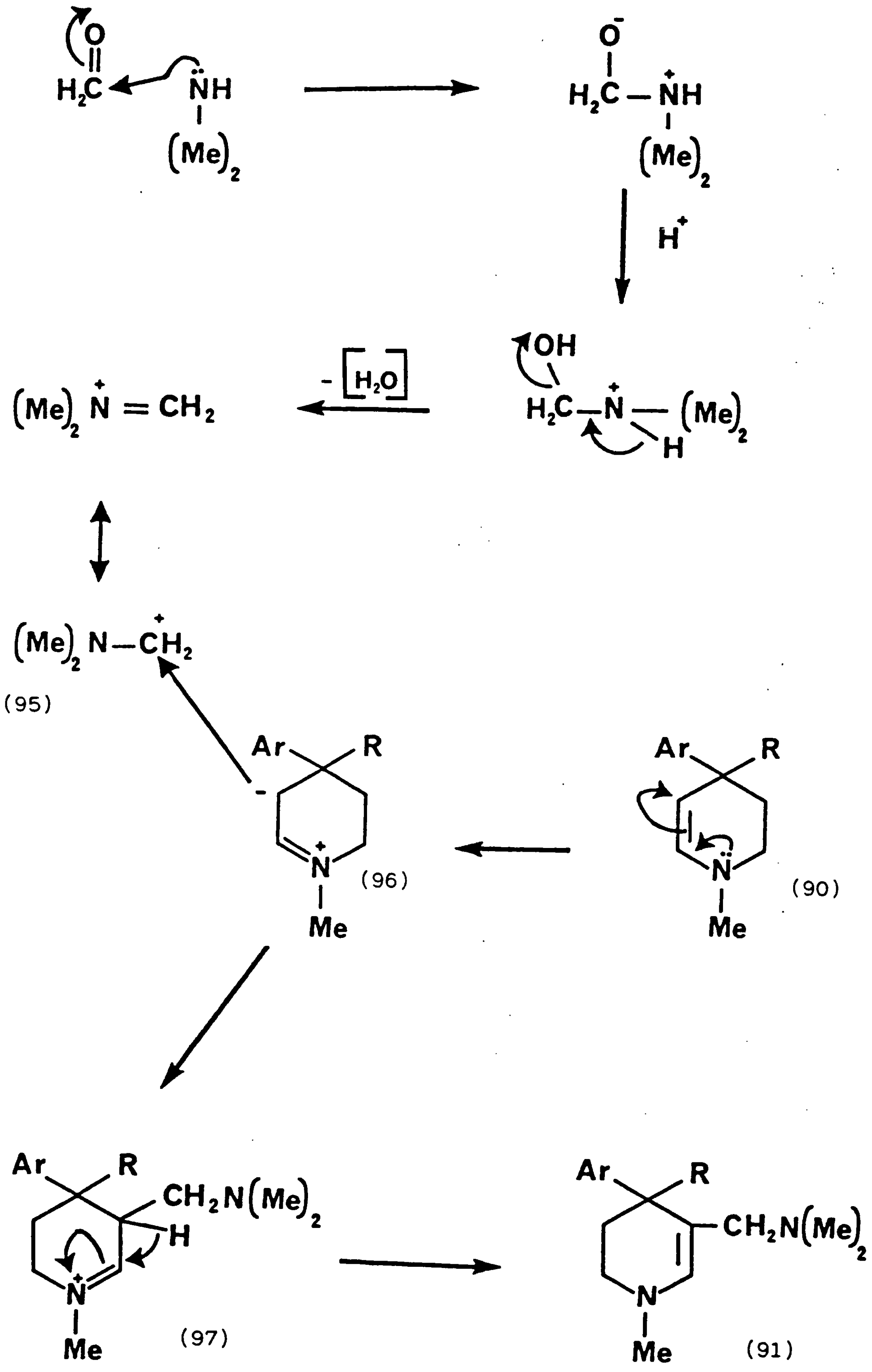
E. The synthesis of 1,4,5,6-tetrahydro-4-(3-methoxyphenyl)-1-methyl-3-dimethylamino methyl-4-(2-methylprop-1-yl)pyridine via the Mannich reaction

The reaction of ammonia or a primary amine or secondary amine (usually as the hydrochloride), formaldehyde and a compound containing at least one hydrogen atom of pronounced activity is known as the Mannich reaction.[142]

This reaction is an extremely useful synthetic reaction of extraordinary wide and varied application, and appears in various modifications in numerous syntheses of nitrogen containing compounds, both acyclic and cyclic.

This general reaction was successfully employed in the present work to secure compound (91a), using (90a) as the sulphate salt, formaldehyde and dimethylamine. The pH of the solution was adjusted to approximately 3.0-4.0 using sulphuric acid.

The reaction is believed to proceed mechanistically as outlined in Scheme 27. Initial attack by the unshared electron pair of nitrogen on the carbonyl atom is followed by protonation and elimination of water to yield the ion (95), which is resonance stabilized. Attack by the carbanion from the enamine (96) on the positive carbon atom of (95) yields (97) which is followed by loss of a proton to yield the Mannich base (91a).

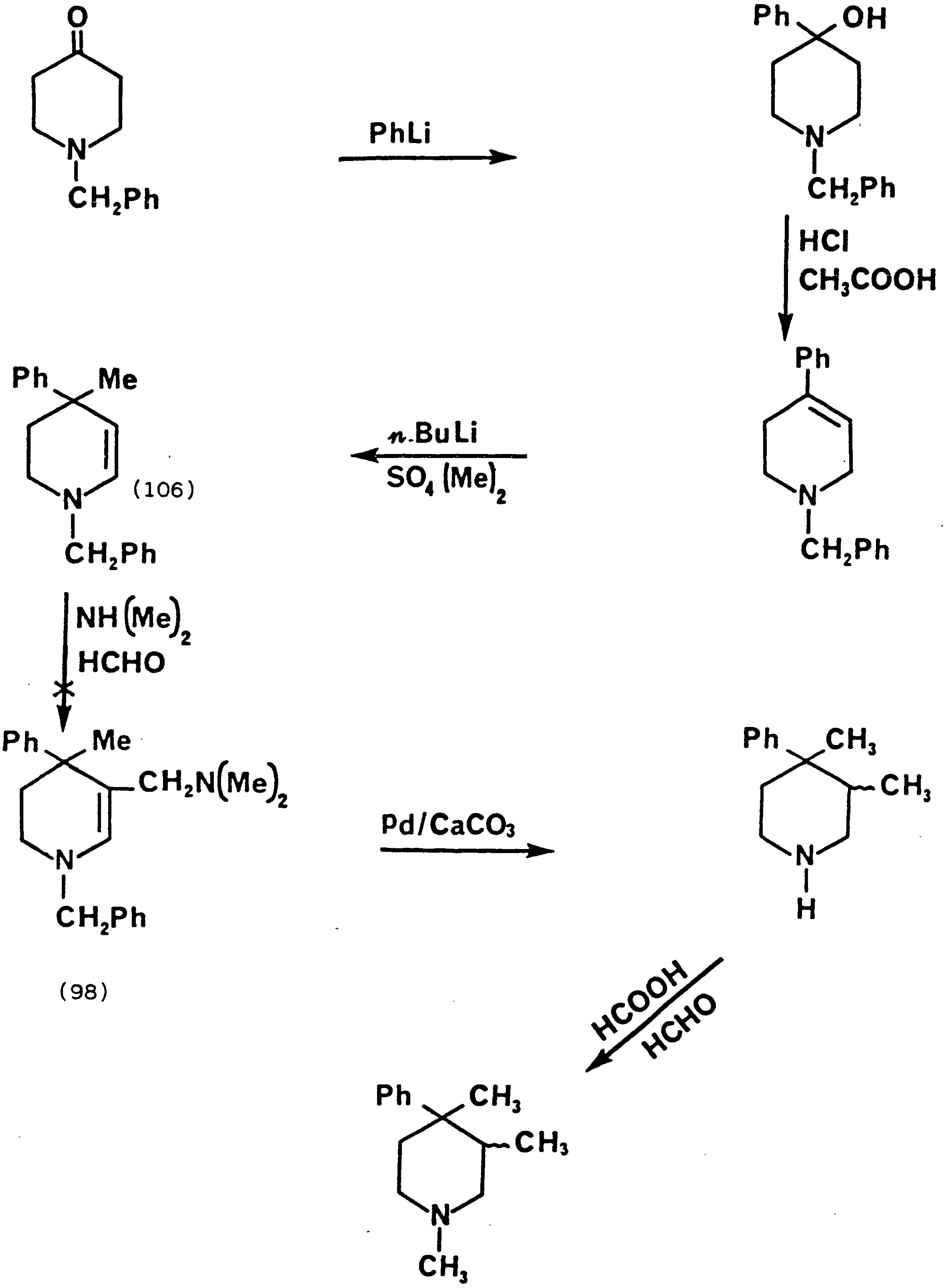

H₂C=O
NH(Me)₂
O⁻
H₂C–NH⁺(Me)₂
H⁺
- [H₂O]
OH
H₂C–N⁺(H)–(Me)₂
(Me)₂N⁺=CH₂
(Me)₂N–CH₂⁺
(95)
Ar
R
(96)
Me
(90)
CH₂N(Me)₂
H
(97)
(91)

Scheme 27

Characterisation of the oily Mannich base (91a) was based on ^{1}H and ^{13}C NMR spectral data, both of which were consistent with structure.

The ^{1}H NMR spectrum displayed only one olefinic signal at 6.11 ppm, due to C2-H, compared with two olefinic signals in the starting material. A notable feature of this spectrum was the C3-$CH_2N(CH_3)_2$) signal at 2.20 ppm (6H).

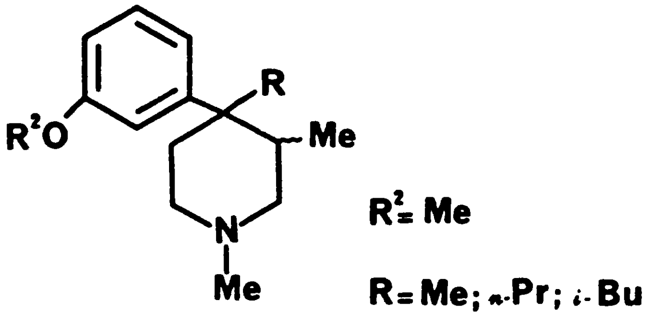
Following the success of this reaction using the N-methyl derivatives, the attempted synthesis of the Mannich base of the 1-benzyl derivative (98; Scheme 28, p. 116) proved unsuccessful, and yielded a mixture, which was impossible to purify. The benzyl group was used again as a protecting group in the attempted synthesis of the C4-methyl analogue, as quaternisation of the 1-methyl derivative was expected.


PhLi
HCl
CH₃COOH
n.BuLi
SO₄ (Me)₂
(106)
NH(Me)₂
HCHO
(98)
Pd/CaCO₃
HCOOH
HCHO

Scheme 28

F. The synthesis of α- and β-4-(3-methoxyphenyl)-1,3-dimethyl-4-(2-methylprop-1-yl)piperidine and the corresponding free phenols

Catalytic hydrogenation of the Mannich base (91a) with palladium on calcium carbonate, in triethylamine as solvent, yielded an isomeric mixture of (54j; R^2 = Me) and (54k; R^2 = Me), as judged by spectral analysis.



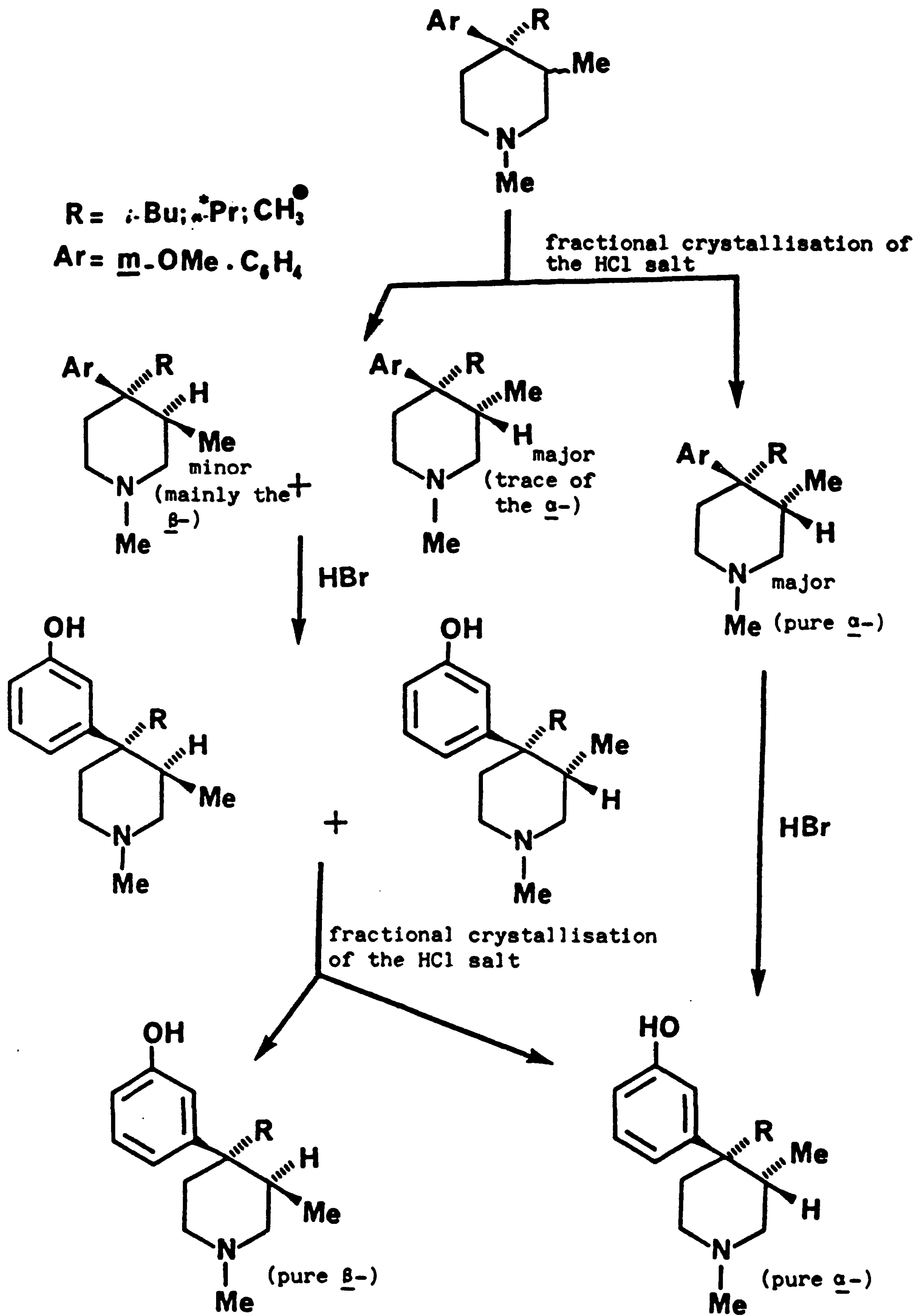
(54)

This reaction actually occurs in two steps. Initially, the *exo* C-N bond is hydrogenolyzed to generate the 3-methyltetrahydropyridine and then the 2,3-double bond in the tetrahydropyridine ring is reduced to afford the desired diastereoisomer.

Basic conditions are preferred in this reaction, in order to increase the quantity of the *α*-isomer according to the Lilly patent.[131] The ^{1}H NMR spectrum of the reduced product indicated disappearance of the olefinic resonance.

The major *α*-isomer (54k) was separated by fractional crystallisation of the hydrochloride salt, while the minor *β*-isomer (54j), which separated along with a trace of the major isomer, was later purified and characterised as the corresponding phenol (see Scheme 29).

Treatment of (54k; R^2 = Me) with HBr (48%) afforded the corresponding phenol. The ^{13}C and ^{1}H NMR of this compound indicated the absence of signal for the $\underline{O}-\underline{CH}_3$.



*The major 4-Pr(c-3-Me/4-Ar) was separated as the oxalate salt, while the minor isomer (t-3-Me/4-Ar) separated as the HCl salt.

●The major 4-Me (c-3-Me/4-Ar) and the minor 4-Me (t-3-Me/4-Ar) were separated as the HCl salts.

Scheme 29

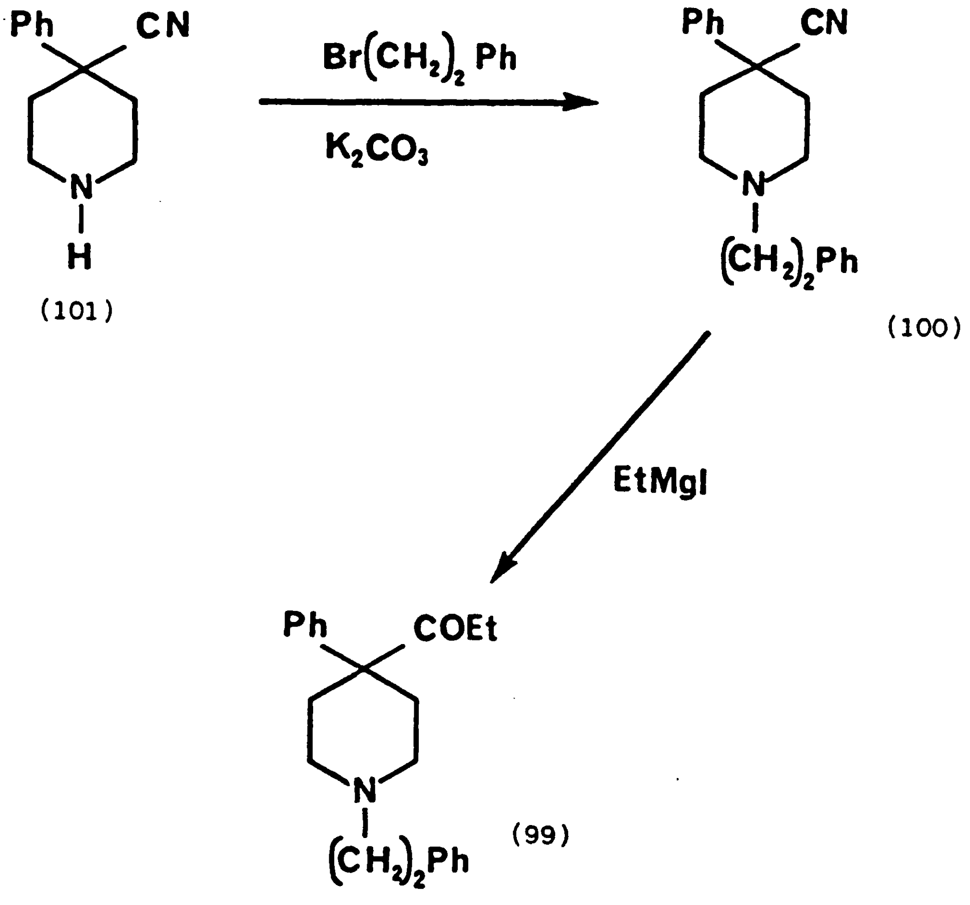
G. The synthesis of some of the methiodide salts of the 4-alkyl-4-arylpiperidines

The general procedure utilized in quaternisation of the basic piperidine was carried out by using methyl iodide and acetone as solvent.

The methiodide salts of compounds (55h; Ar = m.$OMeC_6H_4$ and 54b; R^2 = Me) were prepared as model compounds to aid in configurational assignments of the corresponding N-methyl analogues[133] (see p. 156).

2.3.2.4 Miscellaneous syntheses

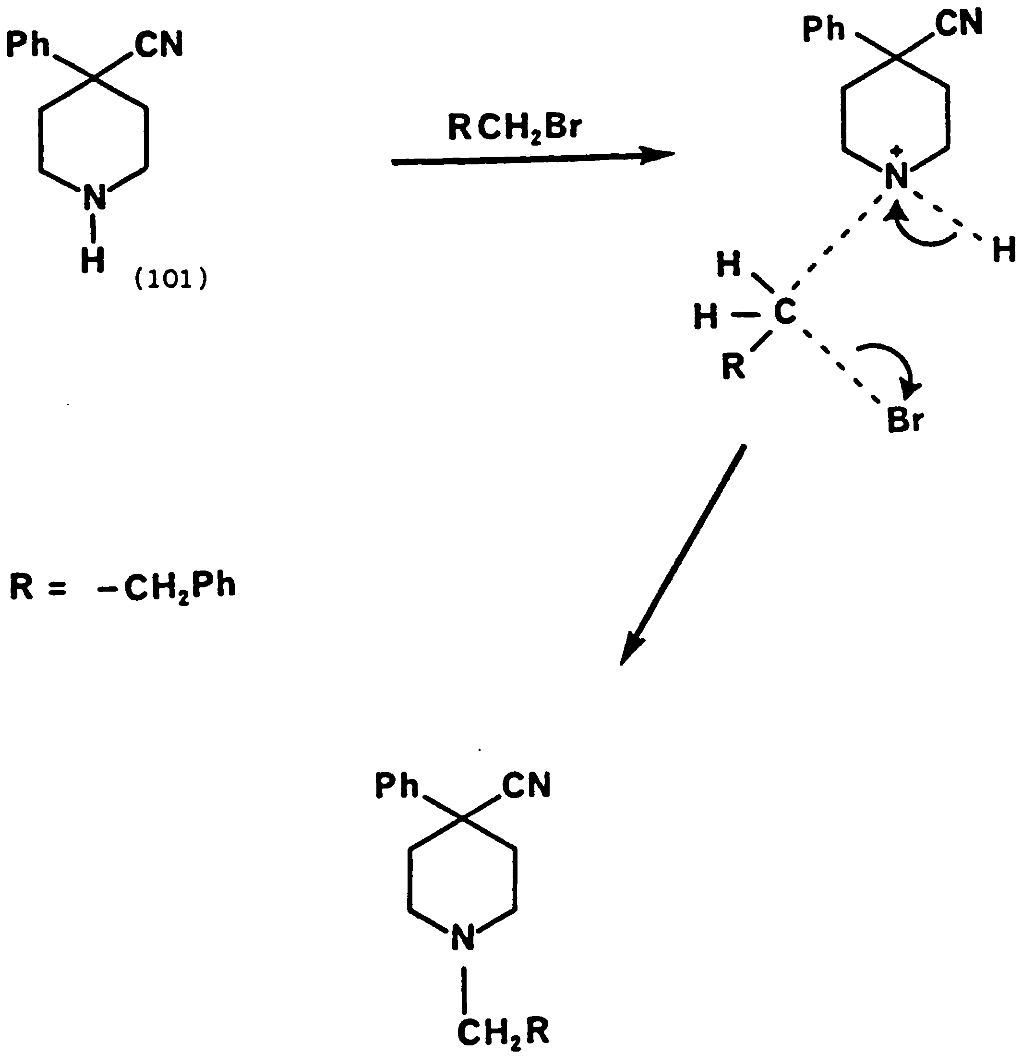
The synthesis of the ketobemidone derivative (99) and the propionate reversed ester of pethidine (42; p. 125) was carried out in order to complete a conformational equilibrium study of hydrochloride salts of pethidine and related central analgesics of the 4-phenylpiperidine class.[143]



Scheme 30

A. The synthesis of 4-cyano-1-phenethyl-4-phenylpiperidine

The synthesis of this compound (100; Scheme 30) was achieved by direct alkylation of the secondary amine (101) with phenethyl bromide. This alkylation is of the nucleophilic category proceeding *via* an S_N2 mechanism as outlined in Scheme 31.



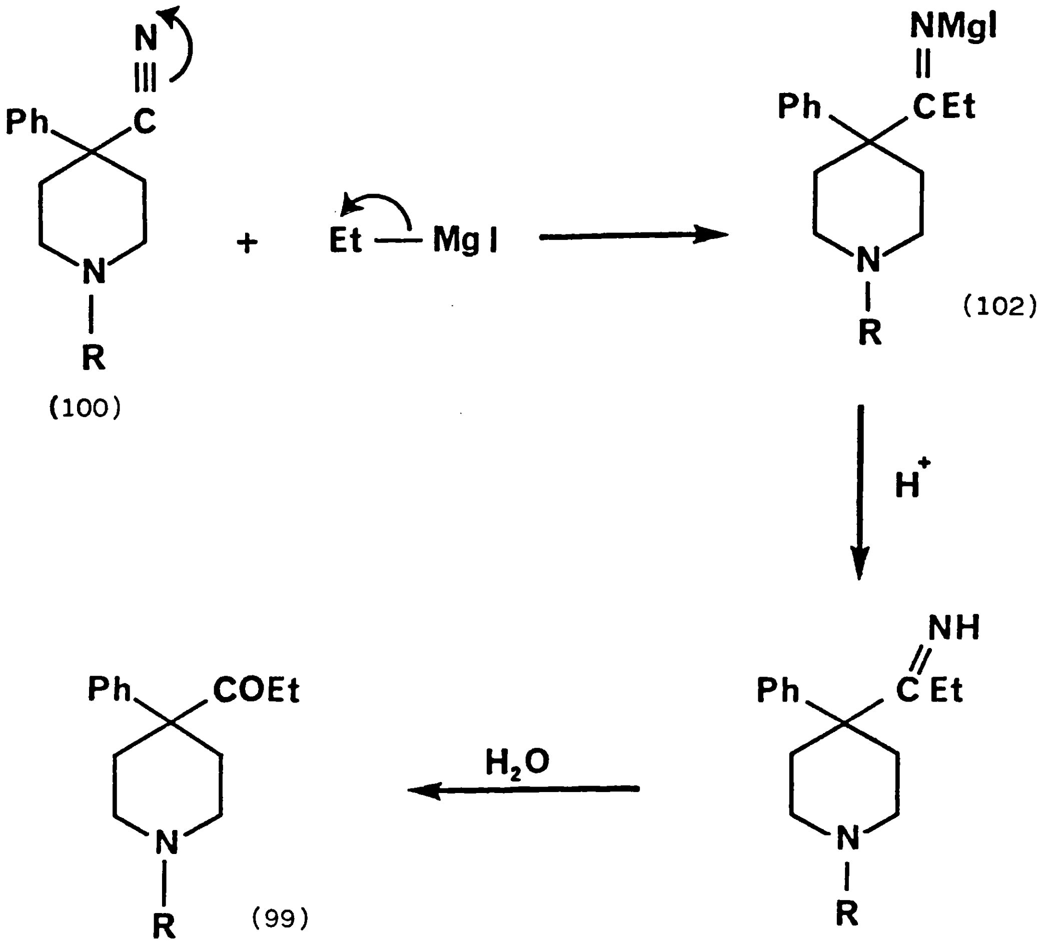
Scheme 31

Characterisation of this compound was based on the spectral data obtained. The ^{13}C and ^{1}H NMR spectra were consistent with the assigned structure and, notably, the ^{13}C spectrum displayed the correct carbon signals for the N-phenethyl group.

B. The synthesis of 1-phenethyl-4-phenyl-4-propionylpiperidine

The ketobemidone derivative (99; Scheme 30) was obtained by treatment of the nitrile (100) with a Grignard reagent prepared from magnesium and iodoethane. The probable mechanism of this reaction involves an initial addition of the Grignard reagent to the cyano group to form an imine salt (102), followed by protonation of the imine salt to yield the corresponding imine, which undergoes rapid hydrolysis to the desired corresponding ketone (99), as illustrated in Scheme 32.

The IR and ^{13}C NMR spectra of the ketone were consistent with the assigned structure. Thus, the IR spectrum showed a strong carbonyl absorption at 1720 cm^{-1}. Ketone $-\overset{O}{\overset{\|}{\underline{C}}}-$ chemical shift at 211.31 ppm was also observed in the ^{13}C NMR spectrum, compared with $-\overset{N}{\overset{|||}{\underline{C}}}-$ chemical shift at 121.73 ppm in the starting material.



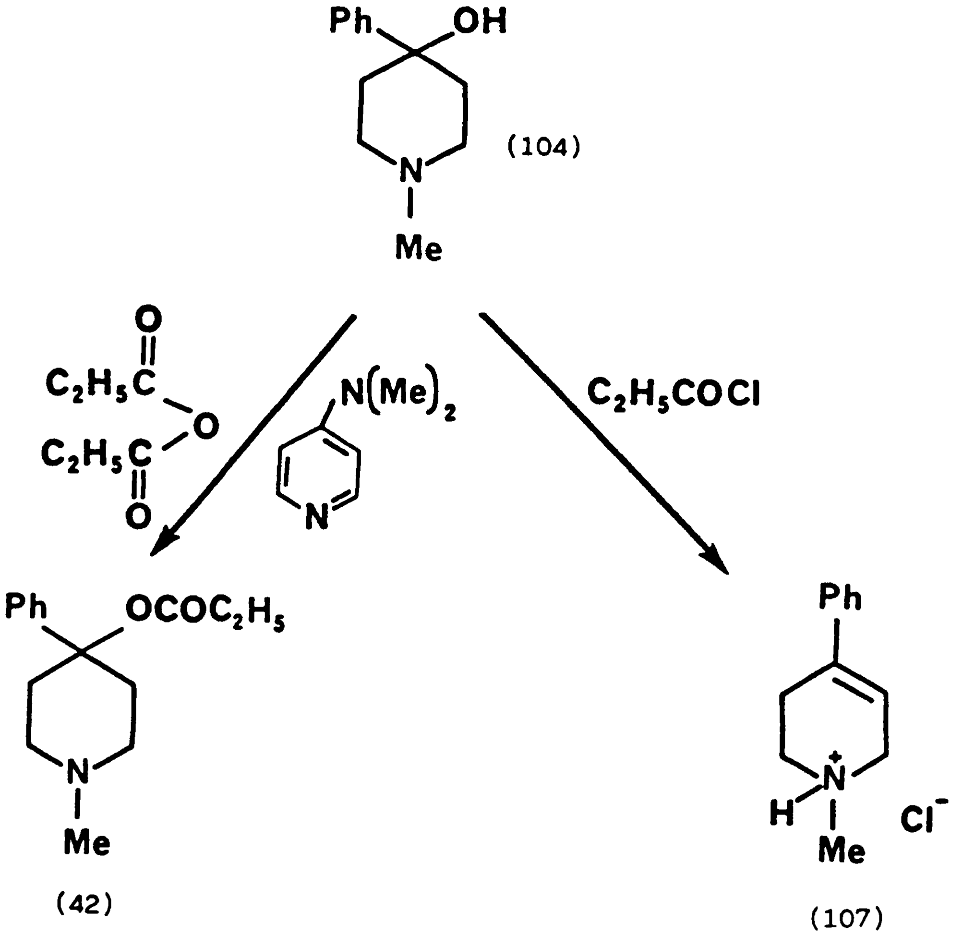
$R = -CH_2CH_2Ph$

Scheme 32

C. The synthesis of 1-methyl-4-phenyl-4-propionoxypiperidine

An initial attempt to secure compound (42) by treatment of the alcohol (104) with propionyl chloride proved unsuccessful, the dehydrated alcohol (107) being the major product.

Esterification of this alcohol was successfully effected utilizing propionic anhydride, with 4-dimethylaminopyridine as acid scavenger (Scheme 33).



Scheme 33

The IR spectrum of this compound (42) displayed a strong absorption at 1740 cm^{-1}, characteristic of ester carbonyl. The ^{13}C NMR spectrum displayed the correct number of carbon signals consistent with structure, characteristic ester carbonyl carbon being noted at 175.57 ppm. The downfield chemical shift of C4 at 77.91 ppm was another characteristic feature of the ^{13}C NMR spectrum of this compound.

2.3.3 Stereochemical (conformational and configurational) assignments to 4-alkyl-4-arylpiperidines by analysis of their ^{1}H and ^{13}C NMR spectra

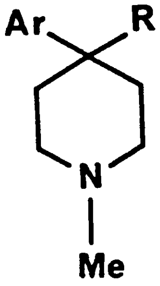
Evidence of the stereochemistry of the 4-alkyl-4-arylpiperidines was sought from NMR data. The ^{1}H NMR spectra of some 3,4-dialkylisomeric analogues of this series displayed complex resonances which precluded any direct stereochemical deductions to be made. Thus, the bulk of the stereochemical information was derived from the ^{13}C NMR data and supported with ^{1}H NMR studies.

The most general method for ^{13}C assignments is by the aid of chemical shift correlation with spectra of closely related compounds of established stereochemistry. The main principle behind the use of ^{13}C NMR data for stereochemical assignments is based on the fact that the effects of a substituent (C3-Me in the present work) on the chemical shift of the parent compound depends not only on the nature of the substituent but also on its spatial orientation in relation to other carbons in the molecule. These substituent effects are significantly noticeable on the immediate α-carbon, as well as on distant carbon atoms in the molecules, especially the γ-carbon. Thus, as a starting point for this study, attention will be given first to the stereochemical assignments of the des C3-methyl analogues (parent compounds).

It is reasonable to assume that conclusions about the stereochemistry of the m-methoxyphenyl derivatives discussed here are equally relevant to their O-demethylated (free phenol) analogues, i.e. the forms in which they will be pharmacologically evaluated.

2.3.3.1 Des C3-Methyl Analogues

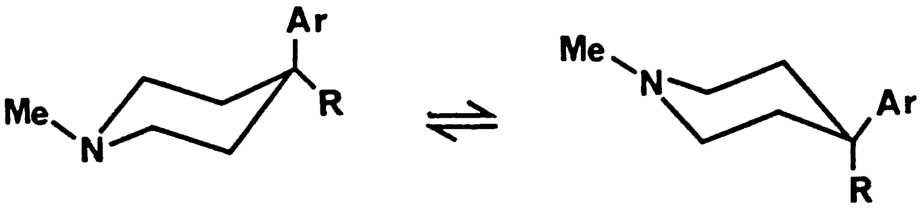
In these analogues, the problem to be solved is one of conformational equilibria, that is, whether the axial 4-aryl chair (55A) or equatorial 4-aryl chair (55B) is the preferred conformation (see Scheme 34)



(55)

R = Me ; *n*-Pr ; *i*-Bu

Ar = m̲ - OMe (OH). C_6H_4



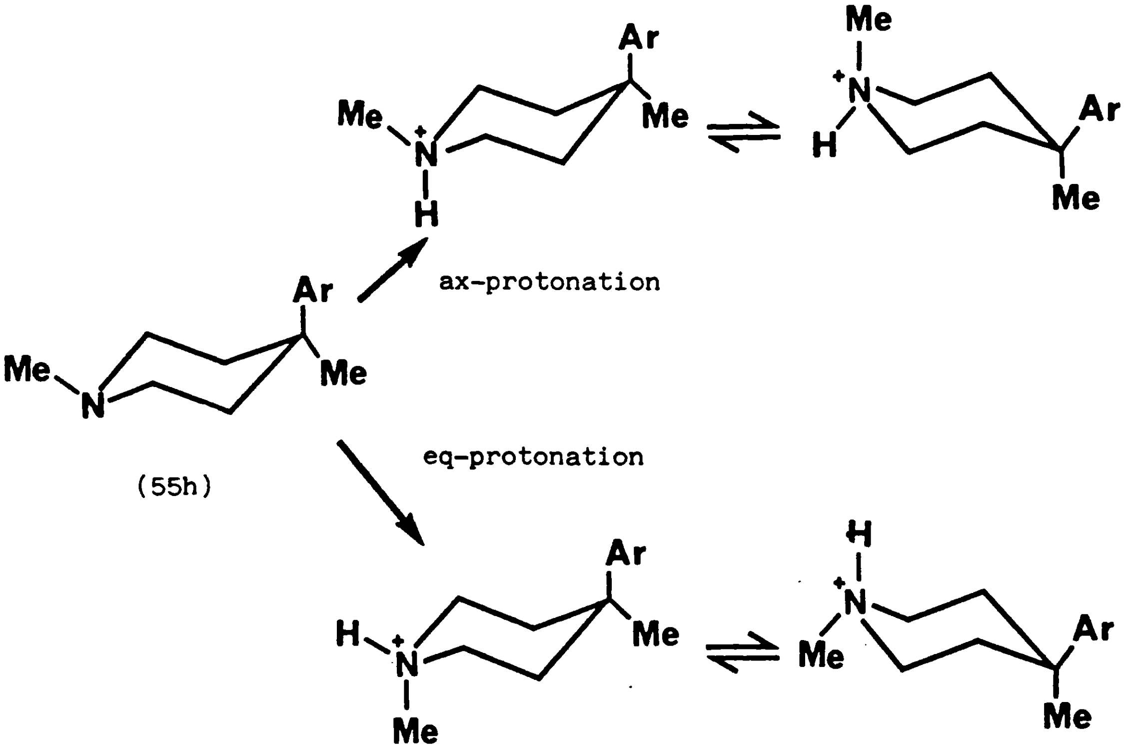
(55A) (55B)

Scheme 34

However, the question of special interest is that of protonated salts as solutes in water (or deuterium oxide).

In bases, because ring inversion and nitrogen inversion rates are rapid, the NMR data reflect that of an averaged conformation.

On the other hand, in salts the proton exchange rates at nitrogen are slow on the NMR time scale and as a result signals due to separate protonated epimers may be resolvable if the two species are significantly populated. In such cases chair-chair interconversions of each epimer need to be considered (Scheme 35).



Scheme 35

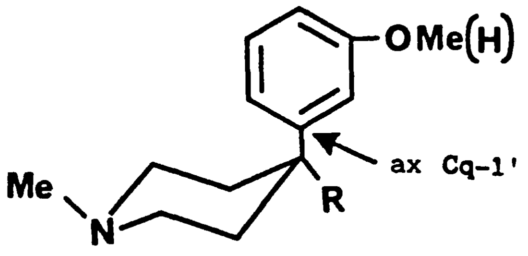
(Epimer equilibrium by assuming the base conformation 55A to be preferred)

Such proved to be the case for the hydrochloride salt of derivative (55h) examined as solute in D_2O, and so it was possible to compare the NMR parameters of the two epimers.

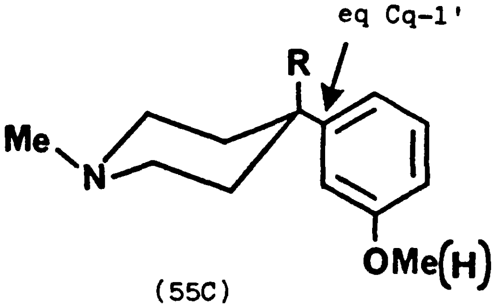
The following factors were utilised in making assignments for the conformational features of the epimers.

1. The aromatic Cq-1' ^{13}C resonance

In the axial 4-aryl conformer (55A) the Cq-1' is higher field than that of the equatorial conformer (55C) because it is the more sterically compressed of the two carbons and hence subject to steric polarization, a phenomenon which is well documented.[61]



(55A)

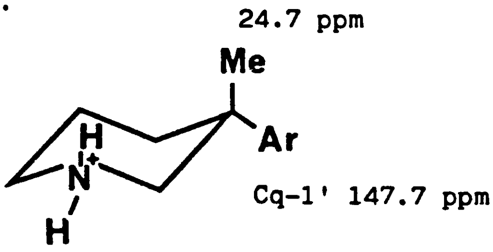


(55C)

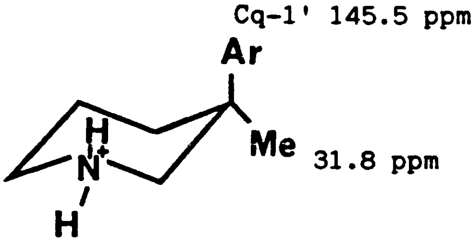
2. The 4-R ^{13}C chemical shift (especially for R=Me)

Independent work on 3-aryl-3-methylpiperidine derivatives[80] has established chemical shift ranges for axial/equatorial methyl resonances (as the HCl)

e.g.



eq 3-Ar chair

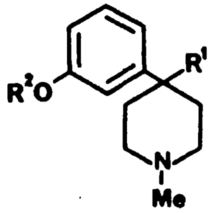


axial 3-Ar chair

The range 23.2-25.8 ppm is associated with axial 3-Me and 30.5-31.8 ppm with equatorial 3-Me for hydrochloride salts in $CDCl_3$ and D_2O (values will be a few ppm to lower field in corresponding bases, due to the removal of the N-protonated effect which is generally a shielding influence).

3. Various ^1H NMR parameters as will be discussed individually for the 4-Me, n-Pr and iso-Bu compounds.

Table 9. ^{13}C NMR of Some 4-Alkyl-4-arylpiperidines[a]

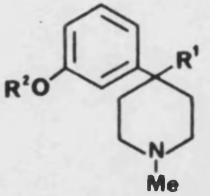


(55)

Compound/Solvent	R^1	R^2	^{13}C Chemical Shifts in ppm from TMS								
			C-(2,6)	C-(3,5)	C-4	4-R^1		N-Me	OMe	Cq-1' (Ar)	Cq-3' (Ar)
						α-and β -$\underline{C}$	Me(Me)$_2$				
55h; HCl in D_2O	Me	H	51.6 (50.8)	33.7 (33.6)	35.3	—	Me: 32.3 (23.4)	42.7 (42.6)	-	145.9 (151.1)	156.1 (155.7)
55ℓ; base in $CDCl_3$	$\overset{\alpha}{CH_2}\overset{\beta}{CH_2}CH_3$	H	52.0	34.8	39.0	α-CH_2: 34.8 or 52 β-CH_2: 16.6	Me: 14.5	45.7	-	147.1	157.8
55ℓ: HCl in D_2O	$CH_2CH_2CH_3$	H	51.3 (50.1)	32.3 (31.3)	36.4 (36.7)	α-CH_2: 46.9 (34.7) β-CH_2: 15.9 (16.1)	Me: 13.5	42.6 (42.1)	-	143.5 (148.5)	155.9 (155.5)
55z: HCl in D_2O	$\overset{\alpha}{CH_2}\overset{\beta}{C}H(Me)_2$	Me	51.0 (53.8)	33.1 (32.2)	38.8 (37)	α-CH_2: 50.0 (43.7) β-CH: 24	Me_2: 24.1 (23.0)	42.6 (42.1)	55.0	143.6	159.3
55z; HCl in D_2O	$CH_2CH(Me)_2$	H	51.0 (53.7)	33.0 (32.1)	38.7 (36.8)	α-CH_2: 50.1 (43.6) β-CH: 23.5 (23.0)	Me_2: 24.06 (23.8)	42.7 (42.1)	-	143.3 (148.4)	156.0 (155.5)
55z; base in $CDCl_3$	$CH_2CH(Me)_2$	H	51.9	35.5	39.3	α-CH_2: 51.9 β-CH: 23.8	Me_2: 24.9	45.7	-	148	157.2

a. Data in parentheses refer to the minor epimer.

Table 10. ^{1}H NMR (δ scale in ppm) characteristics of some 4-Alkyl-4-arylpiperidines



(55)

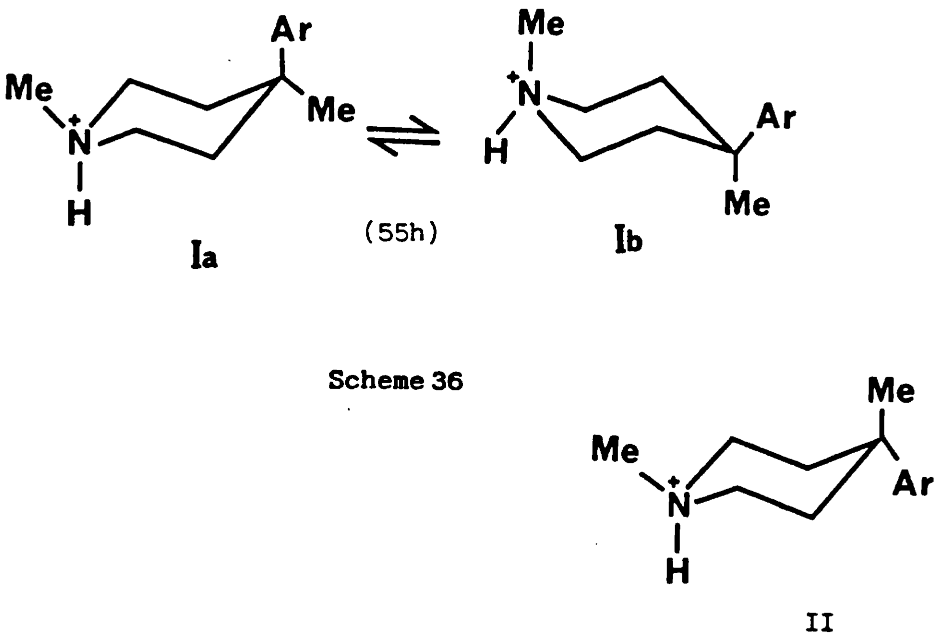
Compound/ Solvent	R^2	R^1	H(2,6)	H(3,5)	N-Me	4-R'		OMe	Ar-H
						α-$C\underline{H}_2$; β-$C\underline{H}_2(C\underline{H})$	Me;$(Me)_2$		
55h, HCl in D_2O	H	Me	eq: 3.36 brd; 13 (3.43 brd; 13.0) ax: 2.80 dt; 13; 13.5; 1.5 (3.27 dt; 13, 13, 3)	eq: 2.56 brd; 14.1 (2.12 brd, 14) ax: 1.89 dt; 14 14, 3 (2.03 dt; 13.6, 13.6, 4)	2.67s (2.88s)	-	Me: 1.19s (1.32 s)	-	5'-H: 7.31 t; 7.8, 2',4' and 6'-H[b]
55ℓ, HCl in D_2O	H	$\overset{\alpha}{CH_2}\overset{\beta}{CH_2}Me$	eq: 3.35 brd; 12.5 (3.42 brd; 12.5) ax: 2.69 brt; (3.24 brt; 13, 13)	eq: 2.48 brd, 14.8 (2.18 brd, 15) ax: 1.81 dt; 14.3, 14.3, 2.5	2.63s (2.89s)	α -CH_2: 1.33 m(1.62m) β-CH_2: 0.8 m[b]	Me: 0.53 t; 7.7 (0.61 t, 7.7)	-	5'-H: 7.19 t; 7.7,7.7 (7.10 t; 8.8) 2',4',6'-H: 6.73-6.8m 4'-H: (6.7 dd; 8.2)
55z; HCl in D_2O	Me	$\overset{\alpha}{CH_2}\overset{\beta}{CH}(Me)_2$	eq: 3.43 brd;12.5 ax: 2.78 brt; 12.5, 12.5 (3.43 brt; 12.5, 12.5)	eq: 2.56 brd; 14.6 (2.26 brd; 14.5) ax: 1.95 brt; 14.4, 14.4 (2.04 brt)	2.71s (2.96s)[d]	α-CH_2: 1.42 d; 4.9 (1.71 brm) β-CH: 1.29 m	Me_2: 0.49 d; 6.4 (0.56 brd)	3.76s (3.70s)	5'-H: 7.29 t; 7.9, 7.9 (7.15 brt) 6'-H: 6.92 d; 7.6; 2'-H: 6.88 brs 4'-H: 6.82 d; 7.9 (6.68 brd)
55z, HCl in D_2O	H	$CH_2CH(Me)_2$	eq: 3.37 brd;12.5 (3.43 brd; 12.5) ax: 2.75 brt; 12.5, 12.5 (3.26 brt; 12.5, 12.5)	eq: 2.53 brd; 14.6 (2.21 brd; 14.9) ax: 1.88 dt; 14.2, 14.2, 4) (1.91 dt; 14.2, 14.2, 4)	2.675 (2.91s)	α-CH_2: 1.38 d; 5.5 (1.68d; 5.5) β-CH: 1.20 m	Me_2: 0.49 d; 6.7 (0.54 d, 6.7)	-	5'-H: 7.19 t; 7.9,7.9 (7.10 t; 7.9,7.9) 2'-H: 6.83 brs 4',6'-H: 6.80-6.75 m 4'-H: (6.68 brd)

a. Chemical shifts in ppm from TMS (external TMS in D_2O) followed by multiplicity and line separations of signal (J in Hz); data in parentheses refer to the minor epimer. Abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; plus combinations such as dt, doublet of triplets; br, broad; nr, near; eq, equatorial; ax, axial.

b. Major and minor signals overlap c. Epimer ratio 2.2:1 d. Epimer ratio 2.85:1 e. Epimer ratio 3.26: 1

A. 4-Aryl-1,4-dimethylpiperidine

Both ^{1}H and ^{13}C spectra of (55h; Ar=$\underline{m}$-OH(OMe).C_6H_4)HCl displayed duplicated signals typical of an epimeric mixture. The higher field Cq-1' ^{13}C chemical shift had the greater intensity, evidence that epimer (I; Scheme 36) predominates over the equatorial 4-aryl chair (II).



Scheme 36

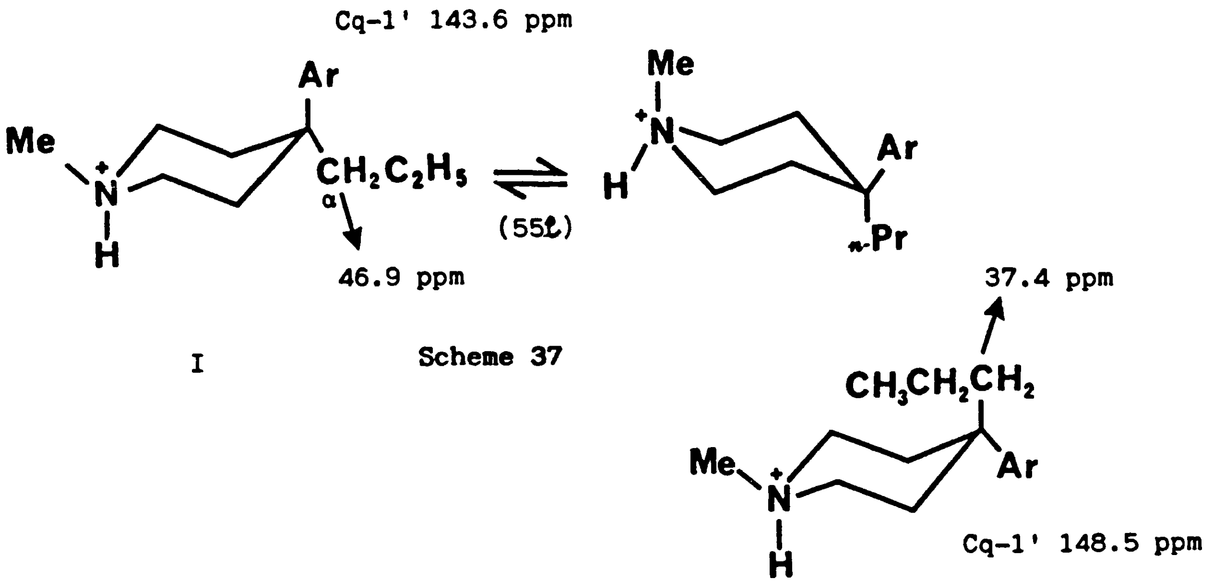
This conclusion was supported by the 4-Me ^{13}C chemical shifts: the more intense lower field signal (32.3 ppm) assigned to 4-Me of (I), which receives a major contribution from an equatorial 4-Me conformer (Ia), and the less intense higher field resonance (23.8 ppm) to the more sterically polarized axial methyl of epimer (II).

Details of duplication of ^{1}H NMR signals of (55h; Ar=*m*-OH.C_6H_4; HCl in D_2O) are shown in Table 10. The major epimer had the higher field *N*-methyl resonance [moved upfield by the contribution from the axial *N*-methyl conformer Ib], axial 2,6-*H* signals (these protons are subject to aromatic shielding in conformation Ia), and axial 3,5-*H* signals (protons deshielded by axial 4-Me in epimer II).[144,145] Similar NMR results were found for the HCl of the OMe derivative with the addition of duplicate OMe proton signals (3.81 and 3.80 ppm). These results agree with the computations of Froimowicz.[93] The epimeric ratio is judged to be about 2.2:1 in favour of the axial 4-aryl chair from integration of the ^{1}H *N*-Me and 4-Me signals.

B. 4-Aryl-1-methyl-4-n-propylpiperidine

^{1}H and ^{13}C NMR spectra of (55ℓ; HCl in D_2O) gave evidence of the presence of epimeric conjugate acids, which was indicated by duplication of signals. The epimeric ratio was calculated to be 2.85:1 from integration of ^{1}H *N*-Me signals.

Following a similar procedure to that employed to deduce the conformation of the 4-Me derivative, evidence that axial 4-Ar chair of (55ℓ; I; Scheme 37) predominates over the minor equatorial 4-Ar chair epimer (II) was obtained by examining the Cq-1' and α-CH_2 (of 4-*n*-Pr) ^{13}C chemical shifts (see Table 9 for ^{13}C NMR results).



I

Scheme 37

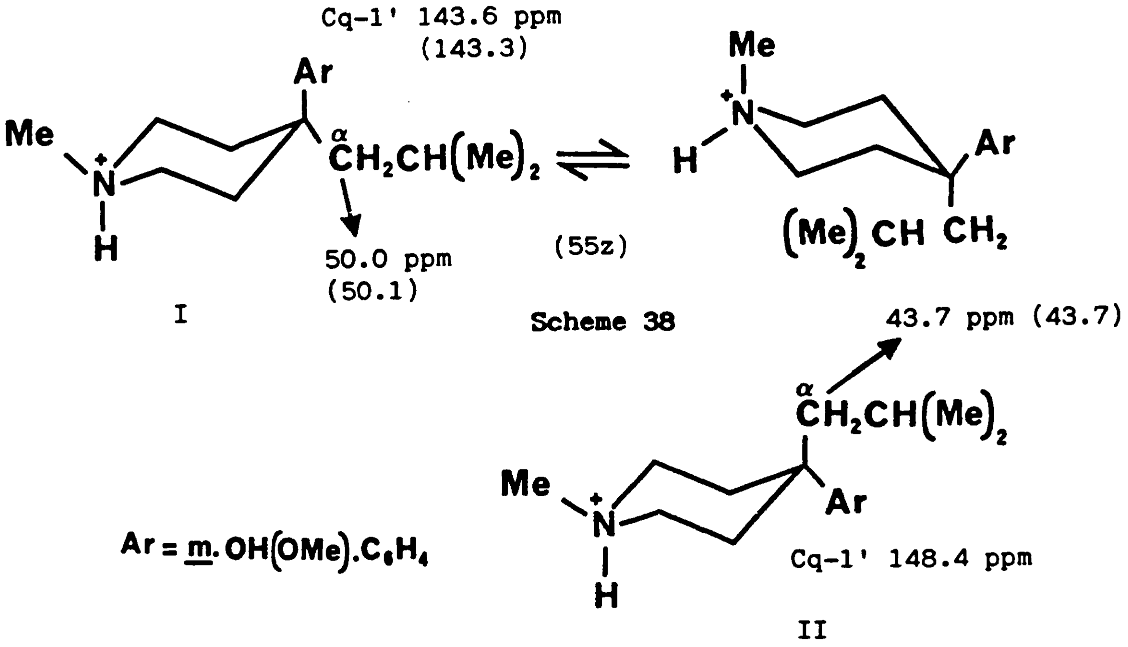
II

This conclusion was supported by analysis of the ^{1}H chemical shifts of N-Me, axial 2,6-H and axial 3,5-H (see Table 10).

C. 4-Aryl-1-methyl-4-(2-methylprop-1-yl)piperidine

Duplication of signals was observed in the ^{1}H and ^{13}C NMR spectra of (55z; Ar=m-OMe(OH).C_6H_4) as the HCl salt in D_2O, evidence of the presence of an epimeric mixture. The epimeric ratio was about 3.26:1 as calculated before.

Likewise, the axial 4-aryl chair (I; Scheme 38) was deduced as the major epimer and the equatorial 4-aryl chair as the minor one (II).

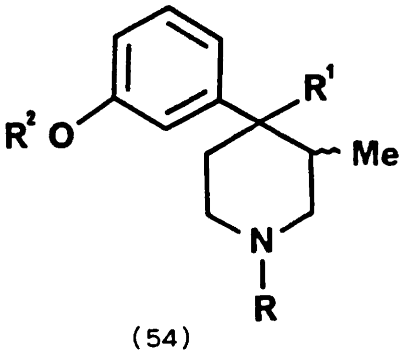


Scheme 38

N-Me, axial 2,6-H and axial 3,5-H ^{1}H resonances (see Table 10 for details of signals duplication) supported this deduction.

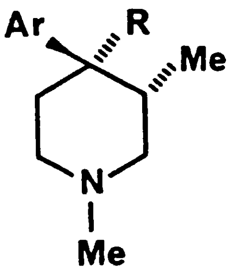
2.3.3.2 The 3-Me series

In these analogues the major isomer with relative configuration *c*-3-Me/4-Ar is designated *α*- and the minor component *β*: *t*-3-Me/4-Ar, with the exception of the 4-isoBu analogues, where the minor isomer was found to have a *cis* relationship and the major isomer a *trans* relationship.

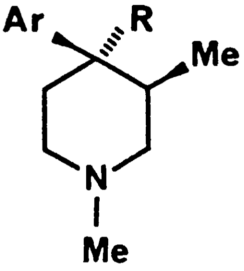


(54)

R^1 = Me ; *n*-Pr ; *i*-Bu
R = Me
R^2 = Me ; H



β: *t*-3-Me/4-Ar



α: *c*-3-Me/4-Ar

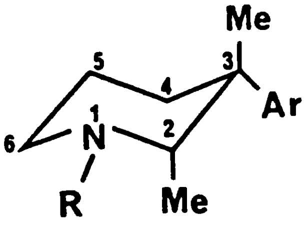
In the following discussion it will be useful to note that the numbering system being applied places emphasis on relative stereochemistry rather than whether the compound is the methyl ether or phenol. For example, the 4-methyl compound is designated (54a) in the β-isomer, and (54b) in the α-isomer, and the specific agent (ether or phenol) under discussion will be highlighted in the relevant tables and sections of the text.

Problems of configuration and preferred conformation

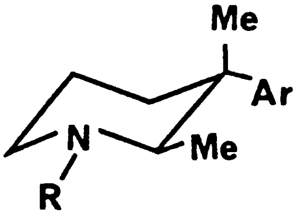
Key NMR parameters for these stereochemical assignments are as follows:

1. The ^{13}C chemical shift of Cq-1' (as discussed before)
2. The ^{13}C chemical shift of 4-R $\left[R=4\text{-}Me;\ 4\text{-}\underline{C}H_2Et;\ 4\text{-}\underline{C}H_2CH(Me)_2\right]$

Although the same arguments as discussed before obtain, chemical shifts will also be influenced by the orientation of the 3-Me group. Appropriate reference data relate to isomeric 2,3-dimethyl-3-arylpiperidines.[80] Isomeric pairs of such derivatives were all found to prefer an equatorial 4-aryl chair conformation and to differ in regard to the orientation of the 3-methyl substituent.



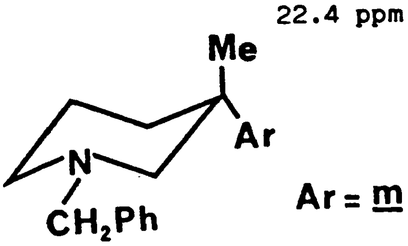
α: c-2-Me/3-Ar



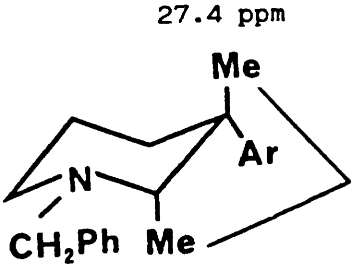
β: t-2-Me/3-Ar

The range 27.2-28.1 ppm is associated with axial 3-Me and 17.0-20.3 ppm with equatorial 3-Me (in the base). One example to illustrate this is the comparison between the isomeric N-benzyl triad of derivatives shown below.

Des 2-Me

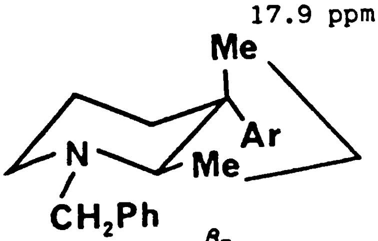


Ar = m-OMe.C_6H_4



deshielding

α-

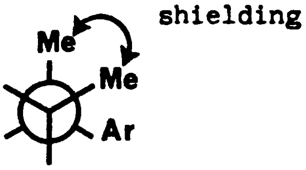


shielding

β-

Explanation of the 3-Me shift variations

The 3-Me chemical shift of the des 2-Me derivative is close to the previously quoted range (see p. 131) for axial Me. When 2-Me is axially oriented (α) and bears an anti-relationship to axial 3-Me, mutual deshielding obtains and the 3-Me chemical shift moves to lower field.[79] On the other hand, when 2-Me is equatorial (β) the two methyl groups sterically compress each other (γ-shielding) and the 3-methyl chemical shift moves to higher field.

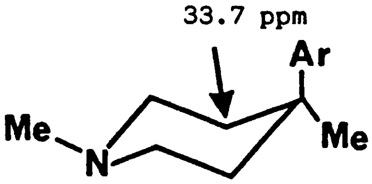


γ-shielding

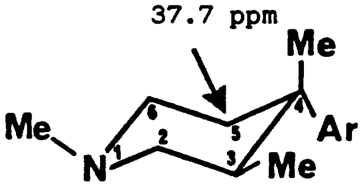
When comparisons are made amongst HCl salts, allowance should be made for the overall shielding influence of protonated nitrogen.

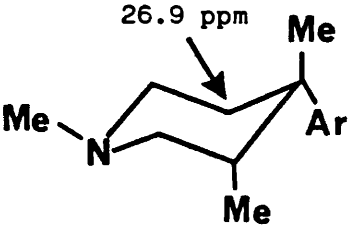
3. The C-5 ^{13}C chemical shift

Again (see p. 64) in a series such as (54a) and (54b), the C-5 chemical shift provides evidence of the orientation of 3-Me. Values for the des-methyl (55h) and equatorial 3-Me derivative (54a) should be similar, while that of the axial 3-Me member should be distinctly to higher field of the previous two because of the steric compression produced by axial 3-Me.[119,120]



(55h)





(54a)

(54b)

4. Various ^{1}H NMR parameters

Of most direct value will be knowledge of the multiplet separations of the 3-H resonance revealed after spin decoupling of the 3-Me proton. Thus, evidence from the vicinal coupling constant (^{3}J) of the 3-H is necessary to confirm the stereochemistry of the 3-Me group.

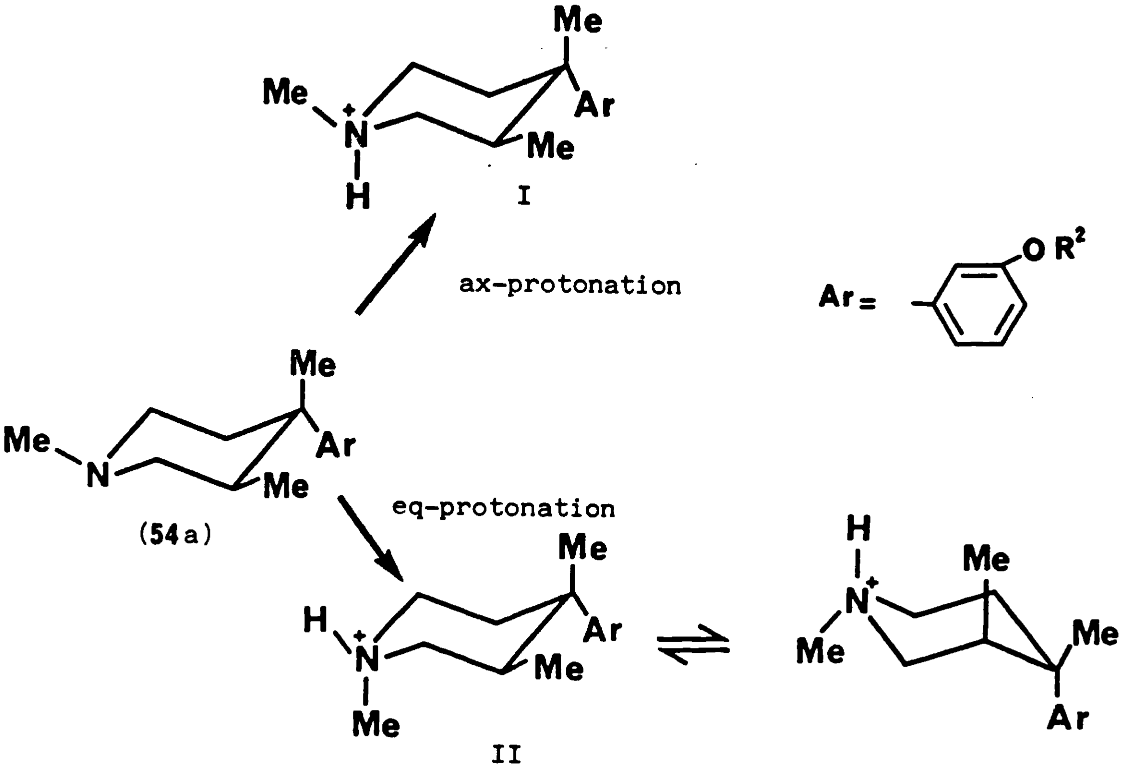
In a six-membered ring chair system the order of magnitude of diaxial (J_{aa}), axial-equatorial (J_{ae}) and diequatorial (J_{ee}) coupling constants in the ^{1}H NMR spectrum can be predicted from the angular relationships of the protons by application of Karplus relationship.[146] ^{3}J Values are therefore largest when the vicinal protons are *trans*-coplanar (dihedral angle (θ) = 180°), slightly less when they are cis-coplanar ($\theta = 0$), and almost zero when the protons are at right angles. Thus, J_{aa} values generally fall within 8-14 Hz, while J_{ae} and J_{ee} values fall within 1-6 Hz.[147]

Other ^{1}H NMR features will be advanced in evidence of stereochemistry later.

5. Existence of protonated epimeric pairs both of significant population

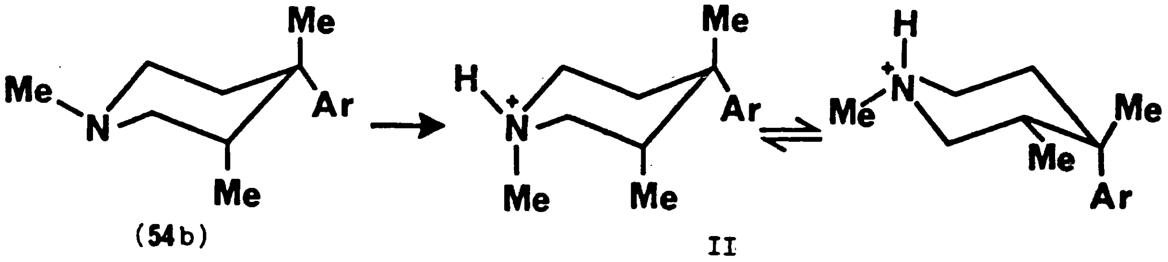
When this situation arises, duplication of ^{13}C and ^{1}H resonances will be observed.

Derivatives of configuration (54a) are expected to give the protonated species (I, Scheme 39) exclusively, since the alternative epimer (II) can only relieve non-bonded interaction of axial N-Me by conversion to an invertomer that carries two bulky axial substituents (see Scheme 39).



Scheme 39

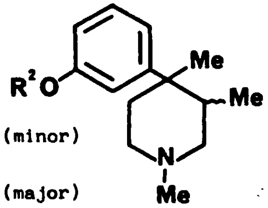
On the other hand, of the two possible epimers of derivative of configuration (54b) the equatorially protonated form may relieve diaxial methyl interactions by inversion to a conformer with a reduced number of axial substituents (see Scheme 40).



Scheme 40

When the 4-R substituent is of a bulk greater than that of methyl, these arguments require modification (see p. 164).

Table 11. ^{13}C NMR of α- and β-4-Aryl-1,3,4-TrimethylPiperidine and Related Compound



54a: t-3-Me/4-Ar (minor)

54b: c-3-Me/4-Ar (major)

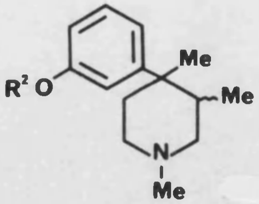
^{13}C Chemical shifts in ppm from TMS

Compound/Solvent	R^2	C-2	C-3	C-4	C-5	C-6	C3-Me	C4-Me	N-Me	Cq-1'(Ar)	Cq-3'(Ar)	OMe	Other Ar carbons
54b; base in $CDCl_3$	Me	58.4	38.7	37.9	30.6	52.1	16.3	27.3	46.5	151.8	159.4	54.8	128.8; 118.1; 112.3; 109.6
54b; HCl in D_2O	Me	56.0	36.1	36.6	26.9	50.4	14.04	25.7	43.4	149.4	158.9	54.9	129.4; 118.4; 117.7; 112.1
54b; base in $CDCl_3$	H	58.4	38.7	37.7	30.6	52.0	16.0	27.3	46.2	151.0	156.4	-	128.8; 117.2; 112.9; 112.2
54b; HCl in D_2O	H	56.2	36.0	36.4	27.7	50.6	13.6	25.4	43.2	149.7	155.4	-	129.7; 117.2; 112.8; 112.2
54a; HCl in D_2O	H	55.8	36.4	36.6	37.7	50.8	11.7	14.0	42.9	149.0	155.4	-	129.7; 117.9; 113.2; 113.0
54b; MeI in $CDCl_3$+DMSO-d_6	Me	64.2	35.5	37.5	31.7 br	59.3	14.1	28.7	eq: 54.9br ax: 50.2br	143.5	158.7	54.4	128.7; 118.5; 113.2; 110.1
75; HCl in D_2O (Ar= C_6H_5)	-	56.6	36.2	36.7	26.9	50.9	14.0	25.9	43.5	147.8	-	-	128.70; 126.4; 125.4
LY 109836 HCl in D_2O (Ar = C_6H_5)	-	56.7	36.4	36.8	27.1	51.0	14.2	26.0	43.5	148	-	-	128.8; 128.6 126.5; 125.5

Table 12. ^{1}H NMR (δ scale in ppm) Characteristics of α- and β-4-Aryl-1,3,4,-trimethylpiperidine and Related Compounds[a]

54a: t-3-Me/4-Ar

54b: c-3-Me/4-Ar



Compound/ solvent	R^2	2-H	3-H	5-H	6-H	3-Me	4-Me	N-Me	Other protons
54b(α), base in $CDCl_3$	Me	m	m	eq: 1.6 brd	m	0.79d; 7.1	1.30s	2.27s	OCH_3: 3.78s; 5'-H: 7.22t; 6'-H: 6.9dt; 2'-H: 6.85t; 4'-H: 6.7dd OCH_3: 3.78s[b]
56b(α), HCl in 1. $CDCl_3$	Me	m	eq: 2.3 m[c] (ax: 2.7m)[d]	m	m	1.25d, 7 (1.05d)	1.45s (1.42)	2.9d; (2.7)	2xCH_3: 3.8s; 2xNH: 11.5 and I2.4 Ar-H[e]
2. D_2O		m	m	eq: 1.74brd; 14	m	0.65d, 7.3	1.26s		OCH_3: 3.63s
54b(α) MeI in $CDCl_3$ and DMSO-d_6	Me	m	2.05m[f]	ax: 0.75brt	m	0.73d, 7	1.08s	3.12, 2.99s	OCH_3: 3.395; 5'-H: 6.88t; 6'-H: 6.52dd; 2'-H; 6.43t; 4'-H: 6.39dd
54b(α); HCl in D_2O	H	m	2.35m[g]	eq: 1.9brd; 15	m	0.69d; 7.3	1.34s (1.31)	2.85s (2.7s)	5'-H: 7.24t;6'-H: 6.87brd; 2'-H: 6.79t; 4'-H: 6.73dd[e]
54b(α); base in $CDCl_3$	H	m	2.00m	m	m	0.79d; 7.1	1.31s	2.28s	5'-H: 7.13t; 6'-2'/H: 6.78; 4'-H: 6.65dt
54a(β); base in D_2O	H	ax: 3.01t; 12.6;12.6 eq: 3.16-3.45m	m 2.42[h]	eq: 1.66dt; 15;2;2 ax: 2.08dt;15;15;6	ax: 3.20t; 13,13,3	0.59d; 6.7	1.29s	2.88s	5'-H: 7.26t; 6'-H: 7.0brd 2'-H: 6.93t; 4'-H: 6.77dd
54a(β); base in $CDCl_3$[j]	Me	m	m	eq: 1.42dt (1.52)	m	0.51d; 6.7 (0.71d; 7)	1.165s (1.27)	2.24s (2.19s)	5'-H: 7.15t;6'-H: 6.95brd; (6.82); 2'-H: 6.92t (6.76); 4'-H: 6.65dd(6.63)[b]
LY 109836; HCl in D_2O (Ar=C_6H_5)	-	ax: 3.48-3.6m eq: 3.28-3.4m	2.4-2.52m[k]	eq: 1.99brd; 14.5 ax: 2.4-2.52m	ax: 3.48-3.6m eq: 3.28-3.4m	0.71d;7.3 0.63d; 7.1	1.41 (1.38)	2.88 (2.78)	Ar-H: 7.25-7.55m
75; HCl in D_{20} (Ar=C_6H_5)	-	ax: 3.45-3.6m eq: 3.25-3.4m	2.35-2.5m	eq: 1.99brd; 14.7	ax: 3.45-3.6m eq: 3.25-3.4m	0.73d; 7.3	1.41 (1.37)	2.91 (2.753)	Ar-H: 7.25-7.55m

Footnotes to Table 12

a. Footnote a from Table 10 (p.133) applies

b. Approximate resonances for Ar-2',4' and 6'-H

c. Identified by 2D.COSY plot and resolved into broad singlet when irradiated the C3-Me doublet at 1.05 ppm.

d. Identified by 2D.COSY plot and resolved into broad singlet when irradiated the C3-Me doublet at 1.25 ppm.

e. In addition to Ar-H signals for the minor epimer.

f. 2 proton multiplet. Forms a broad singlet when irradiated the C3-Me doublet at 0.73 ppm.

g. 2 proton multiplet. Forms a broad singlet when irradiated the C3-Me doublet at 0.69 ppm.

h. Identified by 2D.COSY plot and forms a dd when irradiated the C3-Me doublet at 0.59 ppm.

j. A spectrum of mainly the minor isomer with a trace of the major isomer; data in parenthesis refer to the major isomer (less intense than those of the minor isomer).

k. Identified by 2D.COSY plot and resolved into broad singlet when irradiated the C3-Me doublet at 0.71 ppm.

m. Unresolved signal.

Separation of isomers of 3-methyl-4-alkylpiperidines prepared

The major isomers (4-R=Me and iso-Bu) were separated by fractional crystallisation of the hydrochloride salts, while the minor isomers, which were separated along with a trace of major isomer, were later purified and characterised as the corresponding free phenols (see Scheme 29; p.119). Similarly, major 4-n-Pr was separated from the isomeric mixture as the oxalate salt, while the minor isomer was purified and characterised as the corresponding free phenol (HCl).

I. 3,4-Dimethyl Analogues

^{13}C NMR Analysis

1. Cq-1'

The ^{13}C NMR chemical shifts of Cq-1' of all derivatives (major: R^2=OMe(H); minor: R^2=H; free bases) fell in the range 149-149.7 ppm, an indication of a common equatorial 4-Ar chair conformation (the range 147.4-150.6 ppm is associated with equatorial Ar chair; see p. 138).

2. 4-Me

The 4-Me chemical shifts of major derivatives (bases and HCl salts) fell in the range 25.4-27.3 ppm, lower field than that of 4-Me of the minor phenolic HCl value of 14.0 ppm. These results support a 3,4-diaxial methyl relationship of the major, and a 3-equatorial/4-axial one for the minor isomeric series.

3. C5

Further evidence for the orientation of 3-Me was provided by the C-5 chemical shift. The upfield C-5 chemical shift of the major derivative (R^2 = Me: 29.9 ppm; R^2 = H: 26.7 ppm) compared to downfield (R^2=H: 37.7 ppm) in the minor, gave evidence that the 3-Me group is axially oriented in the major and equatorially in the minor (diastereoisomers).

^{1}H NMR Analysis

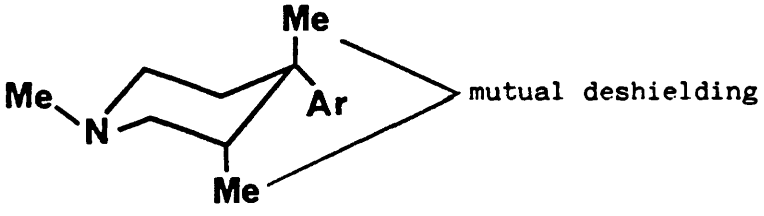
Proof that the C3-Me group has an axial orientation in the major isomer and an equatorial orientation in the minor isomer was provided by examination of the C3-H resonance after spin decoupling the C3-Me doublet.

The ^{1}H NMR spectrum of (54b; R^2=Me; HCl in $CDCl_3$), unlike that in D_2O, was characteristic of an epimeric mixture. Spin decoupling of the C3-Me doublets of the major isomer at 1.05 ppm (R^2=H; HCl in $CDCl_3$) and 0.69 ppm (R^2=H; HCl in D_2O) resolved the C3-$\underline{H}$ resonances into broad singlets. Therefore, the C3-H is equatorially oriented and hence the C3-Me must be axial. On the other hand, spin decoupling of the C3-Me doublet of the minor isomer which gave one protonated epimer (54a; R^2=H; HCl in D_2O) at 0.59 ppm resolved the C3-H resonance into a doublet of doublets with ^2J = 3.5 and 13.6 Hz. These two ^2J values are typically those of an axial-equatorial and an axial-axial coupled proton respectively. Thus, the C3-H is axially oriented and hence the C3-Me is equatorial.

Further ^{1}H NMR evidence

1. 3-Me/4-Me shifts

The down field resonances of both 3-Me and 4-Me (of both HCl salt and free base) in the major isomer relative to the corresponding signals of the minor isomer support the stereochemistry (54b) for the major isomer.

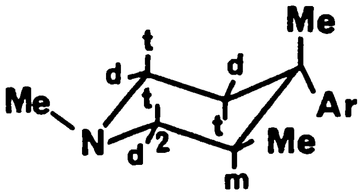


(54b)

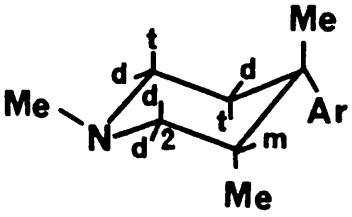
2. Ring protons of phenolic isomeric pair (HCl)

Each isomer possesses seven ring protons. The ^{1}H NMR spectrum of the major isomer displayed 3 groups of 2 protons and one resolved one proton signal, identified as 4 doublets, two triplets and one multiplet. That of the minor isomer displayed one overlapping group of 2 protons and 5 resolved one proton signals, identified as 3 doublets, 3 triplets and one multiplet (see 54b and 54a) in support of the stereochemistry already made. Differences between the 2-H resonances are of steric significance; the major resonance appeared as a broad doublet within multiplet at

3.4-3.55 ppm (or 3.2-3.35 ppm), while that of the minor isomer appeared as a triplet at 3.2 ppm (13, 13, 3 Hz). A triplet for axial 2-H may only arise if the stereochemistry is as shown (54a) because the axial 2-H proton is subject to two large couplings (^{2}J to eq 2-H) and (^{3}J to ax 3-H)). In the major isomer the axial 2-H signal is subject only to one large coupling (^{2}J to eq 2-H) and is lower field than ax 2-H in the minor isomer because it is deshielded by ax 3-Me.[148]



(54a)



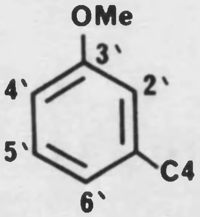
(54b)

3. Ar-Pattern

It is of interest and may be of stereochemical significance that the aromatic signals of the major isomer (54b) are higher field than the corresponding signals of the minor isomer (54a; see Table 13 and Fig. 5).

These differences might arise as a result of the different influence of axial and equatorial 3-Me on the preferred orientations of the piperidine and 4-aryl rings (see also p. 162).

Table 13. Characteristic ^{1}H (δ scale in ppm) Ar-pattern of (54b) and (54a)



Compound/	5't		6'brd		2't (narrow)		4'dd	
Solvent	Low(L)	High(H)	L	H	L	H	L	H
54b, base in CDCl$_3$ (major)	7.22 (8.8 Hz)			6.88 (7.8 Hz)		6.83 (2.3, 2.3 Hz)		6.71 (8.2 Hz)
54a, base[a] in CDCl$_3$ (minor)		7.15 (7.9; 7.9 Hz)	6.95 (7.9, 7.9 Hz)	6.82[b]	6.92 (2.4, 2.4 Hz)	6.72[b]	6.65 (1.8, 7.9 Hz)	below 6.65[b]

a. A spectrum of mainly the minor isomer with a trace of the major.

b. A less intense signal corresponding to the major isomer from the mixture described in footnote a.

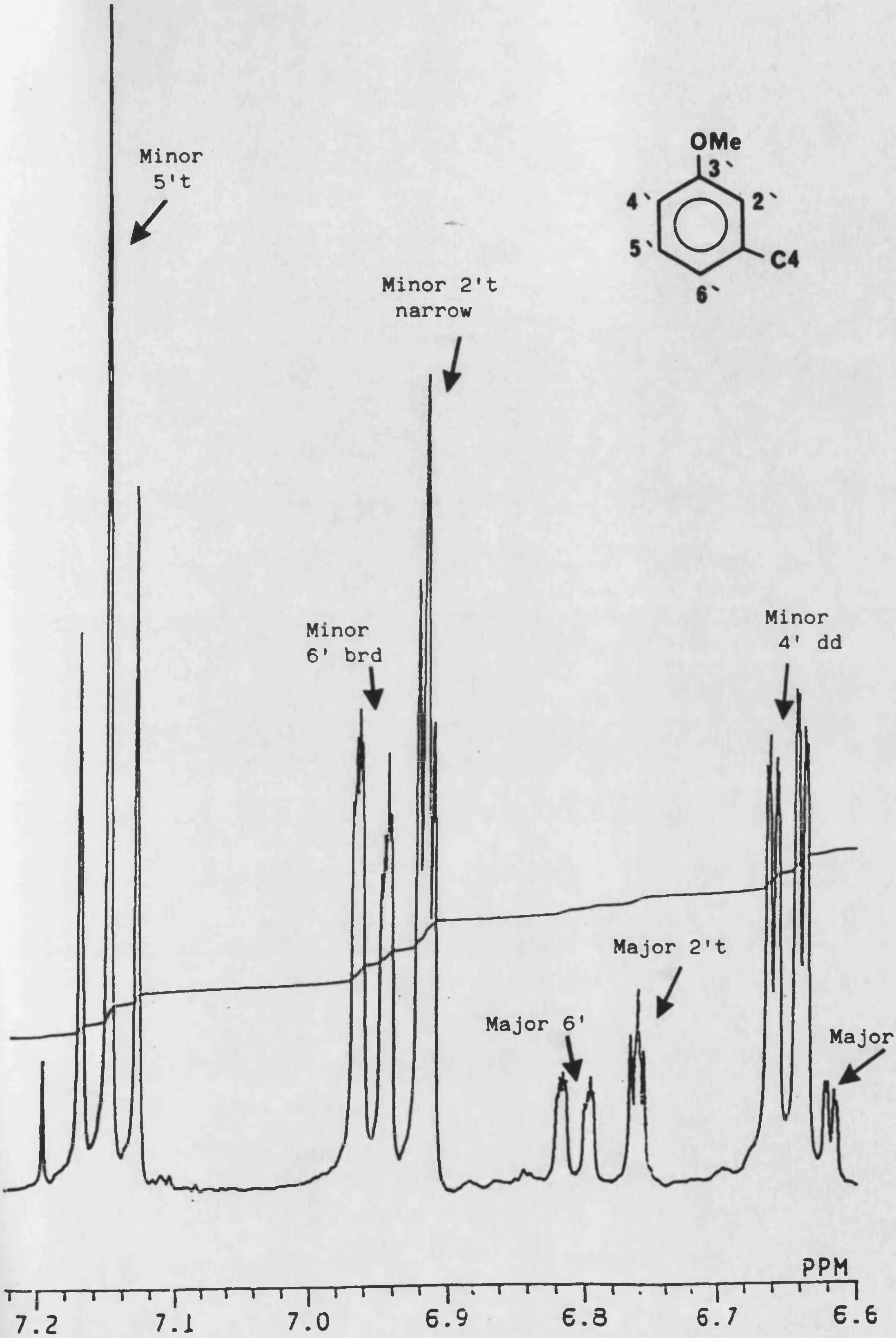


Fig. 5. Partial ^{1}H NMR spectrum (at 270 MHz) of the minor isomer (54a) with a trace of the major isomer (54b) to illustrate the aromatic chemical shift differences between isomeric analogues of 4-aryl-1,3,4-trimethylpiperidine

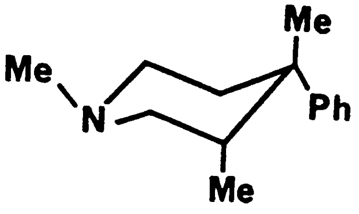
4. Epimers

The ^{1}H NMR spectra of the major isomer (54b; R^2=Me as the HCl in $CDCl_3$ and R^2=H; HCl in D_2O) indicated the presence of epimeric pairs, with both members of significant population (epimer ratio 2:3 in $CDCl_3$, but much greater in D_2O) evidence that one epimer prefers an axial, and the other an equatorial-3-methyl conformation (see p. 143).

The ^{1}H NMR spectrum of the minor isomer (54a; R^2=H; HCl in D_2O) indicated the presence of only a single protonated epimer in support of the configuration already deduced.

The stereochemistry of 1,3,4-trimethyl-4-phenylpiperidine

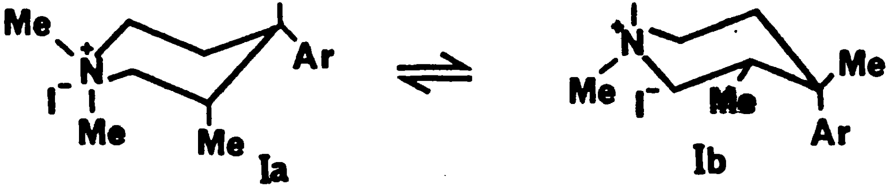
Only one isomer of (75) was isolated. Its NMR features were similar to those of a single isomer form of LY 109836 provided by Dr Dennis Zimmerman. It was deduced from ^{13}C chemical shifts of Cq-1', 4-Me and C-5 that these materials had the same configuration as in the major 4-aryl-3,4-dimethyl analogues (see Tables 11 and 12 for ^{13}C NMR and ^{1}H NMR results).



(75)

The stereochemistry of the methiodide salt of (54b)

The methiodide of the major 3-methyl isomer (54b) was also examined. Its ^{1}H and ^{13}C NMR spectra provided support for the <u>cis</u> 3-Me/4-Ar configuration (Ia) but indicated that the axial 4-aryl chair (Ib) was the preferred conformation.

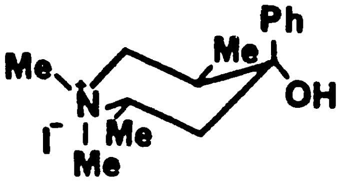


(54b) methiodide

The evidence is as follows:

1. The Cq-1' ^{13}C chemical shift at 143.5 ppm is diagnostic of an axially placed Ar group. A good reference is the Cq-1' chemical shift of the methiodide of α-promedol, which was found to prefer an axial 4-Ph chair conformation.[133]

Cq-1' 142.8 ppm

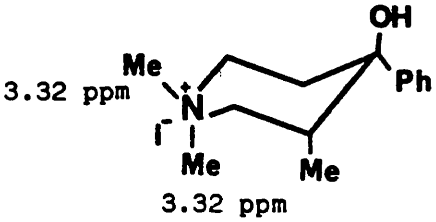


α-Promedol methiodide

2. The C-5 ^{13}C chemical shift at 31.7 ppm is close to values found for C-5 in the des-3-methyl methiodide (30.1 ppm). Thus, C-5 is not subject to steric polarization by 3-Me which implies that the latter is equatorially oriented.

3. The ^{1}H N-Me signals (3.12; 3.05 ppm) have chemical shifts close to values observed for des 3-methyl analogues. For example, N-Me signals of the des-3-Me (4Me) analogue resonate at δ3.20 and 3.02 ppm, and those of the des 3-Me (4-isoBu) at 3.18 and 3.02 ppm. These results indicate that the N-Me protons of the methiodide salt of (54b) are little influenced by the 3-Me substituent. If 3-Me were axial, then the two N-Me shifts would be closely placed, as

found for the methiodide of β-prodinol, shown to prefer an equatorial 4-phenyl chair conformation.[133]

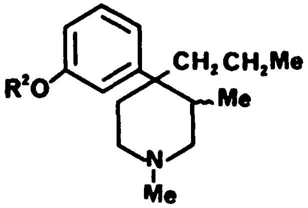


β-prodinol

Table 14. ^{13}C NMR of α- and β—4-Aryl-1,3-dimethyl-4-n-propylpiperdine[a]

54d: c-3-Me/4-Ar (major)

54c: t-3-Me/4-Ar (minor)



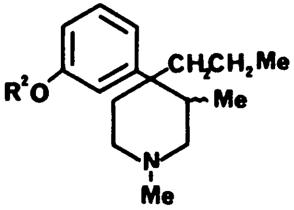
Compound/ Solvent	R^2	C-2	C-3	C-4	C-5	C-6	C3-Me	4-n-Pr CH$_2$	4-n-Pr CH$_2$	4-n-Pr Me	N-Me	OMe	Cq-1'(Ar)	Cq-3'(Ar)	
							^{13}C Chemical shifts in ppm from TMS								
54d; base in $CDCl_3$	Me	58.4	39.0	41.3	26.4	51.9	16.4	40.2	16.6	14.6	46.6	54.9	149.7	159.3	128.6; 118.8 113.1; 109.4
54d; base in $CDCl_3$	H	58.4	39.4	41.16	26.27	51.7	16.3	39.96	16.9	14.7	46.6	-	149.1	156.6	129.2; 118.0 114.1; 112.7
54d; HCl in D_2O	H	56.0	36.4	39.9	23.0	50.2	13.7	38.3	16.2	13.4	43.2	-	147.3	155.5	129.3; 117.9; 112.8; 112.6
54c; HCl	H	57.0	41.0	42.1	28.5	51.7	12.5	43.9	17.6	14.7	44.5	-	147.6	157.2	131.1 (130.7) 120.2 (120.0)
in D_2O		58.7	(33)		(27.9)	(52.8)	(13.9)	(32.4)	(17.0)	(14.9)	(44.1)		(146.1)	(156.8)	115.2 (115.1) 114.7 (114.4)
54c; base in $CDCl_3$[b]	Me	59.2	38.9	42.0	32.7	51.96	14.6	c	16.4	13.7	46.2	54.8	148.1	159.3	128.6; 119.5; 113.7; 109.9

a. Data in parenthesis refer to the minor epimer.

b. A spectrum of mainly the minor isomer with a trace of the major isomer.

c. Unresolved.

Table 15. ^{1}H NMR (δ scale in ppm) of α- and β-4-Aryl-1,3-dimethyl-4-n-propylpiperidine[a]



54d: c-3-Me/4-Ar (major)

54c: t-3-Me/4-Ar (minor)

Compound/ Solvent	R^2	2-H	3-H	5-H	6-H	3-Me	4-n-Pr CH$_2$	CH$_2$	Me	N-Me	OMe	Ar-H
54d; base in CDCl$_3$	Me	ax/eq: 2.48brd; 12 2.58dd; 12,3	1.59[b]	ax: 1.37dt, 13,13,4 eq: 1.78brd,12	ax: nr 2.2m eq: 2.76brd,12	0.73d; 6.8	nr 2.2m	1.05m, 0.63m	0.77t; 7.2	2.27s	3.78s	5'-H: 7.21t; 6'-H: 6.82brd; 2'-H: 6.78t; 4'-H: 6.7dd
54c; base in CDCl$_3$[c]	Me	d	d	d	d	0.79d; 7	d	d	0.9brt	2.27	3.78s	5'-H: 7.15t; 6'-H: 6.95brd (6.82brd) 2'-H: 6.92t (6.76t); 4'-H: 6.65dd (below 6.65dd)
54d; HCl in D$_2$O	H	d	d	d	d		d	d	d	2.83s	-	d
54d; base in CDCl$_3$	H	d	1.95m[e]	d	d	0.67d; 7	nr 2.2m	f	0.76t; 7.1	2.24s	-	5'-H: 7.11t; 6'-H: 6.73brd; 2'-H: 6.64t; 4'-H: 6.60dd
54c; HCl in D$_2$O and CDCl$_3$	H	d	d	d	d	0.51;7 (1.17;7)	d	d	0.57t;6.6 (0.91; 6.6)	2.85s 2.6s	-	d

---

a. Footnote a from Table 10 (p.133) applied.

b. Forms a broad singlet when irradiated the C3-CH$_3$ doublet at 0.73 ppm

c. Footnote b from Table 14 applied.

d. Unresolved signals.

e. Formsa broad singlet when irradiated the C3-Me doublet at 0.67 ppm.

f. Unresolved multiplet (1.06-1.22)

II. 4-Aryl-1,3-dimethyl-4-n-propyl series

Although difficulty was experienced in assigning all NMR signals (e.g. α-CH_2 of 4-*n*-Pr and 4-*iso*-Bu substituents), useful stereochemical information was gained.

Utilization of the principles outlined in Section I (p.149) in analysis of the stereochemistry of the 4-*n*-Pr isomeric analogues provided conclusive evidence supporting the molecular geometry of these isomers.

NMR resonances of stereochemical significance are presented in the following tables (16, 17, and 18); the usual sequence of arguments is followed.

Table 16. Cq-1' ^{13}C chemical shifts (ppm) of the major isomer (54d) and the minor isomer (54c)

Compound	Free base	HCl salt
Major (OMe)	149.7	d
Minor (OMe)[a]	148.1	d
Major (OH)	149.1	147.3
Minor (OH)	d	147.6 (146.1)[b]
		146.4[c] (144.9)

a. A spectrum of mainly the minor isomer with a trace of the major isomer

b Data in parenthesis refer to the minor epimer

c. Data from a second run

d. Not recorded

It may be concluded that both isomers prefer a common equatorial 4-Ar chair conformation (with the possible exception of one of the epimers of the minor diastereoisomer).

Table 17. C-5 ^{13}C Chemical Shifts (ppm) of the Major Isomer (54d) and the Minor Isomer (54c)*

Compound	Free base	HCl salt
Des 3-Me	34.8	32.3 (31.3)[b]
Major (OMe)	26.4	d
Minor[a] (OMe)	32.7	d
Major (OH)	26.3	23.0
Minor (OH)	d	31.0 (27.0 or 26.5) 28.5[c] (27.9)

* Footnotes a, b, c and d from Table 16 apply.

These data provide evidence that 3-Me is axially orientated in the major isomer and equatorially oriented in the minor isomer.

^{1}H NMR Analysis

^{1}H Ar-Pattern

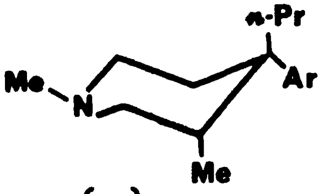
The free base of the major isomer displayed a pattern characteristic of conformation (54d) while that of the minor isomer was of type (54c), as presented in Table 18.

Table 18. Characteristic ^{1}H NMR (δ scale in ppm) Ar-pattern of the major isomer (54d) and the minor isomer (54c) of the 4-Pr series

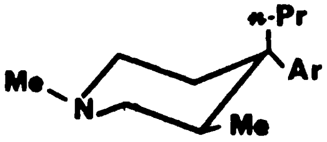
Compound/	5't		6'brd		2't (narrow)		4'dd	
Solvent	L	H	L	H	L	H	L	H
Major base (OMe) in $CDCl_3$ (54d)	7.21 (8.1, 8.1 Hz)			6.82 (7.9 Hz)		6.78		6.69 (1.8, 7.3 Hz)
Minor base[a] (OMe) in $CDCl_3$ (54c)	7.27 (8.2, 8.2 Hz)		6.95 (7.9 Hz)	6.83[b]	6.92 (2.1 Hz)	6.78[b]	6.72 (1.8, 7.3 Hz)	6.7[b]

a. A spectrum of mainly the minor isomer with a trace of the major isomer

b. A less intense signal corresponding to the major isomer from the mixture described in footnote a.



(54d)



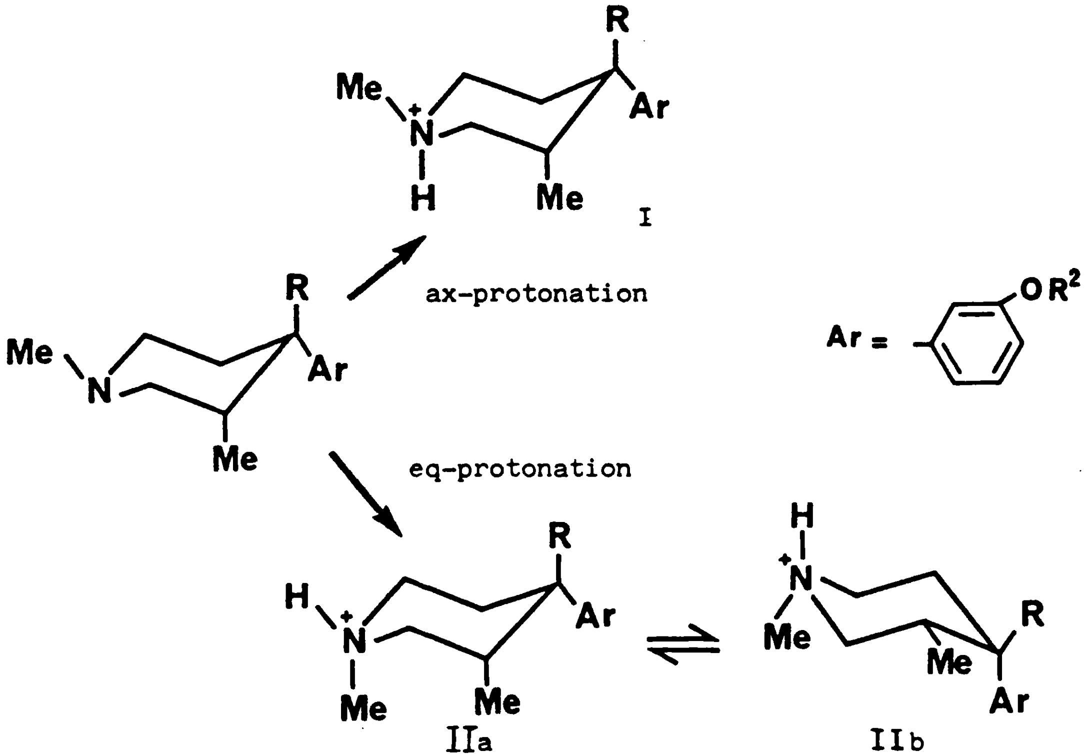
(54c)

Epimers

Evidence so far presented supports the stereochemistry (54d) for the major, and (54c) for the minor, 4-propyl derivatives as bases.

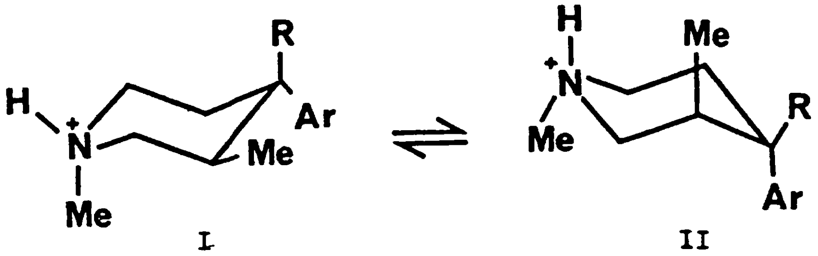
When ^1H NMR spectra of HCl salts were examined, it was surprising that only the spectrum of the minor isomer showed the presence of a pair of significantly populated epimers (*cf*. p. 143). In the previous argument in regard to epimer populations, only the case of 4-methyl derivatives was considered. It is known from study of des 3-methyl analogues that preference for chairs with equatorial 4-alkyl substituents rises with increasing size of the 4-substituent. Epimer formation in 3-methyl-4-alkylpiperidines where 4R = propyl and isobutyl will now be considered.

In derivatives with axial 3-Me, axially protonated epimers (I; obtained exclusively; Scheme 41) are highly preferred due to an absence of 3-Me/4-R interactions and the unfavourable interactions that obtain in the equatorially protonated epimer (II; Scheme 41). Conformer (IIa) is unfavoured by the *N*-Me/3-Me syn diaxial interactions and its invertomer (IIb) by 3-Me/4-R interactions which will be significantly greater than the 3-Me/4-Me interactions of the corresponding 3,4-dimethyl derivatives.



Scheme 41

On the other hand, the equatorially protonated epimer of type (I, Scheme 42) may invert to a chair in which the 4-R group moves to the less hindered equatorial conformation and 3-Me/4-Ar interactions are absent.



Scheme 42

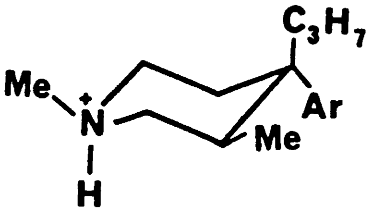
Thus, it may be anticipated that epimers (I/II and III; Scheme 42) will both be significantly populated when the equatorial 3-Me base is protonated, providing a bulky substituent (>Me) is attached to C-4.

Protonated epimers

The ^{1}H NMR spectra of the major 4-n-Pr isomer (54d; R^2=Me as the oxalate and R^2=H as the HCl) indicated the presence of only one N-protonated epimer, while that of the minor isomer (54c; R^2=H;

HCl) indicated the presence of two significantly populated epimers, evidence in support of equatorial 3-Me (54c).

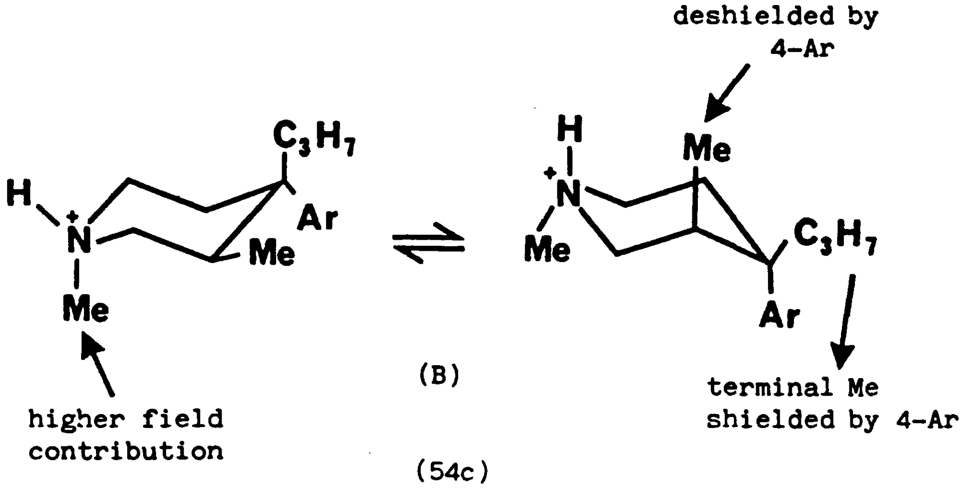
In the ^{1}H NMR spectrum of the minor diastereoisomeric salt, duplication of N-methyl, 3-methyl and 4-CH_2CH_2Me resonances was clear. Relative intensities indicated an epimer ratio of about 1:1. The lower field N-Me chemical shift (2.89 ppm) was close to that of the major diastereoisomeric salt (N-Me; 2.87 ppm), both values being typical of equatorial N-methyl as in (A).



A

(54c)

The N-methyl ^{1}H shift of the second epimer (B; 2.66 ppm) is evidence that this arises from an equatorially protonated base which is in rapid equilibrium with its invertomer as shown in Scheme 43.



(B)

(54c)

Scheme 43

Of the dual 4-$CH_2CH_2\underline{Me}$ triplets (0.98, 0.64 ppm), that at higher field is assigned to epimer (B) and that at lower field to epimer (A). Likewise the lower field 3-Me doublet (1.24 ppm) is assigned to (B) and the doublet at 0.70 ppm to eq 3-Me of (A). Reasons for these assignments are explained in relation to analogous 4-isobutyl epimers (p. 177).

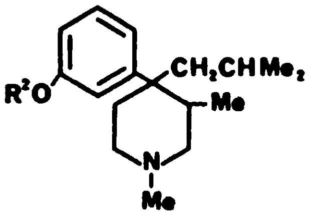
Duplicated ^{13}C NMR signals may also be assigned in terms of the epimers (A) and (B). Cq-1' ^{13}C shift (146.4 ppm) is assigned to epimer (A), while that at 144.9 ppm is assigned to epimer (B). The C-5 ^{13}C shift at 31.0 ppm is assigned to epimer (A) and that at 26.5 (27.0) ppm is assigned to epimer (B), at higher field because it is sterically compressed by axial 3-methyl.

The α-CH_2 signals at 42.4 and 27.0 (26.5) ppm are assigned to epimer (B) and (A) respectively and both are sterically compressed by 3-Me (*cf*, des 3-methyl HCl epimers, 55**l**, p. 135).

Table 19. ^{13}C NMR of α- and β—4-Aryl-1,3-dimethyl-4-(2-methylprop-1-yl)piperidine[a]

54k: t-3-Me/4-Ar (major)

54j: c-3-Me/3-Ar (minor)



^{13}C Chemical shifts in ppm from TMS

Compound/ Solvent	R^2	C-2	C-3	C-4	C-5	C-6	C3-Me	4-isobutyl			N-Me	OMe	Cq-1'(Ar)	Cq-3'(Ar)	
								CH_2	CH	Me_2					
54k; base in $CDCl_3$	Me	59.6	b	42.6	31.9	52.1	14.7	c	23.8	24.9; 24.8	46.4	55.0	148.1	159.3	128.5; 120.1 114.8; 109.95
54k; HCl in D_2O	Me	57.3 (55.7)	33.0 (40.5)	41.1 (41.3)	30.2 (27.4)	51.2 (50.6)	13.0 (11.5)	49.2 (32.3)	22.8 (23.6)	23.9; 23.7 (23.6; 22.9)[d]	43.3 (42.8)	55.0	144.4 (146.5)	159.2 (158.5)	129.7; (129.0); 119.9; 113.4 (113.6); 111.3
54j; base in $CDCl_3$[e]	Me	59.4 (58.3)[f]	39.57 (38.5 br)	42.4 (41.4)	31.75 (26.56)	52.3 (52.0)	16.25 (14.53)	46.0 (24.0)	23.61	24.94 (24.68)	46.5 (46.3)	54.7	147.9 (149.5)	159.2	128.4; 119.9(119.0) 114.1 (113.2); 109.8 (109.4)
54k; base in D_2O	H	59.3	38.9br	42.3	31.6	52.3	14.5	g	23.9	24.9	46.1	-	147.9	156.8	128.7; 119.2; 115.3; 113.2
54k; HCl in D_2O	H	57.4 (55.8)	33.0 (40.6)	40.9 (41.2)	27.5 (30.2)	51.3 (50.7)	13.0 (11.5)	49.2 (32.4)	23.6 (22.8)	23.9 (23.7)	43.2 42.8	- -	144.5 (146.5)	155.8 (155.2)	129.2 (128.96); 119.0 (119.2); 114.0 (114.1); 113.0
54j; base $CDCl_3$	H	58.3	39.9	41.3	26.4	51.9	16.2	45.8	24.3	25.2; 24.6	46.5	-	149.0	156.6	128.96; 118.1; in 114.3; 112.3
54j; HCl in D_2O	H	56.2	37.3	40.0	23.35	50.6	13.65	44.3	23.7	23.8	43.2	-	147.5	155.3	129.2; 118.5; 113.3; 112.6

a. Data in parenthesis refer to the minor epimer.

b. Broad signal at 38.7 ppm or overlapped with N-Me signal at 46.4 ppm.

c. Unresolved overlapped signal at 31.9 ppm.

d. Signal at 22.9 ppm overlapped with that of β-CH at 22.8.

e. A spectrum of mainly the minor isomer with a trace of the major isomer

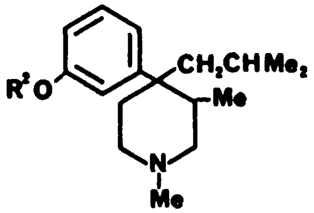
f. Data in parenthesis refer to the major isomer from the mixture described in footnote e (less intense than those of the minor isomer).

g. Signals overlap at 52.1 ppm.

Table 20. Characteristic ^1H NMR (δ scale in ppm) of *c*- and *t*-4-Aryl-1,3-dimethyl-4-(2-methylprop-1-yl)piperidine[a]

54k: *t*-3-Me/4-Ar
(major)

54j: *c*-3-Me/3-Ar
(minor)



Compound/	R^2	3-H	3-Me	$CH_2CH(Me)_2$			N-Me	OMe	Ar-H
Solvent				CH_2	CH	Me_2			
54k; base in $CDCl_3$	Me	b	0.96d	b	b	0.71d; 6.6	2.19s	3.8	5'-H: 7.21t; 6'-H: 6.98d; 2'-H: 6.96brs; 4'-H: 6.72dd
54k; HCl in D_2O	Me	b	1.24d; 7.33 (0.89d; 6.4)	b	b	0.39d; 6.7 (0.48d, 6.7) 0.61d; 7.02 (0.72d; 6.7)	2.90s (2.90s)	3.76s (3.73s)	5'-H: 7.30t (7.22); 6'-H: 6.98 (7.04); 2'-H: 6.98 (6.94); 4'-H: 6.85dd (6.77dd)
54k; HCl in D_2O	H	b	1.21d; 7.3 (0.86d; 6.1)	b	b	0.38d, 6.4 (0.48d, 6.4) 0.58d, 6.4 (0.70d, 6.4)	2.89s	-	c
54j; base in $CDCl_3$	H	1.9 m[d]	0.63d; 7.0	b	1.3m	0.47d; 6.7 0.85d; 6.7	2.32s	-	5'-H: 7.11t; 6'-H: 6.74brd; 2'-H: 6.68t; 4'-H: 6.60dd
54j; HCl in D_2O	H	nr2.3 m[e]	0.67d; 7.3	2.13dd; 1.55dd	1.2m	0.41d; 6.7 0.79d; 6.7	2.85s	-	5'-H: 7.24t; 6'-H: 6.89brd; 2'-H: 6.80t; 4'-H: 6.74dd

a. Footnote a from Table 10 (p.133) applied.

b. Unresolved signal.

c. Unresolved duplicated Ar signals 6.75-7.20 ppm.

d. Identified by a COSY plot and forms a broad singlet when irradiated the C3-CH_3 doublet at 0.63 ppm.

e. Identified by a COSY plot and forms a broad singlet when irradiated the C3-CH_3 doublet at 0.67 ppm.

III. 4-Aryl-1,3-dimethyl-4-isobutyl series

Characteristic stereochemical features are presented as before in Tables 21, 22 and 23; these features were utilized to deduce the stereochemistry of the isomeric pairs encountered in 3-methyl-4-isobutyl derivatives. Difficulty in assigning all NMR signals was also met in this series.

Table 21. Cq-1' ^{13}C chemical shifts (ppm) of the major isomer (54k) and the minor isomer (54j)

Compound	Free base	HCl salt
Major (OMe)	148.1	144.4 (146.5)[c]
Minor[a] (OMe)	b	d
Major (OH)	147.9	144.0 (146.5)
Minor (OH)	149.0	147.0

a. A spectrum of mainly the minor isomer with a trace of the major isomer.

b. Unresolved.

c. Data in parenthesis refer to the minor epimer.

d. Not recorded.

From these data, it is probable that both bases prefer equatorial 4-Ar chair conformations, as does the minor diastereoisomer (HCl) and one epimer of the major diastereoisomer (HCl).

Table 22. C-5 ^{13}C chemical shifts (ppm) of the major isomer (54k) and the minor isomer (54j)

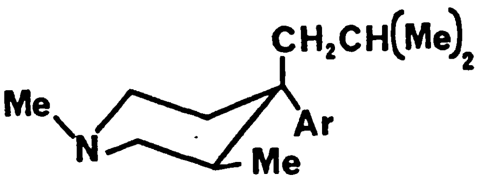
Compound	Free base	HCl salt
Major (OMe)	31.9	30.2 (27.4)[b]
Minor[a] (OMe)	26.6	c
Major (OH)	31.6	27.5 (30.2)
Minor (OH)	26.4	23.4

a. A spectrum of mainly the minor isomer with a trace of the major isomer.

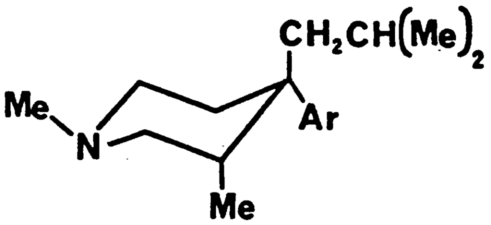
b. Data in parenthesis refer to the minor epimer.

c. Not recorded.

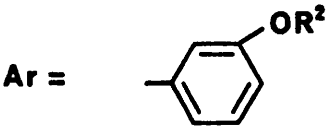
This evidence is in support of an equatorial 3-Me chair for the major isomer (54k) and an axial 3-Me chair for the minor isomer (54j).



(54k)

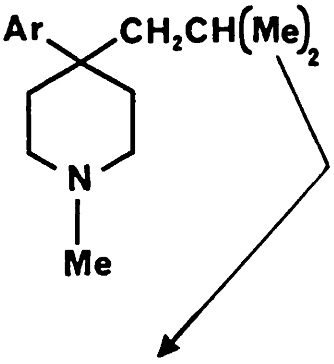


(54j)



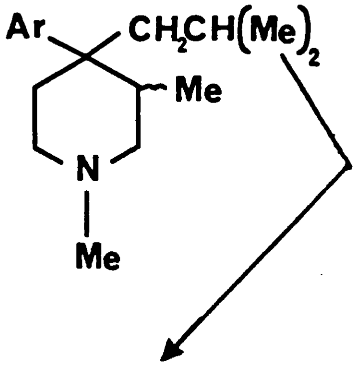
^{1}H NMR Analysis

^{1}H NMR spectra of both isomers (HCl salts, free base of the minor isomer and both epimers of the protonated major isomer) displayed duplicated signals with pronounced chemical shift differences for the terminal methyl groups of the 4-isobutyl substituent, evidence that protons of these two methyl groups are non equivalent, unlike those of the corresponding des 3-methyl derivative.



Symmetric environment

(one 6 proton doublet)



Asymmetric environment

(2 x 3 proton doublets)

1. ^{1}H C3-H

In the minor isomer, irradiation of the C3-Me doublets (R^2=H; free base at 0.63; HCl at 0.67) resolved the C3-H multiplets at 1.9 ppm and 2.3 ppm respectively into broad singlets. Therefore, the C3-H has an equatorial orientation and the C3-CH_3 an axial conformation in the minor series.

The C3-H resonances of the major isomer (free base and HCl salt) were not resolved and appeared as a part of complex multiplet. However, that of the major epimer (R^2=H, HCl) was identified as a multiplet at 2.8 ppm by a COSY experiment and subsequent spin decoupling of the corresponding 3-Me doublet caused this multiplet to reduce to broad singlet, evidence that the major epimer has an axially orientated 3-Me (see later).

2. ^{1}H Ar-Pattern

The free base of the major isomer displayed a pattern characteristic of (54k), while that of the minor isomer was characteristic of (54j; free base) as outlined in Table 23.

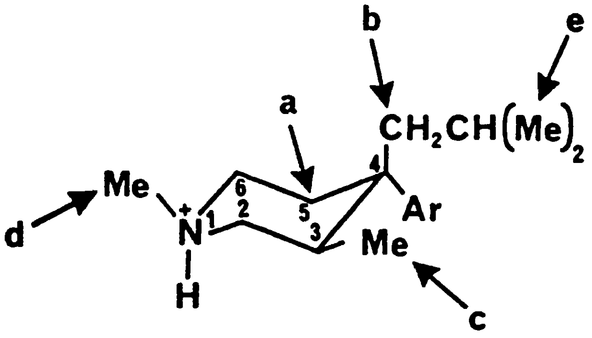
Table 23. Characteristic ^{1}H (δ scale in ppm) Ar-pattern of (54k) and (54j)

Compound/	5't		6'brd		2't (narrow)		4'dd	
Solvent	L	H	L	H	L	H	L	H
Major (OH), base in $CDCl_3$(54k)	7.12 (8.2,8.2 Hz)		6.86[a]		6.87[a]		6.63 (7.0 Hz)	
Minor (OH), base in $CDCl_3$ (54j)	7.11 (7.9,7.9 Hz)			6.74 (8.2 Hz)		6.68[a]		6.60 (7.3 Hz)

a. Unresolved

From evidence already presented it may be deduced that the major base has the stereochemistry (54k). The fact that NMR spectra of HCl salts were typical of epimeric mixtures (see Fig. 6) adds further weight to this assignment (see arguments cf. p. 164). Figure 6 clearly shows duplication of signals due to 3-methyl, terminal methyls of 4-isobutyl (pairs of doublets due to non-equivalent methyl in each epimer) and N-methyl. Assignments of these signals were possible from COSY and spin decoupling experiments. From differences between the ^{13}C and ^{1}H chemical shifts of corresponding epimeric signals, the following conformational conclusions can be drawn.

Less populated epimer



(54k)

a. C-5 has ^{13}C chemical shift (30.2 ppm) typical of equatorial 3-methyl derivatives.

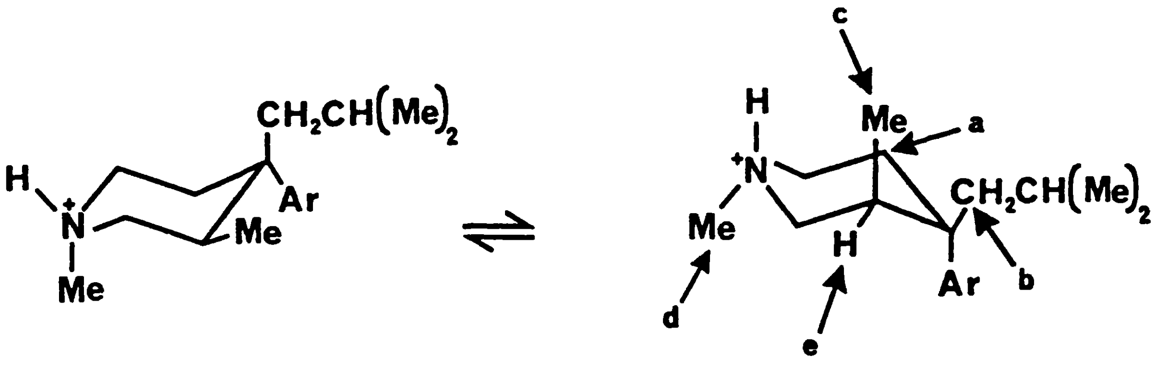
b. $\underline{\alpha}$-CH_2 ^{13}C higher field (32.4 ppm) than α-CH_2 of des 3-Me analogue (43.6) because compressed by eq 3-Me.

c. Sterically compressed by 4-isobutyl; therefore ^{13}C chemical shift at higher field (11.5 ppm) than 3-Me of minor diastereoisomer HCl (13.0 ppm).

d. ^{1}H $\underline{N}$-methyl signal (2.89 ppm) lower field than that of major epimer (2.62 ppm) and characteristic of equatorial $\underline{N}$-Me.

e. ^{1}H 3-methyl (0.86 ppm) and $CH_2CH(\underline{Me})_2$ (0.58, 0.7 ppm) signals higher and lower field respectively of major signals (see below for interpretation).

More populated epimer



preferred

a. C-5 ^{13}C chemical shift (27.5 ppm) approaches value seen in minor diastereoisomeric salt (axial 3-Me).

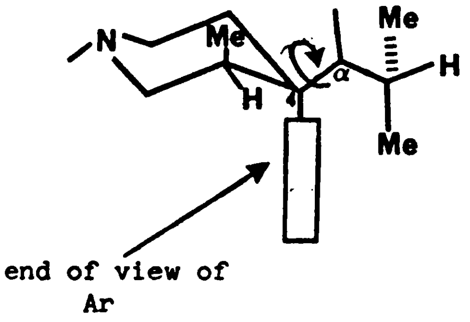
b. α-CH$_2$ ^{13}C resonance moves to lower field (49.2 ppm) when it has an equatorial placement.

c. 3-Me ^{13}C resonance (13.0 ppm) close to 3-Me of minor diastereoisomeric salt.

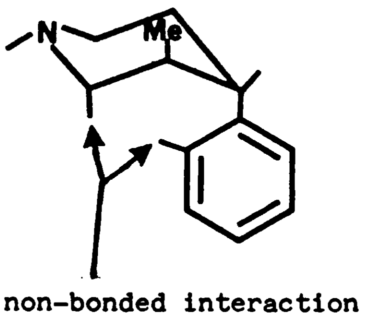
d. ^{1}H N-methyl signal higher field than that of minor epimer because of receipt of axial N-methyl contribution (see p. 135).

e. ^{1}H resonances of 3-Me (1.21 ppm) and 3-H (2.30 ppm) are lower field than corresponding signals of the minor epimer because they fall directly in the deshielding zone of the aryl ring when it is axial (see A).

f. The preferred Ar/piperidine ring conformation will be (A) rather than (B).



(A)



(B)

In conformation (A), as the 4-isobutyl group rotates about the C4-$\underline{\alpha}$-CH_2 bond, the terminal methyls fall within the shielding zone of the aromatic ring and hence resonate at higher field (0.38; 0.48 ppm) than those of the minor epimer (0.58; 0.78 ppm).

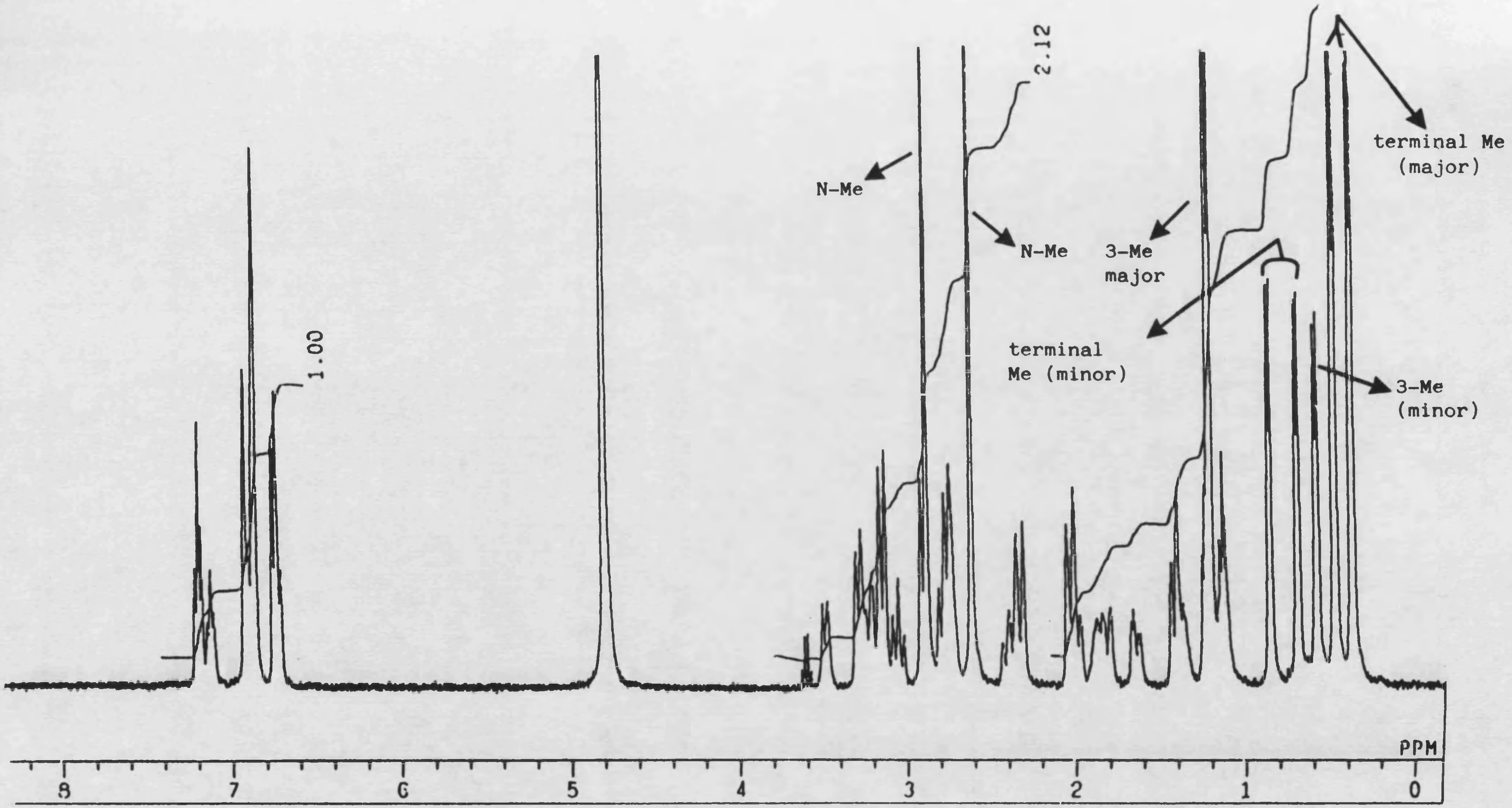


Fig. 6. ^{1}H NMR spectrum of major 4-(3-hydroxyphenyl-1,3-dimethyl-4-(2-methylprop-1-yl)piperidine hydrochloride (54k).

2.4 Pharmacological Evaluation and Concluding Remarks

Phenolic analogues of some 4-alkyl-1,3-dimethylpiperidines and corresponding des 3-methyl analogues (except the 4-methyl derivative) and the phencyclidine derivatives (±)- (69g; OA8), (69h; OA14), (69j; OA13), (+)- (69g; OAD7) and (-)- (69g; OAL7), in addition to compound (99; OA92), related to ketobemidone, have been synthesised and submitted (as the HCl salts) for pharmacological evaluation (in vivo and in vitro) as either narcotic agonists or antagonists. These tests were carried out in laboratories of Janssen Pharmaceutica (JP) and the National Institutes of Health (NIH), Bethesda, USA.

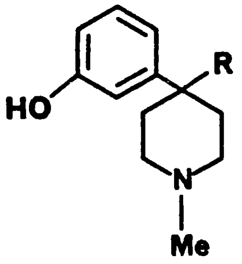
2.4.1 JP Data (In Vivo)

Agonist (morphine-like) activity was assessed in rats by the tail withdrawal test (TWR). This procedure involves immersing the end of the tail of a rat in warm water at 55°C. The response, typically tail withdrawal, is timed before and after intravenous (iv) administration of the test compound. The ED_{50} (mg/kg) of the test compound can be determined as that dose which inhibits tail withdrawal in 50% of the rats.[149]

Antagonist (naloxone; nalorphine-like) activity was assessed in rats treated with fentanyl. Fentanyl is injected subcutaneously (sc) at the very high dose of 0.63 mg/kg which results in pronounced respiratory depression, loss of righting reflexes, lead pipe rigidity and blockade of the pinna and cornea reflexes. The test compound is then given intravenously (over a range of dose levels) and the dose needed to reverse the various effects of fentanyl can be assessed.[149]

2.4.1.1 Des 3-methyl derivatives

a. Agonist Activity (TWR)



(55)

Compound	R	dose (mg/kg)
OA1-16	4-Pr	2.5 3/3 positive
(55ℓ)		0.63 0/3 positive
		Estimated ED_{50} 1.25
OA1-35	4-isoBu	2.5 3/3 positive
(55z)		0.63 0/3 positive
		Estimated ED_{50} 1.25

ED_{50} (mg/kg) for standard opioids are:

Morphine	3.5
Pethidine	6.15
Fentanyl	0.011

From these data it can be concluded that both OA1-16 (4-Pr) and OA1-35 (4-isoBu) are 2-3 times more potent than morphine in the TWR test.

Results from three independent sources quoted a similar order of analgesic potency for the 4-Pr derivative (see below).

McElvain and Clemens (1958) reported an ED_{50} of 2 mg/kg in rats.[86]

Loew *et al*. (1988) reported agonist ED_{50} (mg/kg) values in mice close to those of morphine.[138]

ED_{50}		Test
Morphine	4-Pr	
1.0 (0.5-2.1)	0.9 (0.5-1.6)	writhing sc
3.0 (1.8-4.7)	2.8 (1.7-4.6)	tail-flick sc
0.06 (0.03-0.15)	0.9 (0.4-2.1)	tail-flick icv

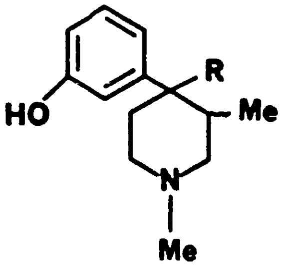
In 1978 Zimmerman *et al*. reported that the 4-Pr derivative was about two times as active as morphine in rats and in mice.[88]

General agreement amongst the three sets of data on the 4-Pr derivative can be concluded.

b. Antagonist activities

Apart from one result for OA1-16, the 4-Pr and 4-iso-Bu derivatives failed to reverse fentanyl induced effects in rats (Table 24) at a dose of 2.5 mg/kg.

2.4.1.2 3-Methyl derivatives



(54)

a. Agonist activities (TWR)

Compound	R	Isomer	Agonist Activity TWR
OA1-10T (54b)	Me	cis 3-Me/4-Ar	ineffective at 2.5 mg/kg
OA1-10B (54a)	Me	trans 3-Me/4-Ar	ineffective at 10 mg/kg
OA1-8T (54d)	Pr	cis 3-Me/4-Ar	ineffective at 2.5 and 10 mg/kg
OA1-33B (54k)	iso-Bu	trans 3-Me/4-Ar	2.5 mg/kg 3/3 positive
			0.63 mg/kg 0/3 positive
			Estimated ED_{50} 1.25 mg/kg
OA1-33T (54j)	iso-Bu	cis 3-Me/4-Ar	ineffective at 2.5 mg/kg
			slight analgesia at 10 mg/kg
			Estimated ED_{50} 10 mg/kg

Activity values reported by Zimmerman *et al.* (see p. 40) for the isomeric 4-methyl and 4-propyl derivatives agree in general with the present findings.

b. Antagonist activities

The results are presented below:

Compound	Antagonist activities (reversal of fentanyl induced effects)
OA1-10T *trans* 3-Me/4-Me	An effective antagonist of fentanyl 2.5 and 0.63 mg/kg. Reverses respiratory depression at even lower dose levels (0.16, 0.04 mg/kg). Approaches value of naloxone in regard to reversal of respiratory depression (see standard data below). Zimmerman reported the compound to possess 1/10 the activity of naloxone in rats and mice.
OA1-10B *cis* 3-Me/4-Me	Some effect at 10 mg/kg in 2 out of 3 rats, no respiratory depression, no loss of righting reflexes, no rigidity, but blockade of cornea and pinna reflexes unrelieved. Ineffective at 2.5 mg/kg. Zimmerman reported this isomer to be a very weak antagonist.
OA1-8T *trans* 3-Me/4-Pr	ineffective at 2.5 mg/kg.
OA1-33T *trans* 3-Me/4-isoBu	ineffective at 2.5 mg/kg (positive response in one out of three rats on respiratory depression).
OA1-33B *cis* 3-Me/4-isoBu	ineffective at 2.5 mg/kg.

Standard Reference Data

Effective ED $_{50}$ values (mg/kg, iv)

Effect	Nalorphine	Naloxone
respiration, depression	-	0.04
loss of rigidity reflexes	-	0.04
Rigidity	0.63	0.02
Pinna reflex	0.63	0.02
Cornea reflex	5.0	0.04
Analgesia	2.5	0.04

2.4.2 NIH Data

2.4.2.1 *In Vitro* Experiments

a. Binding Experiments

Aliquots of a membrane preparation from rat cerebellum were incubated with ^{3}H-etorphine in the presence of 150 mM NaCl and different concentrations of the test agent. Specific binding was determined as the difference obtained in the absence and presence of excess of unlabelled etorphine. The potency is expressed as that concentration required to display half the specific binding of the radioligand (EC_{50} in nM). The EC_{50} of morphine is about 23.6 nM when using 0.5 nM of ^{3}H-etorphine.

b. Mouse Vas Deferens (MVD)

This procedure involves treatment of an isolated, electrically stimulated mouse vas deferens with different concentrations of the test compound. The EC_{50} (nM) can be determined as that concentration which produces 50% inhibition of twitches. The EC_{50} can also be determined in the presence of a selective delta receptor antagonist (an ICI peptide), a non-selective opiate antagonist (e.g. naltrexone) or a di-antagonist (e.g. $\underline{\beta}$-furaltrexamine: $\underline{\beta}$-FNA). The EC_{50} for morphine is about 3.95×10^{-7} (395 nM).

In the case of antagonists, pA_2 values were determined in some cases. The pA_2 value is the negative logarithm of that dose of antagonist that converts the action of a double dose of agonist to that of a single dose.

Table 24. **Binding (EC_{50}, nM), MVD (EC_{50}) and pA_2 data of some 4-alkyl-4-arylpiperidines**

Compound	Binding (nM)	MVD EC_{50} and pA_2
OA1-16 (4-Pr) des 3-Me	146	MVD EC_{50}: 5.58 x 10^{-7} (90% inhibition) Action blocked by naltrexone and β-FNA, but not by the ICI compound. (ICI 174864, δ-antag) This compound approaches the potency of morphine as a μ-agonist.
OA1-10T *trans* 3-Me/4-Me	403	MVD: inactive as agonist and behaves as antagonist pA_2: 6.91 (μ) vs Sufentanil 5.92 (δ) vs DSLET 6.43 (κ) vs 50488H
OA1-8T *trans* 3-Me/4-Pr	1026	MVD: inactive as agonist and behaved as antagonist pA_2: 6.14 (μ) 6.47 (δ) 5.52 (κ)
OA1-33B *cis* 3-Me/4-isoBu	46.3	MVD EC_{50}: 1.31 x 10^{-7} Has opioid action at a lower dose than morphine but lacks antagonist action pA_2: 5.63 (μ) 6.23 (δ) 5.66 (κ)

contraction of the abdominal musculature accompanied by extension of the hind limbs). Mice are injected (sc) with the compound under test, and then phenylquinone is injected (ip) 20 minutes later. The ED_{50} (mg/kg) to inhibit the writhing response in 50% of the test sample can hence be determined.

d. The Hot-Plate Test (MHP)

This test involves the placing of mice on a hot-plate maintained at 57 ± 5°C. Signs of discomfort are shown by the mouse sitting up on its hind legs and licking or blowing its front paws. Hind limb movement is generally used as the end-point.[153]

In Vivo Results

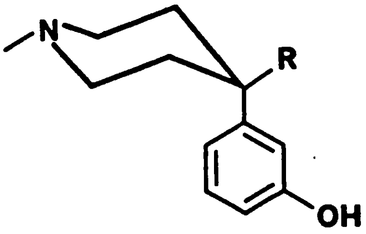
Compound	TFM (ED_{50})	PQM (ED_{50})
OA-16	2.5 (0.1-1.9)	0.4 (0.2-0.9)
OA1-35	0.8 (0.3-2.1)	0.3 (0.1-0.7)
OA -10T	inactive at 1.0, 10.0 and 30	11% at 1.0 22% at 10 23% at 30.0
OA1-33B	17.6 (12.0-26.2)	1.7 (0.5-5.8)
OA1-33T	2.3 (1.2-4.5) Straub tail observed	0.2 (0.1-0.6)

NIH Standard Data (ED_{50} mg/kg)

Drug	TF	TF vs M	PPQ Writhing	HP
Pentazocine	15% at 10.0	18 (12.4-4.26)	1.65 (1.0-2.5)	-
Cyclazocine	17% at 1.0	0.03 (0.02-0.78)	0.011 (0.046-0.03)	-
Nalorphine.HCl	None at 10.0	2.6 (0.69-9.75)	0.6 (0.025-1.44)	-
Naloxone.HCl	None at 10.0	0.035 (0.010-0.93)	No activity	-
Morphine sulphate	5.8 (5.7-5.9)	-	0.23 (0.20-0.25)	-
Pethidine.HCl	7.8 (30-20.6)	Inactive	0.8 (0.3-0.2)	4.1(2.8-6.1)

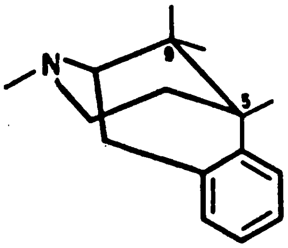
The 4-Pr derivative OA1-16 displayed 2-3 and 10 times the activity of morphine, respectively in the TWR and TFM tests, results in general agreement with published work,[88-91] although the potency values of OA1-16 in mice were higher. In the writhing test the potency of this analogue fell below that of morphine. The 4-iso-Bu analogue OA1-35 and the major 4-isoBu analogue OA1-33B (*t*-3-Me/4-Ar) were as effective as OA1-16 in the TWR test, although less so in the TFM procedure. The minor 4-iso-Bu analogue OA1-33T (*c*-3-Me/4-Ar) and all other derivatives examined had low orders of antinociceptive activities. The *in vitro* data complemented these findings. Although insufficient minor 4-Pr (*t*-3-Me/4-Ar) was isolated for pharmacological evaluation, Zimmerman *et al*.[88-91] found this compound (Picenadrol) to be an agonist in rats (TF) and in mice (WR) with potencies about half those of morphine.

It appears significant that all potent 4-arylpiperidine analogues of this class exhibit a preference (50% or above) for axial 4-aryl chair conformations (55B) when protonated, as established by NMR studies.



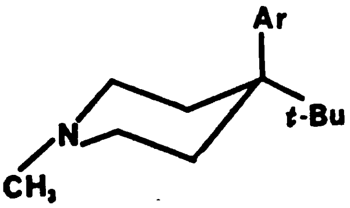
(55B)

These results support the view that 4-arylpiperidine opioid ligands bind to the opioid receptor in a manner similar to that of morphine and its congerers and mimic the geometry of the 4-arylpiperidine moiety of the polycyclic molecules.[156] The most direct analogy is with benzomorphan analgesics (13), as pointed out by Loew *et al*.[129]

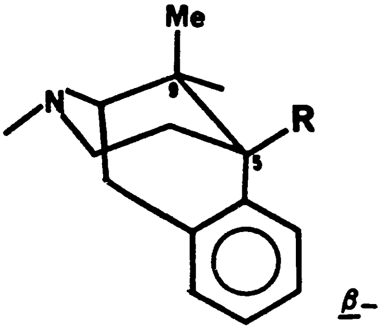


(13)

Thus, several C-9 unsubstituted *N*-methyl derivatives of (13) have been reported with lower alkyl substituents attached to C-5. The 5-methyl derivative had a codeine-like potency but 5-ethyl, 5-*n*-Pr and 5-*n*-Bu analogues all had about one half the activity of morphine in mice by the MHP test.[157,158] The low activity of a *trans* 5-butyl derivative (non-phenolic however) may correlate with the weak antinociceptive properties of the 4-butylpiperidine (110, 1/9 x morphine in the TFM, 1/6 x morphine in the WRM).[129] Both 9-methyl-5-*n*-Pr diastereoisomers of (13) were active (*β*: 10 x morphine, *α*: 0.5 x morphine in the MHP).[157,158]



(110)



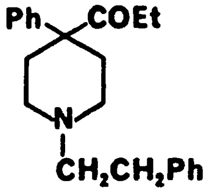
(13a) R = n-Pr
(13b) R = CH_3

The active 4-arylpiperidines OA1-8B (*t*-3-Me/4-Ar) and OA1-33B (*t*-3-Me/4-Ar) closely mimic the geometry of *β*-(13a) in one of their preferred solute conformations (protonated state).

In benzomorphans such as metazocine (5, 9-dimethyl; 13b) and (13a), absolute chirality has a dominant influence upon activity.[159] Thus most of the activity of (±)-(13b) resides in the *laevo* isomer.[14] It is of interest, therefore, that antipodal forms of picenadrol (OA1-8B; *t*-3-Me/4-Ar) differ substantially in potency [(-) 0.1 x morphine, (+) ≡ morphine],[88-91] results which will have even greater import once the absolute configurations of the antipodes have been established.

The only compound found to display prominent activity as an opioid antagonist was the *cis*-diastereoisomer OA1-10T, which reversed all actions of fentanyl in rats at dose levels of 2.5 and 0.63 mg/kg, and effectively countered respiratory depression at even lower dose levels (it approached the potency of naloxone in this respect). The compound was also characterised as an antagonist in the MVD with a pA_2 of 6.91 (μ). The corresponding trans isomer OA1-8B (54c) was a much weaker antagonist versus fentanyl in rats. Neither isomer behaved as an agonist in the TWR test. Results for the cis-isomer OA1-8T (54d) confirm the earlier report of its antagonism of opioids in rats and mice (vs morphine)[88-91]. Both cis diastereoisomers of the 4-Pr and 4-iso-Bu analogues displayed weak antagonistic action in the MVD. However, the latter reversed fentanyl-induced respiratory depression in one out of three rats at a dose level of 2.5 mg/kg.

Pharmacologial Results of the Keto Analogue (99: 0A92)



(99)

1. JP Data

a. Agonist Activity (TWR): ineffective at 2.5 mg/kg

b. Antagonist Activity: ineffective at 2.5 mg/kg in reversing fentanyl-induced effects in rats

2. NIH Data

In vitro Experiments

i. EC_{50}: 1399 nM (Binding)

ii. MVD: inactive at all concentrations tested (10^{-9} - 3 x 10^{-4} nM)

Behaved as an antagonist

iii. pA_2: 7.09 (μ)

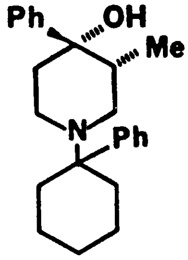
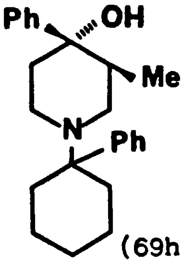
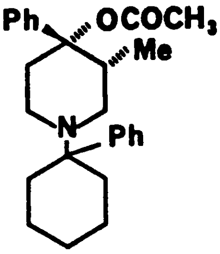
6.39 (δ)

5.94 (κ)

Pharmacological Results of the PCP Analogues

1. JP Data

Agonist Activity (TWR)

Compound	Estimated ED_{50} mg/kg
(±) OA-8  (69g)	1.0
OA-14  (69h)	inactive at 2.5
OA-13 	2.5 (1 out of 3 rats)
OA-D7: (+)-(69g)	1.25
OA-17 : (-)-(69g)	inactive at 2.5
Morphine	3.15 (1981 data)

2. NIH Data

a. In Vitro Experiments

Compound	Binding EC_{50}(nM)	MVD EC_{50}
OA-8	680	14.2×10^{-7} (99.2 ± 8 inhibition) The action blocked by Naltrexone and β-FNA, but not by ICI compound
Pethidine	6000	inactive
Morphine	23.6	3.95×10^{-7}

OA-8 binds less well than morphine and far less effective on MVD.

b. In vivo Experiments

Compound	TF	TF vs M	PPQ Writhing	HP
(±) OA-8	15.3(5.7-41.1) (1/6 died)	inactive at 30	1.2(0.5-3)	0% at 20 and 5
(+) OA-D7	8.7(4.1-18.3)	inactive at 1.0; 10; & 20	0.7(0.3-2.1)	16% at 20
(-) OA-L7	0% at 1.0, 14% at 10, 34% at 30	inactive at 30	2.5(0.7-7.3)	0% at 5 and 20

Comment

TWR Results

The α-racemate (69g) is about three times more effective than morphine and six times more effective than pethidine in this test. Comparative TWR data for the 3-desmethyl analogue (62g, about 2 times the activity of morphine in MHP test)[113] is not available. The absolute configuration of the C-3 chiral centre has the same influence in the PCP derivative (69g) and α-prodine. Structure-activity relationships of the two series differ however in respect of 1) the relative activity of α- and β-diastereoisomers: β- the more active prodine, α- the more active PCP analogue and 2) the importance of O-acylation: vital for activity in the case of the prodines, α-acetoxy ester less active than the α-4-piperidinol in the PCP derivatives.

NIH Data

The α-racemate (69g) was less effective in mice by TF and writhing test procedures than it was in rats by the TW assay. It was half as effective as pethidine in the TF test and equipotent in the writhing test, while compound (+)-(69g) was as effective as pethidine in the TF and writhing test procedures.

3. EXPERIMENTAL

3.1 INTRODUCTION

^{1}H-NMR spectra were recorded on a JEOL GX270 MHz Fourier Transform (FT) NMR Spectrometer unless otherwise stated. The following abbreviations are used to describe resonance appearance in the ^{1}H-NMR spectra: singlet, s; doublet, d; triplet, t; quartet, q; multiplet, m, plus combinations such as dt, doublet of triplets; dd, doublet of doublets; br, broad; eq, equatorial and ax, axial.

^{13}C-NMR spectra were recorded on a JEOL GX270 FT NMR Spectrometer operating at 67.8 MHz unless otherwise stated. The multiplicity of the resonances was obtained from DEPT (Distortionless Enhancement by Polarisation Transfer); when 135 DEPT is applied, CH and CH_3 carbons will give positive signals, CH_2 carbons will be negative and quaternary carbons will be absent, while only CH carbons will give positive signals when the 90 DEPT is applied.

The Infra-red spectra (liquids as films, solids as KBr discs or Nujol mulls) were recorded on a Unicam SP1020 Spectrometer.

Mass spectra were measured on a VG Micromass 7070E Mass Spectrometer operating at 70 ev EI.

Elemental analyses were carried out by Butterworth Laboratories Ltd., Middlesex and Department of Chemistry, University of Bath.

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

Optical rotation readings were recorded on an Optical Activity Ltd., AA-10 Polarimeter, at four different wavelengths including the sodium D line (see appropriate table).

3.2 PHENCYCLIDINE DERIVATIVES DERIVED FROM α—AND β—PRODINE

3.2.1 Methyl 3-methylamino-2-methylpropionate (64)

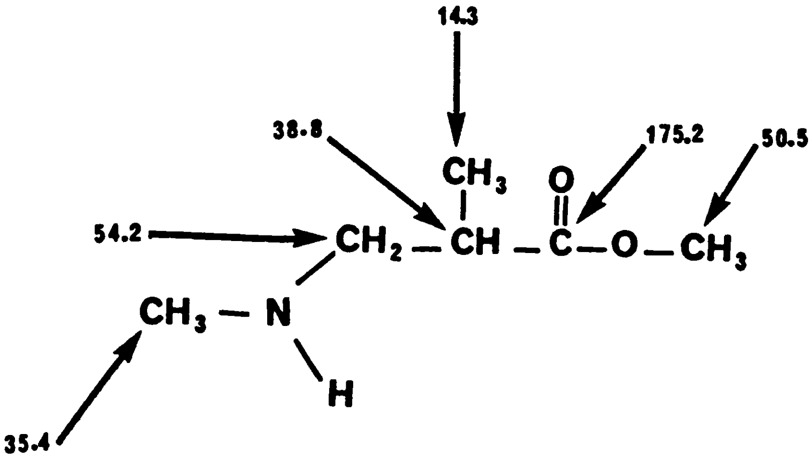
A solution of methylmethacrylate (302 g) in absolute alcohol (180 ml) was added slowly with stirring to a cooled solution of methylamine (200 ml; 33% w/v in IMS) over a period of three hours. After standing for 3 days the ethanol and IMS were evaporated <u>in vacuo</u> and the product was fractionally distilled under reduced pressure to give the title compound (150 g; 57%) as a colourless mobile oil, b.p. 69-72°C/28 mm (Lit.[118] b.p. 65-68°C/20 mm).

ν_{max}: 1740 cm^{-1} ($-\overset{\overset{O}{\|}}{C}-$ str)

δ_H ($CDCl_3$; free base):

1.17 (3H; d; CH-C$\underline{H}_3$), 2.40 (3H; s; H$\underline{N}$-C$\underline{H}_3$); 2.60 - 2.80 (6H; m; C$\underline{H}$-C$\underline{H}_3$; H$\underline{N}$-C$\underline{H}_2$), 3.67 (3H; s, COO-C$\underline{H}_3$).

δ_C ($CDCl_3$; free base):



3.2.2 3 [N-methyl-N-(2-ethyloxycarbonylmethyl)amine]propionate(65)

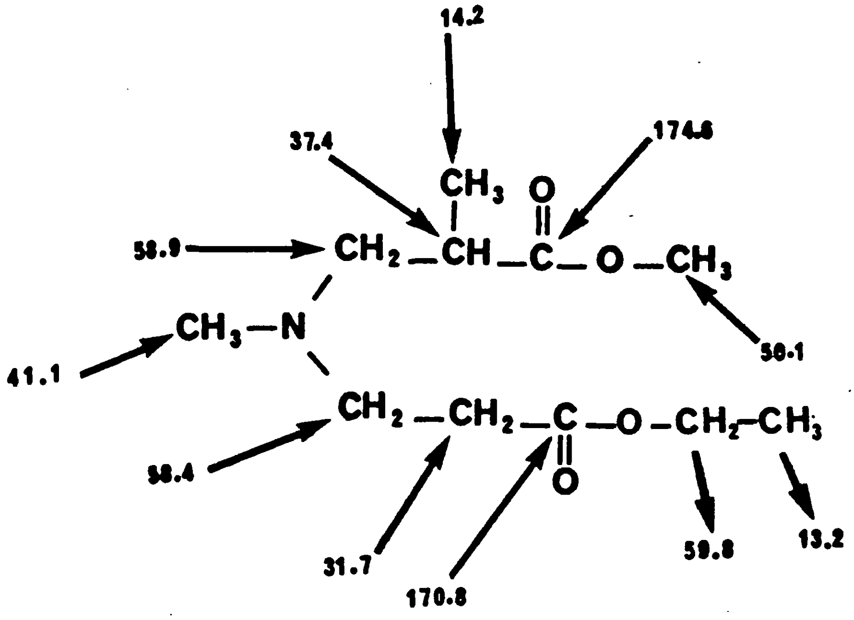
A mixture of methyl 3-methylamino-2-methyl propionate (64; 148 g) and ethyl acrylate (114 g) was left for five days in the dark. The resulting liquid was fractionally distilled under reduced pressure to give the title compound (170 g; 78%) as a colourless oil, b.p. 138-139°C/20 mm (Lit.[118] b.p. 105-107/2.0 mm).

ν_{max}: 1725 cm^{-1} $(-\overset{\overset{O}{\|}}{\underline{C}}-OC_2H_5$ str), 1740 cm^{-1} $(-\overset{\overset{O}{\|}}{\underline{C}}-OMe$ str)

δ_H ($CDCl_3$; free base):

1.06 (3H, d; $CH-C\underline{H}_3$), 1.21 (3H; t; $-CH_2C\underline{H}_3$), 2.18 (3H; s; $\underline{N}-C\underline{H}_3$), 2.21-2.62 (7H; m; $-C\underline{H}_2-C\underline{H}$; $\underline{N}-C\underline{H}_2C\underline{H}_2$), 3.59 (3H; s; $-OC\underline{H}_3$), 4.05 (2H; q; $-OC\underline{H}_2CH_3$).

δ_C ($CDCl_3$; free base):



3.2.3 1,3-Dimethyl-4-piperidone (63)

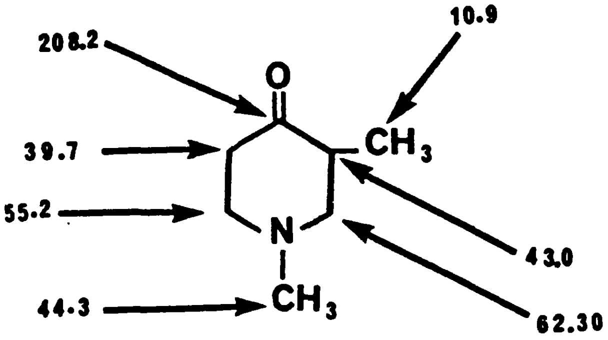
3 [N-methyl-N-(2-ethyloxycarbonylmethyl)amine]propionate (65; 170 g) was added dropwise to a stirred suspension of bird-shot sodium [prepared from sodium (17 g) in dry xylene (396 ml)], and heated gently to maintain the temperature at 60°C. When the initial reaction had subsided, the mixture was refluxed for 3 hours, by which time all the sodium had disappeared. The resulting dark liquid was cooled and added with stirring to ice-water (570 ml). The aqueous layer was separated, washed with ether (2 x 100 ml) and acidified with conc. HCl. After refluxing for four hours the initial vigorous evolution of CO_2 became negligible. The product was concentrated in vacuo to small bulk, made alkaline with solid KOH, the aqueous layer saturated with NaCl, and the dark oily layer then extracted with ether (8 x 250 ml). The organic layer was dried ($MgSO_4$), evaporated under reduced pressure, and the product fractionally distilled in vacuo to give the title compound (60 g; 68%) as a colourless mobile oil, b.p. 58-60°C/10mm (Lit.[118] b.p. 43-43.4/5.5 mm).

ν_{max}: 1750 cm^{-1} ($-\overset{\overset{O}{\|}}{\underline{C}}-$ Str)

δ_H ($CDCl_3$; free base):

0.92 (3H, d; C3-$C\underline{H}_3$), 1.94-2.18 (3H; m; C3-$\underline{H}$; C5-$\underline{H}$), 2.24 (3H; s; $\underline{N}$-$C\underline{H}_3$), 2.95-3.28 (4H; m; C2-$\underline{H}$; C6-$\underline{H}$)

δ_C (CDCl$_3$; free base):



3.2.4 a- and β-1,3-Dimethyl-4-phenyl-4-propionoxypiperidine

1,3-Dimethyl-4-piperidone (63; 60 g) was added dropwise to a stirred solution of phenyl lithium [prepared over one hour from lithium (12.2 g) in dry ether (500 ml) and bromobenzene (136 g)]. After stirring for 24 hours at room temperature, the mixture was added to a mixture of crushed-ice (1000 g) and glacial acetic acid

(105 ml). The aqueous layer was separated and washed with ether (3 x 100 ml; discarded), then basified with strong aqueous ammonia, extracted with ether (5 x 300 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give an oil. This oily isomeric mixture was diluted with petroleum ether (pet. ether b.p. 60-80°C) and the resultant solid was recrystallised from dry ether to give the pure *α*-isomer (68; 70 g; 72%). The pet. ether and ether filtrates were evaporated *in vacuo* to give an *α*; *β* mixture (1:1.2; 16 g; overall recovery 89%), as an oil.

Propionyl chloride (79 g) was added dropwise to a stirred solution of the *α*-isomer obtained above (70 g) in dry toluene (610 ml) and the reaction mixture was refluxed for six hours. The product was cooled, filtered and washed with dry ether to give the *α*- isomer of the title compound as the hydrochloride (40; 75 g, 86%), m.p. 217-219°C (ethanol-ether), (Lit.[57] m.p. 220-221°C).

ν_{max}: 1752 cm^{-1} ($-\overset{\overset{\displaystyle O}{\|}}{\underline{C}}-$ Str).

δ_H: see Table 8. p. 61

δ_C: see Table 7. p. 59

The same procedure described for the esterification of the *α*-isomer was repeated on the *α*, *β*-isomer mixture (16 g) obtained above, in dry toluene (135 ml) using propionyl chloride (18 g) to give the title product as the hydrochloride (21.3 g; 91%). Fractional recrystallisation of the hydrochloride salt from ethanol-ether gave pure *α*-isomer (6.0 g; 26%). The filtrate was evaporated *in vacuo* and recrystallised again from ethanol-ether to give a mixture of *α*- and *β*-isomers (3.2 g). Finally, the filtrate was evaporated *in vacuo* and recrystallised from ethanol-ether to give the β-isomer (41; 8.4 g; 36%), m.p. 200-202°C (ethanol-ether) (Lit.[57] m.p. 199-200°C).

ν_{max}: 1750 cm^{-1} ($-\overset{\overset{O}{\|}}{\underline{C}}-$ Str.).

δ_H: see Table 8., page 61.

δ_C: see Table 7., page 59

3.2.5 α-4-Hydroxy-3-methyl-4-phenylpiperidine (69c)

A suspension of *α*-1,3-dimethyl-4-phenyl-4-propionoxypiperidine (40; 20 g), 2,2,2-trichloroethylchloroformate (26 g) and K_2CO_3 (5.5 g) in dry toluene (250 ml) was refluxed for 2 hours, and then stirred at room temperature for 24 hours. The reaction mixture was diluted with $CHCl_3$ (500 ml), washed with NaOH (2N; 2 x 50 ml), water (2 x 50 ml), HCl (2N; 2 x 30 ml) and finally water (2 x 100 ml). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to yield *α*-3-methyl-4-phenyl-4-propionoxy-1-(2,2,2-trichloroethylcarbonyl) piperidine (69 ; 25 g; 78%), as an oil. The oil was diluted with pet. ether (b.p. 60-80°C), and the solid that settled recrystallised from the same solvent to give the product as a colourless solid, m.p. 158°C.

ν_{max}: 1740 cm^{-1} (-$\overset{\mathrm{O}}{\overset{\|}{\underline{\mathrm{C}}}}$- Str.), 1770 cm^{-1} (N-$\overset{\mathrm{O}}{\overset{\|}{\underline{\mathrm{C}}}}$- Str.).

Zinc dust (12.5 g) was added portionwise to a stirred solution of (69 ; 25 g) in glacial acetic acid (400 ml; 99%). The reaction mixture was refluxed for two hours, and then stirred at room temperature for 10-12 hours. The solid was filtered off and washed with methanol. The organic solvents were evaporated *in vacuo*, and the oily residue dissolved in dichloromethane (DCM; 400 ml). This was washed with NaOH (2N; 3 x 50 ml), water (2 x 70 ml) dried ($MgSO_4$) and evaporated *in vacuo* to give *α*-4-hydroxy-3-methyl-4-phenyl-1-propanoylpiperidine (69a; 5.9 g; 39%), as an oil, which was diluted with ether and the resultant solid recrystallised from the same solvent to give the product as a colourless solid, m.p. 154-155°C.

ν_{max}: 1640 cm^{-1} (-$\overset{\mathrm{O}}{\overset{\|}{\underline{\mathrm{C}}}}$- Str.).

δ_H: see Table 8. p. 61

δ_C: see Table 7. p. 59

m/z: M^{+} 247 (85%), 205 (21%), 190 (84%), 105 (89%), 99 (80%), 57 (100%), see Scheme 6; p. 69 .

Found: C, 72.56; H, 8.84; N, 5.62%

$C_{15}H_{21}NO_2$ requires: C, 72.84; H, 8.56; N, 5.66%

KOH (5 g) was added portionwise to a stirred solution of the *α*-amide (69a; 5 g) in isopropanol (60 ml), and the reaction mixture refluxed for 48 hours. The resulting solution was cooled and the isopropanol evaporated *in vacuo*. DCM (50 ml) was added to the oily residue and the liberated inorganic salt filtered off and washed with DCM (50 ml). The combined organic layer was extracted with HCl (2N; 2 x 20 ml), and the aqueous layer basified with strong aqueous ammonia, extracted with $CHCl_3$ (3 x 40 ml), dried ($MgSO_4$) and evaporated *in vacuo*, to give the title compound (2g; 51%) as an oil. The oil was diluted with pet.ether (b.p. 60-80°C), and the resultant solid recrystallised from the same solvent to give the title compound as a colourless solid, m.p. 130-131°C (Lit.[154] m.p. 125-126°C).

δ_H: see Table 8. p. 61.

δ_C: see Table 7. p. 59.

m/z: M^{+} 191 (100%), 173 (70%), 149 (72%).

Found: C, 63.10; H, 7.88; N, 6.12%.

$C_{12}H_{18}NOCl$ requires: C, 63.30; H, 7.97; N, 6.15%.

3.2.6 α-1-(1-Cyanocyclohexyl)-4-hydroxy-3-methyl-4-phenylpiperidine (69e)

To a solution of α-4-hydroxy-3-methyl-4-phenylpiperidine (69c; 4 g) hydrochloride in water (30 ml) was added a few drops of dilute hydrochloric acid. Cyclohexanone (2 ml) was added and, while stirring vigorously, sufficient alcohol (1 ml, 95%) was added to give a homogeneous solution. A solution of KCN (1.8 g) in water (10 ml) was added dropwise, and vigorous stirring continued at room temperature for 72 hours. The resulting mixture was basified with NaOH (5N) and extracted with $CHCl_3$ (4 x 50 ml). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to give the title compound (3.5 g, 67%) as an oil. The oil was triturated with pet. ether (b.p. 60-80°C) and the resultant solid was recrystallised from the same solvent to give the product as a colourless solid, m.p. 138°C.

δ_H: see Table 8. p. 61.

δ_C: see Table 7. p. 59.

m/z: $M^{+\cdot}$ 298 (28%), 271 (100%), 255 (85%), 105 (52%), 27 (31%).

Found: C, 65.58; H, 8.72; N, 9.00%.

$C_{17}H_{27}N_2OCl$ requires: C, 65.68; H, 8.75; N, 9.01%.

3.2.7 $\underline{\alpha}$-4-Hydroxy-3-methyl-1-(1-phenylcyclohexyl)-4-phenylpiperidine (69g)

A solution $\underline{\alpha}$-1-(1-cyanocyclohexyl)-4-hydroxy-3-methyl-4-phenyl-piperidine (69e; 2.5 g) in dry THF (15 ml) was added dropwise to phenyl magnesium bromide [prepared from Mg (1.8 g) and bromobenzene (11 g) in dry THF (100 ml)]. The reaction mixture was refluxed for 2 hours, and then stirred at room temperature for 24 hours. The resulting mixture was diluted with ether (200 ml) and added to a mixture of crushed ice (100 g) glacial acetic acid (15 ml). The organic layer was separated and washed with NaOH (3N; 3 x 30 ml), dried ($MgSO_4$) and evaporated in vacuo to give the title compound (2.3 g, 76%) as an oil. Treatment of the oil with ethereal-HCl gave the hydrochloride m.p. 230-231°C (methanol).

δ_H: see Table 8. p. 61.

δ_C: see Table 7. p. 59.

m/z: M^+ 349 (49%), 306 (100%), 160 (22%), 91 (47%), 42 (11%), see scheme 11; p. 77 .

Found: C, 73.12; H, 8.15; N, 3.40%.

$C_{24}H_{32}NOCl.\frac{1}{2}H_2O$ requires: C 73.02; H, 8.17; N, 3.55%.

3.2.8 *α*-4-Acetoxy-3-methyl-1-(1-phenylcyclohexyl)-4-phenylpiperidine (69J)

Acetyl chloride (15 ml) was added dropwise to a stirred solution of *α*-4-hydroxy-3-methyl-1-(1-phenylcyclohexyl)-4-phenylpiperidine (69g; 0.5 g) in dry THF (10 ml), and the reaction mixture was refluxed for 12 hours. The resulting solution was cooled and the excess acetyl chloride and THF were evaporated *in vacuo* to give the *title compound* as the *hydrochloride salt* (0.3 g; 60%), m.p. 210-213°C (ethanol-ether).

δ_{max}: 1760 cm^{-1} ($-\overset{\overset{\textstyle O}{\|}}{\underline{C}}-$ Str.).

δ_H: see Table 8. p. 61.

δ_C: see Table 7. p. 59.

m/z: M$^{+\cdot}$ 391 (54%), 348 (100%), 91 (93%).

Found: C, 71.10; H, 7.82; N, 3.15%.

$C_{26}H_{34}NO_2Cl.\frac{1}{2}H_2O$ requires: C, 71.45; H, 7.83; N, 3.20%.

3.2.9 The Synthesis of *β*-4-Hydroxy-3-methyl-1-(1-phenylcyclohexyl)-4-phenylpiperidine (69h)

The same synthetic procedures previously described for the synthesis of the *α*-isomer were employed for the synthesis of *β*-4-hydroxy-3-methyl-1-(1-phenylcyclohexyl)-4-phenylpiperidine. For results see Table 25 and for NMR results see Tables 7 and 8.

3.2.10 Resolution of (±)-α-4-hydroxy-1,3-dimethyl-4-phenylpiperidine (68)

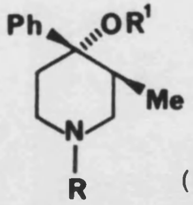
Racemic α-prodinol (68; 20 g) was dissolved in acetone (240 ml) and mixed with (+)-tartaric acid (14.72 g) in methanol (228 ml). Sufficient acetone was added to make a total volume of (800 ml) and the mixture was left for three days at room temperature. The (+)-base, (+)-tartarate salt (16.8 g; 98%) was isolated and recrystallised twice from methanol. The resultant solid had m.p. 163-164°C and $[\alpha]^{25}_{D}$ + 13.5° (C = 1.0 H_2O) (Lit.[69] m.p. 162-163°C with $[\alpha]^{25}_{D}$ + 13.5° (C = 1.0, H_2O) . The (+)-base was regenerated from an aqueous solution of the salt with excess NH_4OH, extracted with ether (3 x 60 ml), dried ($MgSO_4$) and evaporated in vacuo. The remaining solid was recrystallised from petroleum spirit (b.p. 60-80°C) to give (+)-α-4-hydroxy-1,3- dimethyl-4-phenylpiperidine (5.64 g), m.p. 89-90°C, $[\alpha]^{25}_{D}$ + 11.5° (C = 1.0, Me_2CO) [Lit.[69] m.p. 90-91°C $[\alpha]^{25}$ + 11.8° (C = 1.0, Me_2CO)].

Partially resolved (-)- α - 4 -hydroxy-1,3-dimethyl-4-phenylpiperidine was recovered from the resolution mother liquor by addition of base (NH_4OH) and extraction with ether (3 x 50 ml). Solvent was removed in vacuo to give crude (-)-α-4-hydroxy-1,3-dimethyl-4-phenylpiperidine (9.4 g). This base was added to a solution of (-)-tartaric acid (9.62 g) in acetone (1404 ml) and methanol (105 ml), and the mixture was left for thirty days at room temperature. The (-)-base (-)-tartarate salt (12.8 g; 65%) was isolated and recrystallised twice from methanol to yield a solid with m.p. 161-162°C; $[\alpha]_D^{25}$ -13.0°C (C = 1.0, H_2O) [Lit.[69] m.p. 163-164°C; $[\alpha]_D^{25}$ - 12.9° (C = 1.0, H_2O)]. The (-)-free base was regenerated as described for the (+)-isomer, to afford (-)-α-4-hydroxy-1,3-dimethyl-4-phenylpiperidine, m.p. 88-89°C; $[\alpha]_D^{25}$ - 12.5 (C = 1.0, Me_2CO). [Lit.[69] m.p. 89-90°; $[\alpha]_D^{25}$ - 12.0° (C = 1; Me_2CO)] (See Table 26) for full range of optical rotation readings).

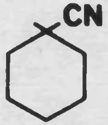
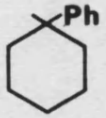
3.2.11 The Synthesis of (-)-α and (+)-α-4-hydroxy-3-methyl-1-(1-phenylcyclohexyl)-4-phenylpiperidine

The synthetic procedures previously described for the synthesis of the α isomer were repeated in order to prepare (+) (69g) and (-) (69g) derivatives. For results see Table 27, p.218 and Table 28, p.219 respectively. The NMR and m/z spectroscopic results of these derivatives were obtained, but are not presented in the thesis, since they are identical to those of the (±)-α-derivatives.

Table 25. The Synthesis of the <u>β</u>-analogues of PCP.



(69)

No	Compound	R	R^1	m.p.(Lit.)	Yield	m/z	Formula	Required %			Found %		
				°C	%	M^+		C	H	N	C	H	N
1	69k	$COOCH_2CCl_3$	COC_2H_5		95								
2	69b	$-COCH_2CH_3$	-H	146-148	43	247 (92%)	$C_{15}H_{21}NO_2$	72.84	8.56	5.66	72.59	8.52	5.58
3	69d	-H	-H	156^b(150-151)	54	191 (82%)	$C_{12}H_{18}NOCl.½H_2O$	61.00	7.66	5.92	61.28	7.82	6.14
4	69f		-H	$134-135^b$	73	298 (76%)	$C_{17}H_{27}N_2OCl.½H_2O$	63.84	8.51	8.76	63.80	8.76	8.82
5	69h		-H	$230-213^s$	76	349 (100%)	$C_{24}H_{32}NOCl.½H_2O$	73.02	8.17	3.55	73.40	8.27	3.52

s Of the hydrochloride salt

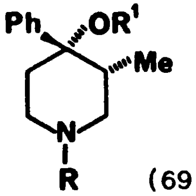
b Of the free base

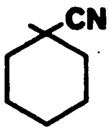
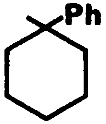
Table 26. Specific Rotation [α] of (+)-α-4-Hydroxy-1,3-Dimethyl-4-Phenylpiperidine-(+)-Tartarate and (−)-α-4-Hydroxy-1,3-Dimethyl-4-Phenylpiperidine-(−)-Tartarate

salt[a]	Wavelength (nm)	$[\alpha]_D^{25}$
(+)-α-4-Hydroxy-1,3-dimethyl-4-phenylpiperidine-(+)-tartarate	589	+ 13.5°
	546	+ 14.0°
	436	+ 19.5°
	365	+ 25.5°
(−)-α-4-Hydroxy-1,3-dimethyl-4-phenylpiperidine-(−)-tartarate	589	− 13.0°
	546	− 15.5°
	436	− 19.0°
	365	− 24.0°

a. Concentration = 1% w/v; Solvent H_2O

Table 2.7. The Synthesis of the (+)-$\underline{\alpha}$-analogues of PCP.

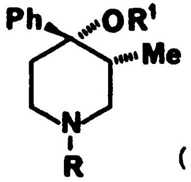

(69)

No	Compound	R	R^1	m.p.(Lit.) °C	Yield %	Formula	Required %			Found %		
							C	H	N	C	H	N
1	40a	CH_3	COC_2H_5	214-215[s] (194-196)[69]	88							
2	69m	$COOCH_2CCl_3$	COC_2H_5		81							
3	69a	COC_2H_5	H	162-163	40	$C_{15}H_{21}NO_2$	72.84	8.56	5.66	72.38	8.44	5.46
4	69c	H	H	134-135[b]	60	$C_{12}H_{18}NOCl$	63.30	7.97	6.15	62.96	7.78	6.00
5	69e		H	144-145[b]	71	$C_{17}H_{27}N_2OCl.\frac{1}{2}H_2O$	63.84	8.51	8.76	64.08	8.89	8.88
6	69g		H	238-239[s]	72	$C_{24}H_{32}NOCl$	74.73	8.37	3.64	74.65	8.31	3.75

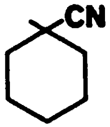
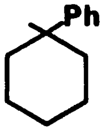
s Of the hydrochloride salt

b Of the free base

Table 28. The Synthesis of the (-)-α-analogues of PCP.



(69)

No	Compound	R	R^1	m.p.(Lit.) °C	Yield %	Formula	Required %			Found %		
							C	H	N	C	H	N
1	40b	CH_3	COC_2H_5	218-219[s](196-197)[69]	85							
2	69m	$COOCH_2CCl_3$	COC_2H_5		82							
3	69a	COC_2H_5	H	171-172	42	$C_{15}H_{21}NO_2$	72.84	8.56	5.66	72.58	8.47	5.41
4	69c	H	H	142-153[b]	64	$C_{12}H_{18}NOCl$	63.30	7.97	6.15	62.91	7.80	6.10
5	69e		H	138-139[b]	72	$C_{17}H_{27}N_2OCl$	65.68	9.01	8.75	65.42	8.92	8.76
6	69g		H	236-237[s]	75	$C_{24}H_{32}NOCl$	74.73	8.37	3.64	74.85	8.21	3.57

s Of the hydrochloride salt

d Of the free base

3.3 THE SYNTHESIS OF 4-ALKYL-4-ARYLPIPERIDINES

3.3.1 Dehydration of α-4-hydroxy-1,3-dimethyl-4-phenylpiperidine

A mixture of α-4-hydroxy-1,3-dimethyl-4-phenylpiperidine (68; 10 g), concentrated hydrochloric acid (83 ml) and glacial acetic acid (155 ml) was refluxed for six h. The mixture was concentrated *in vacuo*, diluted with H_2O (70 ml), basified with strong ammonia, extracted with ether (3 x 80 ml), dried ($MgSO_4$) and evaporated *in vacuo* to yield a mixture of 1,2,5,6-tetrahydro-1,3-dimethyl-4-phenylpyridine and 1,2,5,6-tetrahydro-1,5-dimethyl-4-phenylpyridine (7.6 g; 82%) as an oil. Treatment of the oily residue with ethereal-HCl and subsequent fractional crystallisation from ethanol-ether afforded the 5-Me isomer (71) as the hydrochloride (3.3 g; 36%), m.p. 193° (Lit.[132] 196°C).

The filtrate was evaporated *in vacuo* and recrystallised from the same solvent, yielding an additional crop (1.9 g; overall recovery: 56%) of the pure 5-Me compound. Finally, the filtrate was evaporated *in vacuo* and recrystallised from isopropanol-ether to give mainly the 3-Me isomer with a trace of the 5-Me isomer, which was recrystallised from ethanol-ether to yield the pure 3-Me isomer (72; 0.5 g; 6%), m.p. 191°C (Lit.[132] 189-190°C). The isomers (71) and (72) were readily differentiated by means of ^1H NMR spectroscopy.

5-Me isomer (71)

δ_H ($CDCl_3$; free base):

0.97 (3H; d; C5-CH_3), 2.33 (3H; s, N-CH_3), 2.62 (1H; d x d; C5-H), 2.88-3.10 (4H; m; C6-H, C2-H), 5.80 (1H, m, C3-H), 7.15-7.29 (5H, m, Ar-H).

δ_C (CDCl$_3$, free base):
18.38 (C5-CH$_3$), 31.66 (C-5), 45.48 (N-CH$_3$), 55.01 (C-6), 59.76 (C-2), 121.89 (C-3), 125.65 (Ar-Cm), 126.29 (Ar-Cp), 127.75 (Ar-Co), 140.40 (C-4), 140.50 (Ar-Cq).

3-Me isomer (72)

δ_H (CDl$_3$; free base):
1.62 (3H; s, C3-CH$_3$), 2.82 (3H, s, N-CH$_3$), 1.62 (2H, brs, C5-H), 3.21 (2H, m, C6-H), 3.48 (2H, brs, C2-H), 7.15-7.38 (5H, m, Ar-H).

δ_C (CDCl$_3$; free base):
17.48 (C3-CH$_3$), 28.8 (C-5), 43.16 (N-CH$_3$), 51.00 (C-6), 56.34 (C-2), 122.90 (C-3), 127.11 (Ar-Cm), 128.10 (Ar-Cp), 128.30 (Ar-Co), 130.94 (C-4), 140.30 (Ar-Cq).

3.3.2 1,4,5,6-Tetrahydro-1,4,5-trimethyl-4-phenylpyridine (73)

To a solution of 1,2,5,6-tetrahydro-1,5-dimethyl-4-phenylpyridine (71; 5 g; 0.027 mole) in dry tetrahydrofuran (50 ml) under N$_2$ at -10°C was added *n*-butyl lithium (24 ml; 0.034 mole; 1.4 M in hexane) at such a rate that the temperature was maintained at less than -5°C. The resulting deep red solution was stirred for 15 minutes at -5°C and then cooled to -30°C. Dimethylsulphate (3.4 g; 0.027 mole) in dry tetrahydrofuran (50 ml) at -40°C was added dropwise such that the temperature was maintained at less than -30°C. The final solution was warmed to -10°C, stirred for 30 minutes at this temperature, and the residual n-butyllithium quenched by the addition of H_2O (20 ml). The organic layer was separated, washed with H_2O (10 ml) and then saturated NaCl (10 ml), dried ($MgSO_4$) and evaporated in vacuo to yield a mixture (0.56 g) of the title compound and the corresponding quaternary ammonium salt as an oil.The oily residue was diluted with dry ether and the resultant solid was filtered to yield the quaternary ammonium salt of the title compound (74; 0.4 g), m.p. 157-158°C. The filtrate was evaporated in vacuo to give the title compound (0.1 g) as an oil.

Quaternary ammonium salt (74)

δ_H (D_2O):

0.66 (3H, d, C5-CH_3), 1.58 (3H, s, C4-CH_3), 2.36 (1H, dq, C5-H), 3.02 (1H, t, C6-Hax), 3.66 (1H, brs, C6-Heq), 3.78 (3H, s, N-CH_3ax), 3.81 (3H, s, N-CH_3eq), 5.83 (1H, m, C3-H), 6.46 (1H, d, C2-H), 7.22-7.42 (5H, m, Ar-H).

δ_C(D_2O):

11.73 (C5-CH_3), 27.82 (C4-CH_3), 37.30 (C-4), 40.45 (C-5), 42.27 (N-CH_3, ax), 42.91 (N-CH_3, eq), 49.82 (C-6), 131.64 (C-3), 113.64 (C-3), 131.20(C-2), 145.00 (Ar-Cq), 115.00-119.55 (Other Ar-C).

Found: C, 58.62; H, 7.62; N, 4.22%

$C_{16}H_{25}NO_4S$ requires: C, 58.69; H, 7.70; N, 4.28%.

Free base (73)

δ_H ($CDCl_3$; free base):

0.58 (3H, d, C5-C$\underline{H}_3$), 1.46 (3H, s, C4-C$\underline{H}_3$), 1.93 (1H, m, C5-$\underline{H}$), 2.53 (2H, m, C6-$\underline{H}$), 2.69 (3H, s, $\underline{N}$-C$\underline{H}_3$), 4.34 (1H, d, C3-$\underline{H}$), 5.98 (1H, d, C2-$\underline{H}$), 7.17-7.47 (5H, m, Ar-$\underline{H}$)

δ_C ($CDCl_3$; free base): 14.95 (C5-$\underline{C}H_3$), 28.00 (C4-$\underline{C}H_3$), 38.73 (C-5), 40.06 (C-4), 42.46 ($\underline{N}$-$\underline{C}H_3$), 52.71 (C-6), 106.16 (C-3), 125.50 (Ar-Cm), 126.11 (Ar-Cp), 128.73 (Ar-Co), 133.26 (C-2), 146.20 (Ar-Cq).

Attempts were then made to secure (73) by N-demethylation of the quaternary salt (74) by the following method:

The N-methyl quaternary salt (74; 0.38 g) in methanol (20 ml) was stirred with dry, freshly prepared silver chloride (6 g) for four hours. The resultant solid was filtered off and washed with methanol (15 ml). The washings were combined with the original filtrate and evaporated in vacuo to give an oil, which was dissolved in ethanol (20 ml) and treated with a solution of sodium thiophenate (1.4 g) in ethanol (60 ml). After the mixture had been stirred for 30 minutes, the sodium chloride which separated was filtered off and washed with ethanol (20 ml). The filtrate was evaporated in vacuo, and the oily residue was dissolved in ethyl methyl ketone (100 ml) and refluxed gently under N_2 for 20 hours. The solvent was evaporated in vacuo and the residue was treated with ether (100 ml), followed by extraction with HCl (2N: 2 x 10 ml). The combined aqueous extracts were basified with strong aqueous ammonia, extracted with ether (3 x 10 ml), and the ether dried ($MgSO_4$) and evaporated in vacuo to yield the crude title product (0.07 g; 35%) as an oil. Treatment of this oil with ethereal-HCl afforded the enamine salt (77) as an oil.

The enamine salt (77)

δ_H (D_2O):

0.83 (3H, d, C5-C$\underline{H}_3$), 1.42 (3H, s, C4-C$\underline{H}_3$), 2.54 (1H, q, C5-$\underline{H}$), 3.38-3.42 (2H, m, C3-$\underline{H}$), 3.80 (3H, s, $\underline{N}$-C$\underline{H}_3$), 3.88-4.04 (2H, m, C6-$\underline{H}$), 7.25-7.42 (5H, m, Ar-$\underline{H}$), 8.95 (1H, s, C2-$\underline{H}$)

δ_C (D_2O):

14.00 (C5-$\underline{C}H_3$), 28.41 (C4-$\underline{C}H_3$), 36.60 (C-5), 38.73 (C-4), 39.20 (C-3), 49.53 ($\underline{N}$-$\underline{C}H_3$), 56.90 (C-6), 126.70 (Ar-Cm), 129.64 (Ar-Cp), 133.34 (Ar-Co), 144.31 (Ar-Cq), 179.66 (C-2).

3.3.3 The synthesis of 1,3,4-Trimethyl-4-phenylpiperidine (75)

A. 1,4,5,6-Tetrahydro-1,4,5-trimethyl-4-phenylpiperidine (73; 0.08 g) in ethanol (30 ml) was hydrogenated at room temperature over palladium (5%:, Pd on C; 0.1 g) at 60 p.s.i., in a rocking Parr apparatus for 12 h. The catalyst was filtered off and the filtrate evaporated in vacuo to yield the crude title compound (0.05 g; 62%) as an oil. Treatment of this oil with ethereal-HCl afforded the hydrochloride salt m.p. 193-194°C (ethanol-ether). (Sample supplied by D. Zimmerman, m.p. 188-189°C; Mix m.p. 184-188°C). This compound is a pure, single isomer (see p.167).

δ_H: see Table 12, p. 147.

δ_C: see Table 11 , p.146.

B. Sodium borohydride (0.06 g) was added to a stirred solution of the enamine salt (77) obtained in section 3.3.2B in ethanol (2 ml). The resulting mixture was stirred for 3 h at room temperature. The excess of sodium borohydride was destroyed by the addition of HCl (2 N; 1 ml), followed by water (10 ml), which was then basified with concentrated aqueous ammonia and extracted with ether (3 x 5 ml). The combined organic extract was washed with H_2O (2 x 4 ml), dried ($MgSO_4$) and finally evaporated in vacuo to yield the crude title compound (0.035 g; 69%) as an oil. Treatment of this oil with ethereal-HCl afforded the hydrochloride salt, m.p. 189-191°C (ethanol-ether). Thin layer chromatography (TLC) and ^1H NMR analysis have shown this compound to be identical with the material obtained above (Section A).

3.3.4 1,3-Dimethyl-4-piperidone methiodide (80)

Methyl iodide (35 g) was added dropwise to a stirred solution of 1,3-dimethyl-4-piperidone (63; 30 g) in acetone (250 ml). The reaction mixture was stirred for two hours. The solid produced was filtered off and washed with dry ether to give the title compound (60 g; 40%), m.p. 170-172°C (Lit.[155] 184-185°C) as a colourless solid. Its purity was considered sufficient for use in the subsequent reactions.

ν_{max} : 1740 cm^{-1} $(-\overset{\overset{O}{\|}}{C}-)$

3.3.5 1-Benzyl-3-methyl-4-piperidone (78)

1,3-Dimethyl-4-piperidone methiodide (80; 50 g), benzylamine

(21 g) and water (19 ml) were combined, and the resulting mixture was warmed to give a clear solution. The reaction mixture was left overnight at room temperature. The oily layer which separated was extracted with ether (6 x 100 ml), dried ($MgSO_4$) and then evaporated *in vacuo* to give a dark oil, which was distilled under vacuum to give the title product (15 g; 33%), b.p. 100-110°C/0.2 mm. (Lit.[41], b.p. 110-115°C/0.3 mm).

ν_{max} : 1755 cm^{-1} ($-\overset{\overset{O}{\|}}{C}-$ str)

δ_H ($CDCl_3$; free base):
0.97 (3H, d, C3-C$\underline{H}_3$), 3.60 (2H, s, Ar-C$\underline{H}_2$), 7.25-7.37 (5H, m, Ar-$\underline{H}$).

3.3.6 **α- and β-1-Benzyl-4-hydroxy-4-(3-methoxyphenyl)-3-methylpiperidine (83)**

Sec-Butyl lithium (86 ml; 0.12 mole; 1.4 M in hexane) was added dropwise to a stirred solution of *m*-bromoanisole (22 g; 0.12 mole) in dry tetrahydrofuran (60 ml) under N_2 at -55°C. The resulting suspension was stirred at this temperature for 1 h and this was followed by the addition of 1-benzyl-3-methyl-4-piperidone (78; 15 g; 0.08 mole) in dry tetrahydrofuran (100 ml) at a rate such that the temperature was maintained below -40°C. When the addition was complete, the temperature was allowed to rise to approximately -20°C over about 1 h and then to room temperature over a further 1 h period. Residual *sec*-butyl lithium was quenched by the addition of saturated NaCl (50 ml), followed by the addition of H_2O (50 ml). The organic layer was separated, washed with NaOH (2N; 100 ml), H_2O (2 x 50 ml), dried ($MgSO_4$) and evaporated *in vacuo* to yield a mixture of the title compound (22.2 g; 72%) as an oil, which was employed in the next synthetic step.

ν_{max} : 3060-3300 cm^{-1} (O-H str.).

3.3.7 Dehydration of α- and β-1-benzyl-4-hydroxy-4-(3-methoxyphen 1)-3-methylpiperidine

The isomeric mixture (83) obtained in Section 3.3.6 (12 g) was treated with concentrated HCl (100 ml) and glacial acetic acid (190 ml) by the same procedure described in Section 3.3.1 to yield a mixture (10 g; 88%) of 1-benzyl-1,2,5,6-tetrahydro-4-(3-methoxyphenyl)-5-methylpyridine (84) and the corresponding 3-methyl isomer (85). Treatment of the oily residue with ethereal-HCl, and subsequent fractional crystallisation from ethanol-ether, afforded the 5-Me isomer (7 g; 61.1%), m.p. 227°C (ethanol). (Lit.[132], 225-226°C).

The 5-Me isomer (84)

δ_H ($CDCl_3$; free base): 1.01 (3H, d, C5-$C\underline{H}_3$), 2.44-2.59 (2H, m, C6-Hax, C2-Hax), 3.03-3.23 (2H, m, C2-Heq, C6-Heq), 3.56 (2H, s, -$C\underline{H}_2$Ph), 3.76 (3H, s, $O\underline{CH}_3$), 5.85 (1H, dt, C3-$\underline{H}$), 6.73-7.39 (9H, m, Ar-$\underline{H}$).

δ_C ($CDCl_3$; free base):

18.64 (C5-$\underline{C}H_3$), 32.41 (C-5), 53.80 (C-6), 55.04 (O$\underline{Me}$), 57.21 (C-2), 111.96 (C-3), 138.59 (Ar-Cq), 141.02 (C-4), 142.35 (Ar-1'), 159.51 (Ar-3'), 114.01-129.06 (other aromatic carbons).

3.3.8 1-Benzyl-4-hydroxy-4-phenylpiperidine (108)

1-Benzyl-4-piperidone (30 g) was treated with phenyl lithium [prepared from lithium (5 g) and bromobenzene (58 g) in dry ether (300 ml)] by the same procedure described in Section 3.2.4 to yield the title compound (40 g; 94%) as an oil.

ν_{max} : 3460 cm^{-1} (O-H str.).

δ_H ($CDCl_3$; free base):

1.64 (2H, dd, C3/5-$\underline{H}$eq), 2.08 (2H, dt, C3/5-$\underline{H}$ax), 2.43 (2H, dt, C2/C6-$\underline{H}$ax), 2.70 (2H, brd, C2/6-$\underline{H}$eq), 3.51 (2H, s, C$\underline{H}_2$-Ph), 7.16-7.47 (10H, m, Ar-$\underline{H}$).

δ_C ($CDCl_3$; free base):

38.14 (C-5/3), 49.10 (C-2/6), 69.98 ($\underline{C}H_2$-Ph), 70.93 (C-4), CH_2-Ar-$\underline{C}$q (138.04), C4-Ar-$\underline{C}$q (148.39), other aromatic carbons (124.45-129.10).

3.3.9 1-Benzyl-1,2,5,6-tetrahydro-4-phenylpyridine (109)

1-Benzyl-4-hydroxy-4-phenylpiperidine (108; 15 g) was treated with concentrated HCl (120 ml) and glacial acetic acid (225 ml) by the same procedure described in Section 3.3.1 to yield the crude title product as an oil. This oil was diluted with petroleum ether (b.p. 40-60°C), the resultant solid (starting material) was filtered off and the filtrate was evaporated *in vacuo* to yield the title compound (11.5 g; 82%) as an oil.

δ_H ($CDCl_3$; free base):

2.55 (2H, m, C5-$\underline{H}$), 2.69-3.16 (4H, m, C2-$\underline{H}$, C6-$\underline{H}$), 3.62 (2H, s, -$\underline{CH_2}$-Ph), 6.05 (1H, m, C3-$\underline{H}$), 7.16-7.37 (10 H, m, Ar-$\underline{H}$).

δ_C ($CDCl_3$; free base):

27.86 (C-5), 49.78 (C-6), 53.16 (C-2), 62.53 ($\underline{C}H_2$-Ph), 121.72 (C-3), 134.73 (C-4), 138.10 (CH_2-Ph-$\underline{C}$q), 140.67 (4-Ph-$\underline{C}$q), other aromatic carbons (124.71-129.03).

3.3.10 1-Benzyl-1,4,5,6-tetrahydro-4-methyl-4-phenylpyridine (106)

1-Benzyl-1,2,5,6-tetrahydro-4-phenylpyridine (109; 10 g; 0.04 mole) in dry tetrahydrofuran (100 ml) was treated with n-butyl lithium (32 ml; 0.045 mole; 1.4 M in hexane) and then with dimethylsulphate (5.1 g, 0.04 mole) by the same procedure described in Section 3.3.2, to yield the crude product (6.4 g; 60%) as an oil. An attempt to distill this mobile oil under vacuum failed and therefore it was employed in the next synthetic step without any further purification.

δ_H ($CDCl_3$; free base):

1.40 (3H, s, C4-$\underline{CH_3}$), 1.81-1.97 (2H, m, C5-$\underline{H}$), 2.51-2.78 (2H, m, C6-$\underline{H}$), 3.96 (2H, s, $\underline{CH_2}$-Ph), 4.48 (1H, dxd, C3-$\underline{H}$), 6.14 (1H, d, C2-H), 7.09-7.41 (10 H, m, Ar-H).

3.3.11 4-Hydroxy-4-(3-methoxyphenyl)-1-methylpiperidine (93)

Sec-Butyl lithium (221 ml; 0.31 mole; 1.4 M in hexane) was added dropwise to a stirred solution of *m*-bromoanisole (45.9 g; 0.25 mole) in dry tetrahydrofuran (110 ml) under N_2 at -55°C. The resulting suspension was stirred at -50°C for 1 h. and this was followed by the addition of 1-methyl-4-piperidone (92; 80 g; 0.27 mole) in dry tetrahydrofuran (100 ml) at a rate such that the temperature was maintained below -40°C. When the addition was complete, the temperature was allowed to rise to approximately -20°C over about 1 h., and then to room temperature over a further 1 h. period. Residual *sec*-butyl lithium was quenched by the addition of saturated NaCl (100 ml), followed by the addition of H_2O (100 ml). The organic layer was separated, washed with NaOH (2N; 100 ml), H_2O (2 x 50 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give the crude title product as an oil. This was diluted with hexane (150 ml) and the resultant solid was filtered. The isolated crystalline product was dried in a vacuum oven to provide the pure product (50.6 g; 87%), m.p. 112-113°C (Lit.[53], m.p. 112-113°C).

δ_H ($CDCl_3$; free base):

1.68 (2H, d, eq C3/5-Heq), 2.11 (2H, td, C3/5-Hax), 2.24 (3H, s, N-CH_3), 2.44 (2H, dt, C2/6-Hax), 2.57 (2H, d, C2/6-Heq), 3.76 (3H, s, OCH_3), 6.74-7.26 (4H, m, Ar-H)

δ_C ($CDCl_3$; free base):

38.11 (C-3/5), 46.10 (N-CH$_3$), 51.41 (C-2/6), 54.10 (OCH$_3$), 70.02 (C-4), 110.60 (Ar-2'), 112.00 (Ar-4'), 116.83 (Ar-6'), 129.10 (Ar-5'), 150.50 (Cq-1'), 159.45 (Cq-3').

3.3.12 1,2,5,6-Tetrahydro-4-(3-methoxyphenyl)-1-methylpyridine (89)

A mixture of 4-hydroxy-4-(3-methoxyphenyl)-1-methylpiperidine (93; 24 g), concentrated HCl (250 ml) and glacial acetic acid (470 ml) was refluxed for 12 hours, and then concentrated *in vacuo*. The oily residue was diluted with H_2O (300 ml), basified with strong aqueous ammonia, extracted with ether (4 x 100 ml), dried ($MgSO_4$) and evaporated *in vacuo* to yield the crude title product (23 g; 82%), as a dark oil. The oily residue was diluted with petroleum ether (b.p. 40-60°C) and the resultant solid was filtered off. The filtrate was evaporated *in vacuo* to give the title compound (20.50 g; 73%), as an oil.

δ_H ($CDCl_3$; free base):

2.52 (2H, m, C5-H), 2.60 (2H, m, C6/2-Hax), 2.33 (3H, s, N-CH$_3$), 3.03 (2H, d, C6/2-Heq), 3.70 (3H, s, OCH$_3$), 6.01 (1H, dt, C3-H), 6.70-7.35 (4H, m, Ar-H).

δ_C ($CDCl_3$; free base):

27.57 (C-5), 45.10 (N-CH$_3$), 51.64 (C-6), 54.32 (C-2), 54.36 (OCH$_3$), 110.34 (Ar-2'), 111.54 (C-3), 116.86 (Ar-4'), 121.37 (Ar-6'), 128.57 (Ar-5'), 141.81 (Cq-1'), 144.00 (C-4), 159.06 (Cq-3').

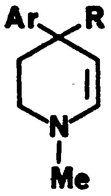
3.3.13 1,4,5,6-Tetrahydro-4-(3-methoxyphenyl)-1-methyl-4-(2-methylprop-1-yl)pyridine (90a)

To a solution of 1,2,5,6-tetrahydro-4-(3-methoxyphenyl)-1-methylpyridine (89; 6 g; 0.03 mole) in dry tetrahydrofuran (84 ml) under N_2 at -10°C was added n-butyl lithium (15 ml; 0.047 mole; 2.5 M in hexane) at such a rate that the temperature was maintained at less than -5°C. The resulting deep red solution was stirred for 15 minutes at -5°C and 1-bromo-2-methylpropane (5.1 g; 0.037 mole) in dry tetrahydrofuran (70 ml) added dropwise at such a rate that the temperature was maintained at less than -5°C. The reaction mixture was stirred for 10 minutes at -5°C, and the residual n-butyl lithium quenched by the addition of H_2O (40 ml). The organic layer was separated, washed with H_2O (20 ml) and then saturated NaCl (20 ml), dried ($MgSO_4$) and evaporated in vacuo to give the crude title product (6.8 g; 92%), which was purified according to the following procedure. To a solution of the crude product obtained above (6.8 g) in hexane : ethyl acetate (68 ml, 44:24) was added silica gel (6.8 g) to produce a slurry, which was stirred for 2 hours at room temperature. The slurry was filtered off and washed with hexane : ethyl acetate (73 ml; 48:25). Evaporation of the solvent mixture in vacuo gave 1,4,5,6-tetrahydro-4-(3-methoxyphenyl)-1-methyl-4-(2-methylprop-1-yl)pyridine (5.2 g; 70%) as an oil.

δ_H : see Table 31, p. 235.

δ_C : see Table 30, p. 234.

Table 29. **The Synthesis of some 4-alkyl-4-aryl-1,4,5,6-tetrahydro-1-methylpyridines**



(90)

Ar = C_6H_4-OMe (*m*)

Compound	R	Yield (%)[D]
a	*iso*-Bu[A]	70
b	*n*-Pr[B]	63
c	Me[C]	39

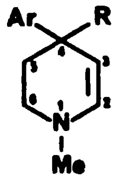
A. Results for the 4-*iso*-Bu derivative in this table and subsequent tables are presented for comparative reasons.

B. *n*-Propylbromide was employed as alkylhalide

C. See Section 3.3.20 for full experimental conditions.

D. Of of the purified 4-alkyl compound from the corresponding 4-aryl-1,4,5,6-tetrahydro-1-methylpyridine (89).

Table 30. ^{13}C NMR of Some 4-Alkyl-4-aryl-1,4,5,6-tetrahydro-1-methylpyridines.[a]



Ar = m.OMe.C_6H_4

(90)

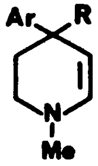
		^{13}C Chemical shifts (ppm; TMS internal standard)											
Compound	R	C-2	C-3	C-4	C-5	C-6	N-Me	4-R α- and β-C	 Me; Me_2	OMe	Cq-1'	Cq-3'	Other Ar-C
a	$\overset{\alpha}{C}H_2\ \overset{\beta}{C}H\ (Me)_2$	136.23	103.14	40.31	37.50	b	42.13	α-CH_2: c β-CH_2: 24.60	Me_2:25.04; 25.00	54.81	152.00	159.00	128.41; 119.62; 114.10; 109.63
b	$\overset{\alpha}{C}H_2\ \overset{\beta}{C}H_2\ CH_3$	136.32	103.00	40.02	37.01	46.30	42.18	α-CH_2: 45.9 β-CH_2: 17.16	Me: 14.60	54.80	151.60	159.10	128.51; 119.43; 114.0; 109.92
c	Me	135.81	105.41	nr38.70	38.50	46.32	42.23	—	Me: 30.60	54.71	152.70	159.03	128.54; 118.91; 113.26; 109.92

a. Bases in $CDCl_3$

b. Signals overlap at 146.20 ppm

c. Unresolved.

Table 31. ^{1}H NMR (δ scale in ppm) of Some 4-Alkyl-4-aryl-1,4,5,6-tetrahydro-1-methylpyridine[a]



(90)

Ar = $\underline{m}$-OMe . C_6H_4

Compound	R	$\underline{N}$-$\underline{Me}$	C2–H	C3–H	C5–H	C6–H	O$\underline{Me}$	Other protons
a	$-\overset{\alpha}{C}H_2\overset{\beta}{C}H(Me_2)$	2.54, s	5.93, d	4.64, d	c	ax:eq: 2.53–2.70, m	3.80,s	Ar–$\underline{H}$: 6.64–7.21, m $-C\underline{H}_2CH$: 16.2, m $-CH_2C\underline{H}$: 1.22, m $-CH(\underline{Me})_2$: 0.74, d and 0.91, d
b	$-\overset{\alpha}{C}H_2\overset{\beta}{C}H_2CH_3$	2.54, s	5.40, d	4.81,dxd	d	ax/eq: 2.44–2.74, m	3.75,s	Ar–$\underline{H}$: 6.70–7.22,m $-CH_2-\underline{C}H_2$: 1.26–1.31, m $-CH_2-CH_2-CH_3$: 0.81, t $-C\underline{H}_2-CH_2$: 1.52–1.82, m
c	Me	2.57, s	6.7, d	5.92, d	b	ax/eq: 2.43–2.73, m	3.80,s	Ar–$\underline{H}$: 6.70–7.22, m C4–$\underline{Me}$: 1.38, s

a. Bases in $CDCl_3$

b. Signals overlap (1.60–1.73 m)

c. Signals overlap (1.73 – 2.01 m)

d. Signals overlap (1.81 – 2.10 m)

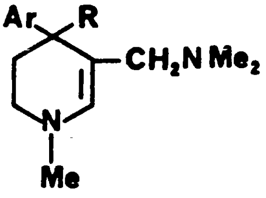
3.3.14 1,4,5,6-Tetrahydro-4-(3-methoxyphenyl)-1-methyl-3-dimethylaminomethyl-4-(2-methylprop-1-yl)pyridine (91a)

To a solution of aqueous formaldehyde (1.5 g; 37%) and aqueous dimethylamine (2.1 g; 40%) in H_2O (15 ml) was added enough concentrated H_2SO_4 to adjust the pH of the reaction mixture to 3-4. A solution of 1,4,5,6-tetrahydro-4-(3-methoxyphenyl)-1-methyl-4-(2-methylprop-1-yl)pyridine sulphate [prepared by the extraction of (90a, 5 g) with H_2SO_4 (2.5 M; 2 x 8 ml) from a solution in hexane (10 ml)] was added, and the pH adjusted to 3-3.5 by the addition of H_2SO_4 or dimethylamine. The mixture was stirred at approximately 60-70°C for 2 h. while maintaining the pH of the reaction mixture between 3-3.5. The solution was cooled to room temperature and added to NaOH (25%; 30 ml). The resulting suspension was extracted with hexane (4 x 25 ml). The combined organic extracts were washed with H_2O (5 x 15 ml), dried ($MgSO_4$) and evaporated in vacuo to yield the title product (2.27 g; 74%) as an oil.

δ_H : see Table 34, p. 239.

δ_C : see Table 33, p. 238.

Table 32. The Synthesis of some 4-alkyl-4-aryl-1,4,5,6-tetrahydro-3-dimethylaminomethyl-1-methylpyridines



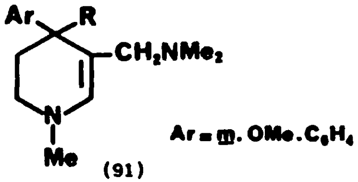
(91)

Ar = C_6H_4-OMe(m)

Compound	R	Yield (%)[A]
a	iso-Bu	78
b	n-Pr	74
c	Me	63

A. Of the crude Mannich base from the corresponding 4-alkyl-4-aryl-1,4,5,6-tetrahydro-1-methylpyridine (90).

Table 33. ^{13}C NMR of some 4-Alkyl-4-aryl-3-dimethylaminomethyl-1,4,5,6-tetrahydro-1-methylpyridines.



(91)

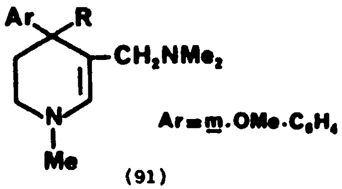
		^{13}C Chemical shifts (ppm; TMS internal standard)												
		C-2	C-4	C-5	C-6	N-Me	C3-$CH_2N(Me)_2$		4-R		OMe	Cq-1'	Cq-3'	Other Ar-C and C-C
Compound	R						CH_2	Me_2	α- and β-C	Me; $(Me)_2$				
a	$CH_2CH(Me)_2$	136.40	43.95	33.61	b	42.90	60.80	45.60	α-CH_2: b β-CH_2: 24.60	Me_2: 26.5 26.4	54.91	151.54	159.6	128.35; 120.01; 114.33; 110.15; 109.11
b	CH_2CH_2Me	136.50	42.90	36.20	46.20	43.10	60.60	45.80	α-CH_2: 40.00 β-CH_2: 18.00	Me: 14.90	55.01	151.70	159.1	128.50; 120.00; 114.20; 110.15; 108.90
c	Me	136.00	39.30	c	46.20	42.75	61.30	45.20	-	Me: 26.60	54.80	151.31	159.1	128.50; 119.40; 113.52; 110.11; 110.47

a. Bases in $CDCl_3$

b. Signals overlap at 46.30 ppm

c. Unresolved

Table 34. ^1H NMR (δ scale in ppm) of some 4-Alkyl-4-aryl-3-dimethylaminomethyl-1,4,5,6-tetrahydro-1-methylpyridines.[a]



(91)

Compound	R	N-Me	C2-H	C5-H	C6-H	$C3-CH_2$	$N-(Me)_2$	OMe	Other protons
a	$-\overset{\alpha}{C}H_2\overset{\beta}{C}H(Me)_2$	2.62, s	6.10, s	d	c	2.44, d	2.20, s	3.80,s	Ar-H: 6.70-7.21, m $\alpha-CH_2$: d; $\beta-CH$: d $CH(Me)_2$: 0.79, d; 1.04, d
b	$-\overset{\alpha}{C}H_2\overset{\beta}{C}H_2CH_3$	2.67, s	6.11, s	d	ax/eq: 2.42-2.71, m	2.23, s	2.20, s	3.80,s	Ar-H: 6.70-7.30, m $\alpha-CH_2$: d; $\beta-CH_2$: d $-CH_2-CH_3$: 0.94, t
c	Me	2.62, s	6.00, s	b	ax/eq: 2.64-2.90, m	2.40, d	2.11, s	3.80,s	Ar-H: 6.70-7.30, m C4-Me: 1.52, s

a. Bases in $CDCl_3$

b. Major signals overlap (1.83-2.10 ppm)

c. Signals overlap (2.70-2.80)

d. Unresolved signal

3.3.15 α- and β-4-(3-methoxyphenyl)-1,3-dimethyl-4-(2-methylprop-1-yl)piperidine

The Mannich base (91a; 4 g) in triethylamine (80 ml) was hydrogenated over palladium (5%; Pd on $CaCO_3$; 2 g) at 60 p.s.i., in a rocking Parr apparatus at 50°C for 24 hours. The catalyst was filtered off and the filtrate evaporated <u>in vacuo</u> to yield the crude title product (2.73g,80%) as an oil. Treatment of the oily residue with ethereal-HCl, and subsequent fractional crystallisation from methanol-ether yielded the <u>major isomer</u> (54k R^2 = Me; 1.1 g), m.p. 187-188°C. The filtrate was evaporated <u>in vacuo</u> and recrystallised from ethanol-ether to yield mainly the <u>minor-isomer</u> (54j; R^2 = Me; 0.4 g) with a trace of the major isomer. All attempts to obtain the pure minor isomer failed and therefore it was decided to purify the corresponding phenols.

δ_H : see Table 20, p. 171.

δ_C : see Table 19, p. 170.

Microanalysis : see Table 36, p. 247.

3.3.16 Major 4-(3-Hydroxyphenyl)1,3-dimethyl-4-(2-methylprop-1-yl) piperidine (54k, R^2 = H)

Major 4-(3-Methoxyphenyl)1,3-dimethyl-4-(2-methylprop-1-yl) piperidine (54k; R^2 = Me; 0.9 g) was treated with aqueous HBr (4.5 ml; 48%) and the solution refluxed for 6 hours. The mixture was cooled, diluted with H_2O (10 ml), neutralised to pH 8 with concentrated aqueous ammonia, and extracted with ether (4 x 15 ml), which was dried ($MgSO_4$) and evaporated in vacuo to yield the crude title product (0.64g,75%) as a yellowish solid. Treatment of this solid with ethereal-HCl afforded the hydrochloride salt, m.p. 256-258°C (methanol-ether).

δ_H : see Table 20. p. 171.

δ_C ; see Table 19. p. 170.

Microanalysis : see Table 37, p. 248.

3.3.17 Minor 4-(3-Hydroxyphenyl)-1,3-dimethyl-4-(2-methylprop-1-yl) piperidine (54k; R^2 = H)

The diastereoisomeric mixture (minor with a trace of major) obtained in Section 3.3.15 (0.6 g) was treated with HBr (3.5 ml; 48%) by the same procedure described in Section 3.3.16 to yield a mixture (0.44 g; 76%) mainly of the minor isomer with a trace of the major isomer as a yellowish oil. Treatment of this oil with ethereal-HCl, and subsequent fractional crystallisation from methanol ether, yielded the minor-isomer (54j; R^2 = H; 0.32 g), m.p. 220-222°C.

δ_H : see Table 20. p. 171.

δ_C : see Table 19. p. 170.

Microanalysis : see Table 37, p. 248.

3.3.18 4-(3-Methoxyphenyl)-1-methyl-4-(2-methylprop-1-yl)piperidine

(55z; Ar = m-OMe.C_6H_4)

1,4,5,6-Tetrahydro-4-(3-methoxyphenyl)-1-methyl-4-(2-methylprop-1-yl)piperidine (90a; 3 g) in ethanol (60 ml) was hydrogenated at room temperature over palladium (5% Pd on C; 1 g) at 80 p.s.i., in a rocking Parr apparatus, for 12 h. The catalyst was filtered off and the filtrate evaporated *in vacuo* to yield the crude title compound (2.42g,82%), as an oil. Treatment of the oil with ethereal-HCl afforded the hydrochloride salt, m.p. 192-193°C (ethanol-ether).

δ_H : see Table 10. p. 133.

δ_C : see Table 9. p. 132.

Microanalysis : see Table 35, p. 246.

3.3.19 4-(3-Hydroxyphenyl)-1-methyl-4-(2-methylprop-1-yl)piperidine

(55a, Ar = m-OH.C_6H_4)

4-(3-Methoxyphenyl)-1,3-dimethyl-4-(2-methylprop-1-yl)piperidine (2 g) was treated with aqueous HBr (8 ml; 48%) by the same procedure described in Section 3.3.16 to yield the title compound (1.4 g; 74%), as a yellowish solid. Treatment of this solid with ethereal-HCl afforded the hydrochloride salt m.p. 181-182°C (ethanol-ether).

δ_H ; see Table 10. , p. 133.

δ_C ; see Table 9, p. 132.

Microanalysis: see Table 33, p. 246.

3.3.20 1,4,5,6-Tetrahydro-4-(3-methoxyphenyl)-1,4-dimethylpyridine (90c)

To a solution of 1,2,5,6-tetrahydro-4-(3-methoxyphenyl)-1-methylpyridine (89; 10 g; 0.05 mole) in dry tetrahydrofuran (140 ml) under N_2 at -10°C was added n-butyl lithium(24.9 ml; 0.078 mole; 2.5 M in hexane) at such a rate that the temperature was maintained at less than -5°C. The resulting deep red solution was stirred for 15 minutes at -5°C and then cooled to -30°C. Dimethylsulphate (6.25 g; 0.05 mole) in dry tetrahydrofuran (90 ml) at -40°C was added dropwise such that the temperature was maintained at less than -30°C. The final solution was warmed to -10°C, stirred for 30 minutes at this temperature, and then worked up by the same procedure described in Section 3.3.13, to give an oil. The oily residue was treated with dry ether and the resultant quaternary ammonium salt filtered off. The filtrate was evaporated *in vacuo* to give the crude product, which was purified by the same procedure described in Section 3.3.13, to yield the title compound (4.2 g; 29%), as an oil.

δ_H; see Table 31. p. 235.

δ_C ; see Table 30. p. 234.

The same synthetic procedures previously described for the synthesis of the α- and β-4-iso-Bu and the corresponding 3-desmethylanalogues were employed for:

3.3.21 The synthesis of 4-n-propyl analogues

a. α-4-(3-Hydroxyphenyl)-1,3-dimethyl-4-n-propylpiperidine (54d)

For results, see Table 37 . p. 248.

For NMR results, see Table 14;15.

b. β-4-(3-Hydroxyphenyl)-1,3-dimethyl-4-n-propylpiperidine (54c)

For results, see Table 37. p. 248.

For NMR results, see Table 14; 15 .

c. 4-(3-Hydroxyphenyl)-1-methyl-4-n-propylpiperidine (55b)

For results, see Table 35.

For NMR results, see Table 9; 10.

3.3.22 The synthesis of 4-methyl analogues

a. Major 4-(3-Hydroxyphenyl)-1,3,4-trimethylpiperidine (54b)

For results, see Table 37.

For NMR results, see Table 11; 12 .

b. Minor 4-(3-Hydroxyphenyl)-1,3,4-trimethylpiperidine (54a)

For results, see Table 37.

For NMR results, see Table 11; 12.

c. 4-(3-Hydroxyphenyl)-1,4-dimethylpiperidine (55h)

For results, see Table 35.

For NMR results, see Table 9; 10.

3.3.23 4-(3-Methoxyphenyl)-1,4-dimethylpiperidine methiodide

4-(3-Methoxyphenyl)1,4-dimethylpiperidine (55h; 0.05 g) in acetone (3 ml) was treated with iodomethane (0.1 g) by the same procedure described in Section 3.3.5 to yield the corresponding methiodide salt, m.p. 235-236°C. See page 156 for discussion of NMR results.

3.3.24 Major 4-(3-Methoxyphenyl)-1,3,4-trimethylpiperidine methiodide

Major 4-(3-Methoxyphenyl)-1,3,4-trimethylpiperidine (54b; 0.15 g) in acetone (4 ml) was treated with iodomethane by the same procedure described in Section 3.3.5 to yield the title compound (0.18 g; 75%), as a colourless solid, m.p. 205-207°C (methanol).

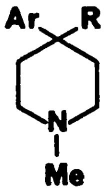
δ_H see Table 12. p. 147.

δ_C see Table 11. p. 146.

Found: C, 50.98; H, 6.89; N, 3.65%.

$C_{16}H_{26}NOI$ requires: C, 51.21; H, 6.98; N, 3.73%.

Table 35 The synthesis of some 1,4-dialkyl-4-arylpiperidines



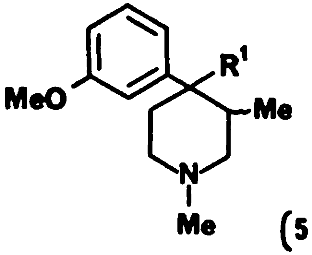
(55)

Compound	R	Ar	m.p. (Lit. m.p.) °C	Rec. Solvent	Yield %	Formula	Required C	Required H	Required N	Found C	Found H	Found N
55z	iso-Bu	C_6H_4-OMe(m)	192-193	EtOH/Et_2O	82	$C_{17}H_{28}NOCl$	68.55	9.47	4.70	68.40	9.42	4.65
55ℓ	n-Pr	C_6H_4-OMe(m)[A]			85							
55h	Me	C_6H_4-OMe(m)	166-168	EtOH/Et_2O	78							
55z	iso-Bu	C_6H_4-OH(m)	181-182	EtOH/Et_2O	76	$C_{16}H_{26}NOCl$	67.71	9.23	4.94	67.62	9.10	4.92
55ℓ	n-Pr	C_6H_4-OH(m)	178-179(187-190)[86]	EtOH/Et_2O	74	$C_{15}H_{24}NOCl$	66.77	8.97	5.19	66.58	8.87	5.10
55h	Me	C_6H_4-OH(m)[B]	200-201(214-215)[86]		69							

A. The hydrochloride salt of this compound could not be recrystallised;therefore,characterisation of this compound was based on the free phenol.

B. Attempts to purify this compound were unsuccessful.

Table 36. Synthesis of some 1,3,4-trialkyl-4-(3-methoxyphenyl)piperidines



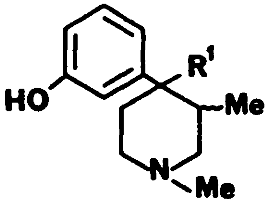
(54)

Compound	R^1	Yield[A] %	Recrystallisation Solvent	m.p. (Lit.) (°C)	Formula	Required %			Found %		
						C	H	N	C	H	N
54k	iso-But (major)	78	Methanol-ether	187-188	$C_{18}H_{30}NOCl$	69.34	9.69	4.49	69.00	9.80	4.32
54d	n-Pr[B] (major)	77	Ethanol-ether	225-227	$C_{17}H_{28}NOCl$	68.55	9.47	4.70	68.77	9.66	4.58
54b	Me (major)	80	Methanol-ether	195-196	$C_{15}H_{24}NOCl$	66.77	8.97	5.19	67.1	9.11	5.00

A. Yield for isomeric mixtures obtained from hydrogenation of the precursor Mannich base. Purification and characterisation of the minor isomer in each case was achieved on the free phenols (see Table 30).

B. This compound was initially separated from the isomeric mixture as the oxalate salt and had m.p. 191-193 (methanol), then the free base was liberated and converted to the hydrochloride salt for characterisation.

Table 37. Synthesis of some 1,3,4-trialkyl-4-(3-hydroxyphenyl)piperidines

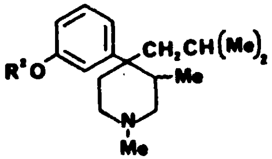


(54)

Compound	R^1	Yield[A] %	Recrystallisation Solvent	m.p. (°C)	Formula	Required %			Found %		
						C	H	N	C	H	N
54k	iso-But (major)	75	Methanol-ether	256-258	$C_{17}H_{28}NOCl$	68.55	9.42	4.70	68.2	9.63	4.55
54j	(minor)	76	Methanol-ether	220-221	$C_{17}H_{28}NOCl$	68.55	9.42	4.70	68.4	9.71	4.63
54d	n-Pr (major)	74	Ethanol-ether	260-261	$C_{16}H_{26}NOCl$	67.71	9.23	4.93	67.37	9.15	4.80
54c	(minor)	72	Methanol-ether	230-232	$C_{16}H_{26}NOCl$	67.71	9.23	4.93	67.42	9.12	4.78
54b	Me (major)	72	Methanol-ether	190-191	$C_{14}H_{22}NOCl$	65.74	8.67	5.48	65.40	8.74	5.22
54a	(minor)	73	Ethanol-ether	182-183	$C_{14}H_{22}NOCl.\tfrac{1}{2}H_2O$	63.51	8.37	5.29	63.31	8.32	5.28

A. Yield from *O*-demethylation of precursor methoxyphenylpiperidines. The major isomers came from pure methoxyphenylpiperidines and the minor isomers from impure methoxyphenylpiperidines (containing a trace of major).

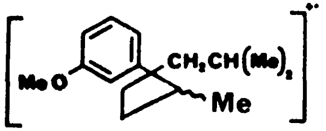
Table 38. Percent Abundance of Diagnostic Fragment Ions of Some Isomeric Analogues of 4-Aryl-1,3-dimethyl-4-(2-methylprop-1-yl)piperidines



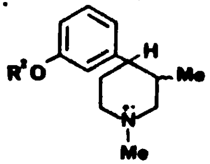
					Ion Type[a]								
No	Compound	Isomer Designation	R^2	$M^{\dagger}$	A	B	C	D	E	F	G	H	Other
1	54k	$\underline{\alpha}$-	Me	66	25	100	-	80	30	25	43	43	$\underset{\underset{Me}{\vert}}{\overset{+\cdot}{N}} = CH_2$; 33%
2	54k	$\underline{\alpha}$-	H	18	51	100	43	34	21	25	49	49	$[CH_2 = CH_2]^{+\cdot}$; 34%
3	54j	$\underline{\beta}$-	H	41		100	-	26	20	-	44	44	$CH_2 = \overset{+}{N} = CH_2$; 33%

a. Ion types

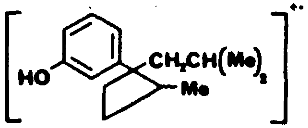
A.



B.

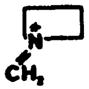


C.



D.

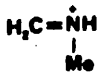
E.



F.

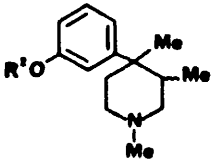
G.

H.



$H_2C{=}\underset{\underset{Me}{\vert}}{\overset{+}{N}}H$

Table 39. **Percent Abundance of Diagnostic Fragment Ions of Some Isomeric Analogues of 4-Aryl-1,3,4-trimethylpiperidines.**



					Ion Type[a]						
No	Compound	Isomer Designation	R^2	$M^{+\cdot}$	A	B	C	D	E	F	G
1	55b	α	Me	30	100	30	-		38	25	-
2	55b	α	H	43	100	33	-		34	26	-
3	55a	β	H	62	100	46	38		32	46	-
4	75(Ar=Ph)		-	49	89	-	-	100	62	50	97

a. Ion types

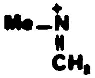
A.
D from Table 38 applied

B.
E from Table 38 applied

C.
F from Table 38 applied

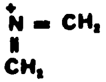
D.

E.



$Me-\overset{+}{N}=CH_2$

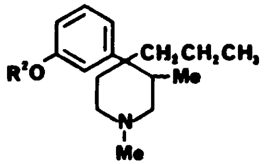
F.



$\overset{+}{N}=CH_2$, $=CH_2$

G.
G from Table 38 applied

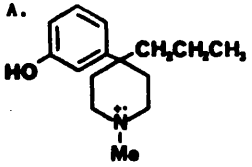
Table 40. **Percent Abundance of Diagnostic Fragment Ions of Some Isomeric Analogues of 4-Aryl-1,3-dimethyl-4-*n*-propylpiperidines.**



							Ion type[a]				
No	Compound	Isomer Designation	R^2	$M^{+\cdot}$	A	B	C	D	E	F	G
1	54d	α	Me	100	-	-	72	100	26	-	34
2	54d	α	H	21	21	-	-	90	53	48	100
3	54c	β	H	28	-	100	-	100	34	67	-

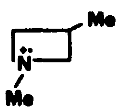
a. Ion types

A.



B.

C.



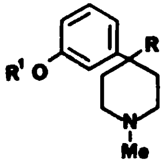
D.
D from Table 38 applied

E. E from Table 38 applied

F. G from Table 38 applied

G. H from Table 38 applied

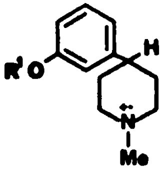
Table 41. **Percent Abundance of Diagnostic Fragment Ions of Some 4-Alkyl-4-aryl-1-methylpiperidines.**



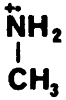
						Ion type[a]					
No	Compound	R	R^1	$M^{\dagger}$	M^{+1}	A	B	C	D	E	F
1	55h	Me	Me	34	-	-	93	100	21	43	-
2	55ℓ	$Ch_2CH_2CH_3$	H	36	-	38	57	100	23	42	-
3	55z	$CH_2CH(Me)_2$	Me	b	100	75	67	100	-	-	34
4	55z	$CH_2CH(Me)_2$	H	b	90	85	51	100	28	-	33

a. Ion types

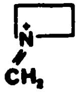
A.



B.



C.



D.

G from Table 38 applied

E.

$CH_2{=}\overset{+}{N}{=}CH_2$

F

H from Table 38. applied

b. $M^{\dagger}$ not seen in 70 eV E.I. spectrum; M^{+1} observed in iso-BUT CI spectrum

3.3.25 Attempted Synthesis of:

a. 1,4,5,6-Tetrahydro-1,3,4-trimethyl-4-phenylpyridine (105) from 1,2,5,6-tetrahydro-1,3-dimethyl-4-phenylpiperidine

1,2,5,6-tetrahydro-1,3-dimethyl-4-phenylpyridine (72; 2.5 g; 0.013 mole) in dry tetrahydrofuran (25 ml) was treated with *n*-butyllithium (12 ml, 0.017 mole) and then with dimethylsulphate (1.7 g; 0.013 mole) in dry tetrahydrofuran (10 ml) by the same procedure described in Section 3.3.2. This procedure yielded a mixture of unconverted starting material and the corresponding quaternary methosulphate.

b. 1-Benzyl-1,4,5,6-tetrahydro-4-(3-methoxyphenyl)-1,4,5-dimethylpyridine methylmethosulphate (79)

1-Benzyl-1,2,5,6-tetrahydro-4-(3-methoxyphenyl)-5-methylpyridine (84; 4 g; 0.014 mole), was treated with *n*-butyllithium (14 ml; 0.02 mole, 1.4 M in hexane) and then with dimethylsulphate (4.5 g; 0.035 g) in dry tetrahydrofuran (50 ml), by the same procedure described in Section 3.3.2. This procedure yielded a mixture of the quaternary methosulphate salts of the starting material and required product which could not be separated by the author.

δ_H (D_2O):

0.58 and 0.82 (2xd; C5-C$\underline{H}_3$), 1.92 (s; C4-C$\underline{H}_3$), 3.68 and 3.78 (2xs, $\underline{N}$-C$\underline{H}_3$), 4.32 (d; C3-$\underline{H}$), 5.82 (m; C3-$\underline{H}$ of starting material), 6.21 (d; C2-$\underline{H}$).

c. 1-Benzyl-1,4,5,6-tetrahydro-3-dimethylaminomethyl-4-methyl-4-phenylpyridine (98)

The crude 1-benzyl-1,2,5,6-tetrahydro-4-methyl-4-phenylpyridine (106; 5.0 g) was treated with aqueous formaldehyde (1.5 g; 37%) and aqueous dimethylamine (2.75 g; 40%) by the same procedure described in Section 3.3.14 to yield a mixture which proved impossible to purify.

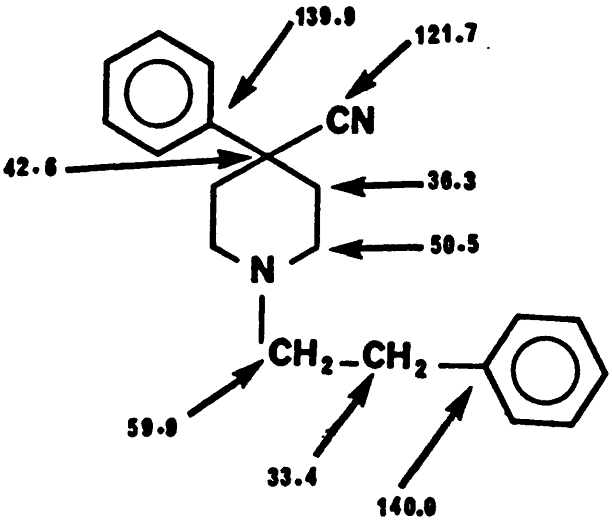
3.4 MISCELLANEOUS SUBSTANCES

3.4.1 4-Cyano-1-phenethyl-4-phenylpiperidine (100)

Phenethylbromide (3 g) was added dropwise to a stirred suspension of 4-cyano-4-phenylpiperidine (101; 2.8 g) and K_2CO_3 (6 g) in absolute alcohol (60 ml). The resulting mixture was refluxed for 48 hours. The ethanol was evaporated in vacuo to give an oil, which was dissolved in HCl (20 ml; 2N), and then washed with ether (3 x 5 ml; discarded). The aqueous layer was basified with concentrated aqueous ammonia, extracted with ether (4 x 10 ml), dried ($MgSO_4$) and finally evaporated in vacuo to yield the title compound (3.5 g; 79%) as an oil, which was employed in the next synthetic step.

δ_H ($CDCl_3$; free base):
2.09 (4H, m, C3/5-$\underline{H}$), 2.54 (2H, m, C2/6-$\underline{H}$ax), 2.68 (2H, m, C2/6-$\underline{H}$eq), 2.82 (2H, dt, $\underline{CH_2}$-Ph), 3.06 (2H, dt, $\underline{N}$-$\underline{CH_2}$) 7.20-7.50 (10 H, m, Ar-$\underline{H}$).

δ_C($CDCl_3$; free base):



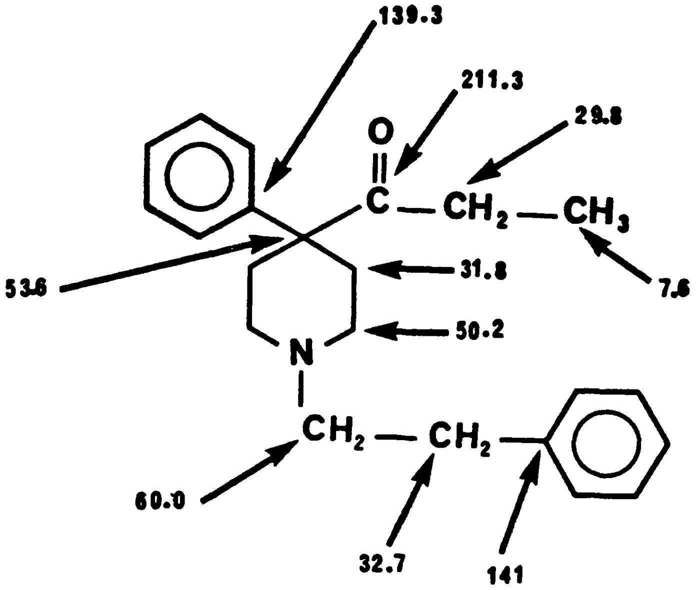
3.4.2 1-Phenethyl-4-phenyl-4-propionylpiperidine (99)

To the Grignard reagent [prepared from magnesium (1.3 g) and iodoethane (7.8 g) in dry ether (60 ml)] was added 4-cyano-1-phenethyl-4-phenylpiperidine (100; 3.4 g) in dry toluene (40 ml). The ether was immediately evaporated *in vacuo* and the reaction mixture was refluxed for 1 h. After cooling, ammonium chloride (4 g) in H_2O (20 ml) was added. The organic layer was separated, and the aqueous layer washed with toluene (3 x 5 ml). The combined organic washings were added to the original organic layer and the whole refluxed with HCl (60 ml; 2N) for 30 min. The aqueous layer was separated, washed with toluene (2 x 15 ml; discarded), basified with potassium hydroxide pellets, extracted with ether (3 x 50 ml), dried ($MgSO_4$) and evaporated *in vacuo* to yield *1-phenethyl-4-phenyl-4-propionylpiperidine* (3.1 g, 82%) as an oil. Treatment of this oil with ethereal-HCl afforded the hydrochloride, m.p. 215-217°C (ethanol ether).

ν_{max} : 1720 cm^{-1} ($-\overset{\text{O}}{\overset{\|}{\text{C}}}-$ str.)

δ_H : see Table **42** , p.259.

δ_C ($CDCl_3$; free base)



m/z : M^{+1} 322 (61%), 230 (100%).

Found: C, 73.70; H, 7.90; N, 3.87%.

$C_{22}H_{28}NOCl$ requires: C, 73.83; H, 7.88; N, 3.91%.

3.4.3 1-Methyl-4-phenyl-4-propionoxypiperidine (42)

4-Dimethylaminopyridine (0.18 g) was added to a stirred solution of 4-hydroxy-1-methyl-4-phenylpiperidine (104; 0.25g)and propionic anhydride (10 ml), and the reaction mixture was stirred for 48 hours at room temperature. The resulting solution was poured into acetic acid (50 ml; 50%). The aqueous solution was washed with ether (4 x 50 ml; discarded), basified with Na_2CO_3 and extracted with ether (4 x 50 ml). The combined organic extracts were washed with water (10 x 15 ml), dried ($MgSO_4$) and finally evaporated <u>in</u> <u>vacuo</u> to yield the crude title product (0.21 g; 70%) as an oil. Treatment of this oil with ethereal-HCl afforded the hydrochloride, m.p. 196-197°C (ethanol-ether).(Lit.[40] m.p. 183-184°C.)

δ_{max} : 1740 cm^{-1} (C=O str.).

δ_H ; see Table 42. p. 259.

Found: C, 63.60; H, 7.71; N, 4.92%.

$C_{15}H_{22}NO_2Cl$ requires: C, 63.48; H, 7.82; N, 4.94%.

δ_C($CDCl_3$;free base)

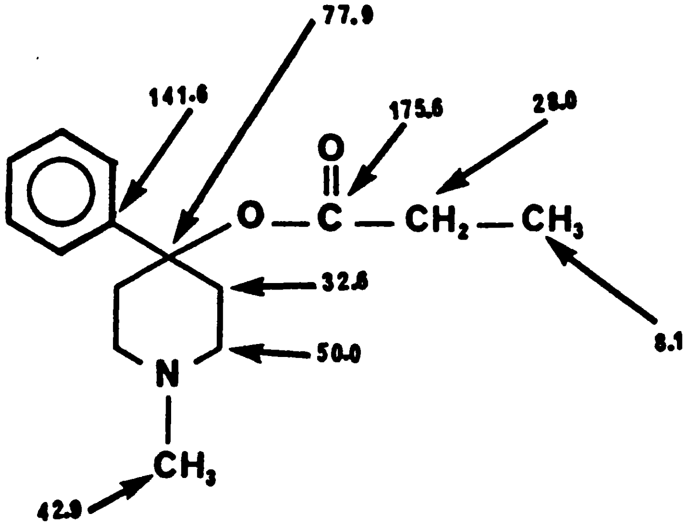


Table 42. ^{1}H NMR Characteristics of reversed ester of pethidine and related compound (HCl in D_2O)^{a,e}

Compound	H(2,6)	H(3,5)	N-Me	Ph-CH_2	N-CH_2	-CH_2[b]	-CH_3[b]	Ar-H
99	eq:	eq:						
	3.68,brd,13.40	c		c	3.36,q,5.59	2.38,q,6.25	0.8,t,7.15	7.22-7.51,m
	(3.56,brd,13.40)[d]				(3.22,q,5.59)	(2.38,q,11.58)	(0.74,t,7.15)	
	ax:	ax:						
	c	2.24,dt,13.78						
		2.12,dt,14.29						
42	eq:	eq:	2.93,s			2.48,q,7.5	1.06,t,7.5	7.35-7.45,m
	3.53,brd,12.5	2.72,brd,14	(2.89,s)				(0.99t)	
	ax:	ax:						
	3.36,dt,12,12,2	2.29,dt,14,14,4						

a. Chemical shifts in ppm from external TMS, followed by multiplicity and line separations of signals; data for minor epimers in parentheses.

b. Signal of 4-COC_2H_5 or $OCOC_2H_5$

c. Major signal overlaps eq. 3,5(H), ax. 2,6(H) and Ph-CH_2

d. Epimer ratio in this compound is about (1:1).

e. Spectra recorded on a JEOL EX400 MHz FT NMR spectrometer.

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