Stereochemical studies of narcotic analgesics related to pethidine and fentanyl.

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STEREOCHEMICAL STUDIES OF NARCOTIC ANALGESICS RELATED TO PETHIDINE AND FENTANYL.

Submitted by

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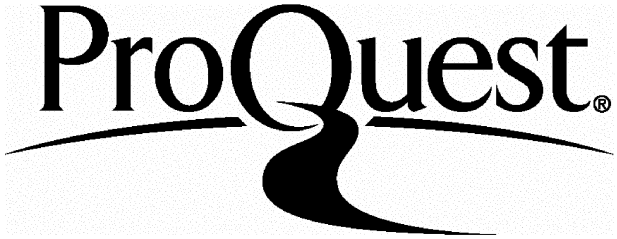
This research has been carried out in the School of Pharmacy and Pharmacology of the University of Bath, under the supervision of Dr. A.F. Casy, D.Sc., Ph.D., F.P.S., C.Chem., F.R.S.C.



To Maggie for her love and understanding.

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ABSTRACT

A brief survey of synthetic narcotic analgesics, with particular attention to the C-methyl substituted reversed esters of pethidine and the 4-anilinopiperidine analgesics (fentanyl analogues), is given. The 2- and 3-monomethyl, and the 2,6-, 2,5-, and 3,5-dimethyl analogues of the reversed ester of pethidine have been thoroughly investigated from both a stereochemical and structure-activity point of view, but this was not the case with the 2,3-dimethyl analogues, which was therefore a subject of the present thesis.

The syntheses and characterisation of the isomeric 2,3-dimethyl analogues of the reversed ester of pethidine, including a novel route to the precursor 1,2,3-trimethyl-4-piperidone, are described. The relative stereochemistry of the precursor alcohols and their corresponding esters have been unambiguously established by spectroscopic techniques. The solute conformation of the isomeric alcohols and their corresponding esters were determined by ^{13}C-n.m.r spectroscopy, supplemented by ^{1}H-n.mr and Infra-red dilution studies, while the solid state conformation of the alcohols were determined by X-ray crystallography. Stereochemical structure-activity correlations in the 2,3-dimethyl analogues were in close agreement with established stereochemical structure-activity pattern in the reversed esters of pethidine, and they further highlight the significance of the enantiotopic C-methyl

substitution on the activity of the 4-phenyl piperidine analgesics.

The syntheses of the isomeric 3-allyl fentanyl and the N-methyl analogues, and the 3-propyl analogues,and their stereochemistry are also described. This aspect of the work was undertaken in order to establish the similarities or otherwise in the stereochemical structure-activity relationships of the 3-alkyl fentanyls and the corresponding 3-alkyl substituted reversed ester of pethidine. The pharmacological results, however, suggested there were no similarities in the relative modes of uptake of the two groups at the analgesic receptor site.

The syntheses of the phenolic analogues of the reversed ester of pethidine, the 3-methyl analogue, and the N-phenethyl derivatives were also undertaken in order to further investigate the effects of phenolic substitution on their opiate properties. The relative configuration and solute conformations of the derivatives were established by ^{13}C-n.m.r spectroscopy. The results of the pharmacological tests confirmed the earlier report that a 4-(m-hydroxyphenyl) substitution in the reversed ester of pethidine led to abolition of activity, but it however failed to substantiate an earlier claim that the phenolic analogue of β-prodine, a potent narcotic agonist, was transformed into an antagonist devoid of any agonist activity.

The chemistry and stereochemistry of the Prins product from a 4-substituted 1,2,3,6-tetrahydropyridine and

excess of formaldehyde, a substituted bicyclic nonane, are also discussed in the appendix.

C O N T E N T S

C H A P T E R O N E

C H A P T E R T W O

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CHAPTER ONE

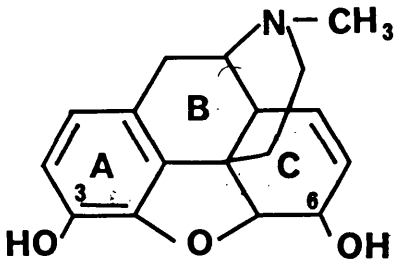
SECTION ONE: Introduction

The search for effective pain relieving means has been an age-long endeavour of mankind. Over the ages, various methods and means have been employed depending on peoples' understanding, and views about the mechanism of pain. Nevertheless, no single method has enjoyed so wide an acceptability and stood the test of time as long as the use of opium.

Opium has been used as drug at least since the classical Greek times not only because it deadens pain, but because it also produces a sense of well-being in the user. The word, opium, was derived from the Greek word 'opion', poppy juice, because the drug is present in the milky exudate obtained by incising the unripe seed-pod of the poppy, Papaver somniferum. This not withstanding, the Summerians were believed to have used crude opium as drug as early as 4,000 BC for its ability to relieve pain and produce a state of euphoria at the same time, hence they called it 'hul gil' - joy plant (Fairley, 1978). However, despite the long history behind opium, it was not until 1803 when a young German pharmacist, Sertuner, isolated an alkaloid from opium which he called morphine after Morpheus, the Greek god of dreams, that the modern concept and story of narcotic analgesic began. By the middle of the 19th century therefore, the use of pure morphine rather than the crude opium preparations had spread widely.

Unfortunately, apart from its pain relieving properties, morphine also affects many of the vital centres in the brain; respiration is depressed, the emetic centre is stimulated resulting in nausea and vomiting, the pupil of the eye becomes constricted and vision is affected. In addition to this, tolerance develops with repeated use and the user soon becomes emotionally and physically dependent on the drug, the lack of which precipitates characteristic abstinence syndromes. The toxicity and undesirable effects of morphine were, however, not fully recognised until the drug became an established feature of clinical practice. Therefore, with increased use, the number of addicts grew so rapidly that addiction to morphine soon became a significant social problem. This prompted the search for non-addictive synthetic opiates, lacking the undesirable effects of morphine while retaining the pain-relieving properties.

Morphine itself was synthesised in 1952 by Gates and Tschudi who confirmed the structure (1) originally proposed by Gulland and Robinson in 1923. However, because of the



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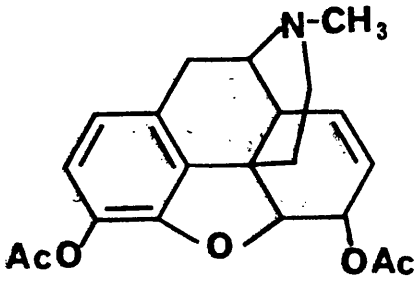
relatively complex five-ring system of the morphine skeleton, attention was first focused on variations of the multi-ring system, especially the more chemically amenable ring C. Efforts in this direction have produced distinct groups of analgesics with morphine-like activities, namely, the derivatives of morphine, the morphinans, the benzomorphans, and the oripavines. Apart from these groups, a number of structurally unrelated groups of compounds have been found, over the years, to possess morphine-like activities, some of which are used clinically.

Derivatives of Morphine

Earlier modifications to morphine involved derivatisation of the 3- and 6-hydroxyl groups. Diacetyl morphine (2, Heroin), one of the earlier known examples, was erroneously introduced into clinical practice as a non-addictive opiate, but it soon turned out to be even more addictive than morphine when enough patients had used it for a long enough time (Eddy, 1953). Etherification of the phenolic group led to a reduction in the activity of morphine.



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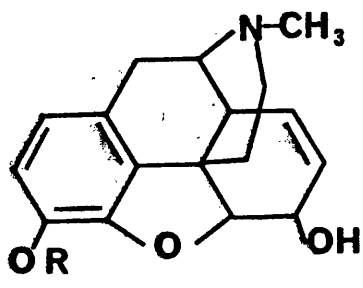


3 R = Me

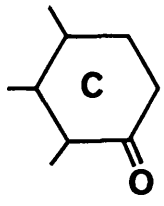
4 R = Et

5 R = CH_2Ph

6 R = CH_2CH_2N O

Nevertheless, a number of these phenolic ethers, the best known example being codeine (3), have found use in clinical practice for the relief of mild to moderate pain, and as antitussive agents. Other clinically used examples include the ethyl (4, Dionine), the benzyl (5, Peronine), and the β-4-morpholinoethyl (6, Pholcodine) ethers.

Several useful drugs having morphine-like potencies have also been produced by chemical transformations of ring C of morphine. Hydromorphone (7, Dilaudid), metopon (8), and oxymorphone (9, Numorphan) are some of examples of these derivatives in clinical use. These derivatives, however, offer no real advantage over morphine since the incidence of undesirable side effects in them, especially the addictive liability, parallels if not exceeds those of morphine.



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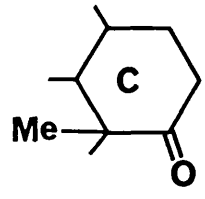

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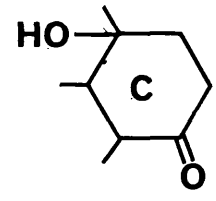

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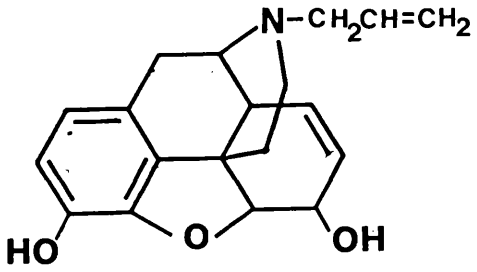
Among the several N-alkylated derivatives of morphine examined, the N-allyl compound (Nalorphine, 10) was of particular significance since it antagonises a wide spectrum of morphine activities, hence its use as an antidote in morphine poisoning (Woods, 1956). Although nalorphine lacks analgesic properties in laboratory animals,

it is a potent, essentially non-addicting, analgesic in man, and this property has led to the development of several clinically useful analgesics based on morphine antagonists (Martin, 1967). However, because of its severe undesirable psychotomimetic side effects, nalorphine is not used clinically. Another morphine antagonist that is of much interest is the N-allyl analogue of oxymorphone (Naloxone, 11) which, because of lack of demonstrable analgesic activity, is considered an almost pure antagonist.



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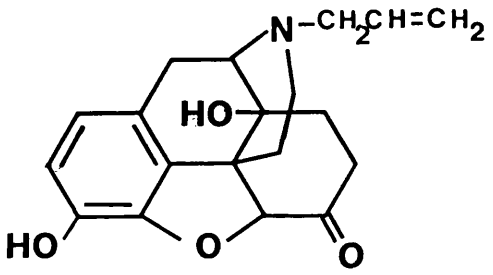

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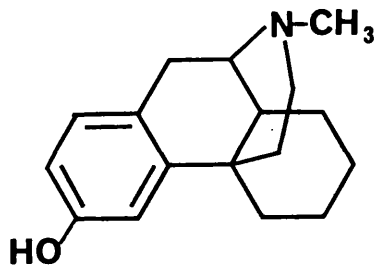
The Morphinans and Isomorphinans

This group represents a more simplified modification of the morphine skeleton. Among the various derivatives, racemorphan (12), was the first clinically valuable agent.



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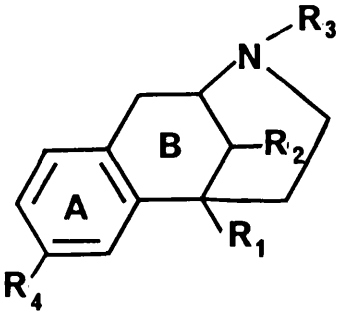
It has twice the activity of morphine, but with greater

addictive liabilty (Isbell & Fraser, 1953). The activity of racemorphan however resides in the laevo-isomer, levorphanol. Structure-activity relationships in the morphinans mirror those of morphine. Thus methylation of the phenolic group results in a large decrease in potency, while replacement of the N-methyl group by N-allyl gives a potent morphine antagonist, levallorphan (Fromhertz & Pellmont, 1952).

The 6,7-Benzomorphans.

The synthesis of the 6,7-benzomorphan derivatives (13) was accomplished by May and Murphy (1955) while investigating the effects of a further reduction in size of the morphine skeleton. 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 an added cis/trans geometric isomerism on the derivatives. The isomer with the configuration in which R_1 and R_2 are cis



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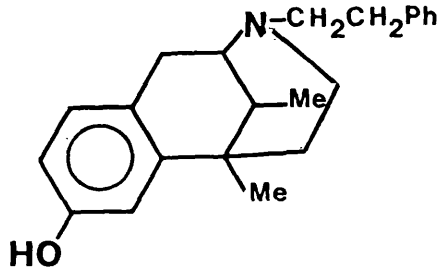
in relation to ring B is designated alpha (α- isomer) and the trans-orientation, beta (β-isomer). Analgesic potency in these compounds is, therefore, influenced not only by

their absolute configuration, but by the relative disposition of the groups in space as well. For instance, the β-isomers are generally more potent than the α-isomers, whereas the agonist activity in all cases tested resides mainly in the laevo-isomers (Ager, Jacobson, and May, 1969). Apart from this, structure-activity relationships in the benzomorphans roughly parallel those of morphine. The clinically important 6,7-benzomorphan derivatives include phenazocine (14, Narphen) and the N-3,3-dimethylallyl analogue, pentazocine (15, Fortral).



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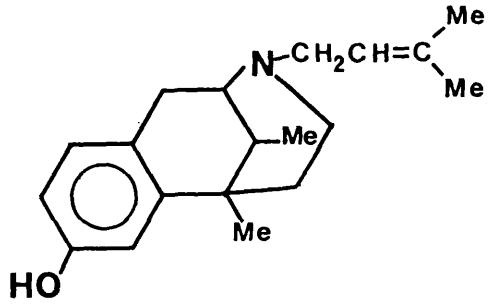

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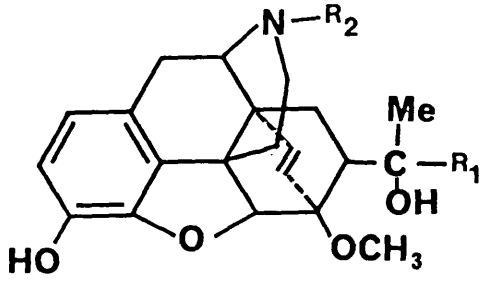
Pentazocine is a feeble antagonist of morphine, but a fairly effective analgesic in man with a lower addictive liability than morphine, hence pentazocine is exempt from international narcotic legislation. Despite its low potency, it is one of the most promising clinical analgesic yet developed from analgesic antagonists (Fraser & Rosenberg, 1964; Beaver et al, 1966).

The Oripavines

These are derivatives of the Diels-Alder adducts derived from thebaine (the diene component), and vinyl methyl

ketones and other dienophiles (Bentley & Hardy, 1967). The resultant ketonic adducts have activities comparable to those of morphine, but the derived tertiary alcohols(16) are much more potent. For example, etorphine (16, R_1 = n-Propyl, R_2 = Me) is 850 times as active as morphine in mice, 1700 times in rats, and 8600 times in guinea pigs by subcutaneous injection (Blane et al, 1967). Several derivatives, including derivatives of the analogue with reduced



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6,14-endo-etheno bridge, have been prepared and activities vary widely within the group. The free phenols are far more potent than the O-methylated analogues. However, unlike the morphine derivatives, N-allyl or N-CPM* substitution does not always produce antagonists. Such substituents only do so in derivatives where the R_1 substituent is short. For example, when R_1 is methyl, the N-CPM derivative (16, R_1 = Me, R_2 = CPM) is an active morphine antagonist, whereas the congener with a longer chain substituent (16, R_1= C_3H_7, R_2= CPM) is a potent analgesic in rats (Lister, 1964; Blane et al, 1967). Activities in these

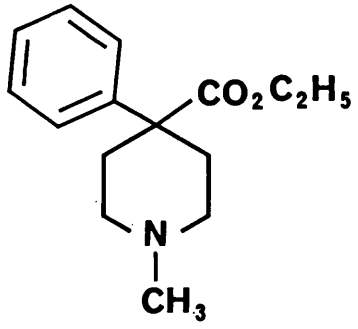
* N-cycloproylmethyl

compounds are also influenced by the stereochemistry of the carbinol chain. At very low doses, these compounds induce catatonia in animals, and their main use therefore, has been for immobilising large animals for game conservation and veterinary purposes (Harthoon, 1967).

Buprenorphine (16, R_1= t-Bu, R_2= CPM) is the most promising clinically useful analgesic derived from the oripavines. It is a mixed agonist with 75 times the activity of morphine, and about 4 times as active as nalorphine as an antagonist. Buprenorphine failed to produce physical dependency after chronic administration to monkeys and mice, and showed a longer duration of action than morphine (Cowan, Lewis & Macfarlane, 1977; Cowan, Doxey & Harry, 1977). These facts have encouraged its examination as a clinical agent, and it is marketed as Temgesic.

The 4-Phenylpiperidine Analgesics

Pethidine (17, Meperidine) represents the fore-runner of the 4-phenylpiperidine analgesics, and by hind-sight recognised as a fragment of the morphine skeleton (18, bold lines). Although originally intended as a spasmolytic



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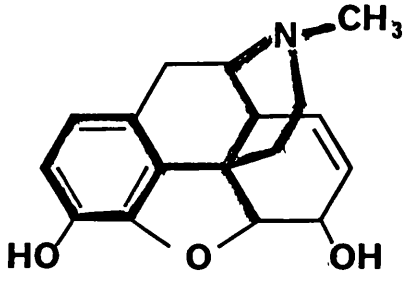

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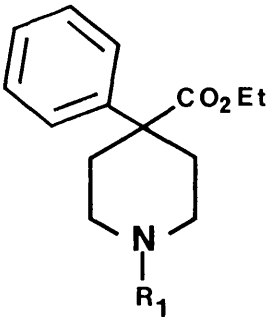
agent (Eisleb & Schumman, 1939), pethidine still ranks today among the most used synthetic narcotic analgesics, especially in the relief of labour pain (Casy,1978). This can be attributed to its lower level of toxicity and the shorter duration of action compared to morphine (Lasagner & Beecher, 1954). Although tolerance to pethidine develops only slowly and its addictive liablity judged lower than that of morphine, at equivalent dosage, pethidine is as depressant on respiration as morphine, and morphine-like side effects such as nausea and vomiting frequently occur (Eddy, Halbach & Braenden, 1956). Analogues of pethidine in clinical use include phenoperidine (19a, Jenkins & Das, 1966), anileridine (19b, Eddy, Lee & Harris, 1959), and piminodine (19c, Dekornfeld & Lasagna, 1960).



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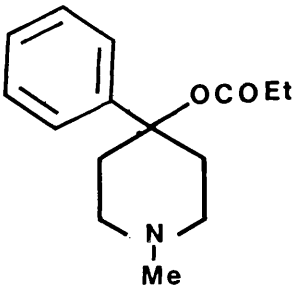
a). R= $PhCH(OH)CH_2CH_2$-

b). R= $p\text{-}NH_2C_6H_4(CH_2)_2$-

c). R= $PhNH(CH_2)_5$-

Replacement of the ethoxycarbonyl group of pethidine by a propionoxy group transforms it into the so-called reversed ester of pethidine (20) to which much attention will be devoted in this thesis. Such a replacement is generally attended by increase in analgesic potency regardless of the N-substituent (Janssen & Eddy, 1960), though



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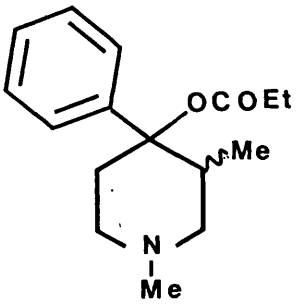

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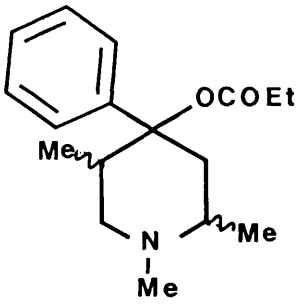
N-phenethyl substitution also generally leadsto increase in the analgesic potency of the reversed esters. Alkylation of the piperidine ring produces isomeric compounds whose potency depends not only on the nature of the C-alkyl substituent, but also on the stereochemistry of the product as well (Beckett, Casy & Kirk, 1959; Mashkovskii & Abramova, 1956; Randall & Lehman, 1948). Examples of such derivatives used clinically are, alphaprodine (21, trans 3-Me/4-Ph) and trimeperidine (22, γ-isomer, cis 2-Me/Ph, trans 5-Me/Ph).



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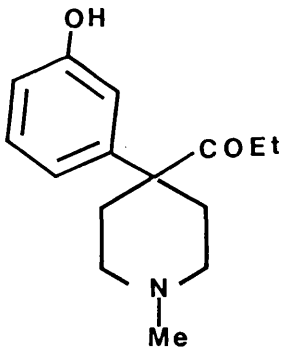
Substituted derivatives of the 4-phenylpiperidine analgesics differ quite remarkably from the fused ring systems such as the morphine and the benzomorphan derivatives.

Most attempts to produce antagonists by linking the basic nitrogen atom to groups such as allyl, allyl derivatives, and CPM, modifications which produce antagonists in the morphine and benzomorphan derivatives, have led to agonists having no power to block opiate receptors (Casy, Simmonds & Staniforth, 1968). In addition to this, hydroxylation of the 4-phenyl group, a situation which increases analgesic potency in the fused ring systems, generally lead to a marked reduction or complete loss of activity in the 4-phenylpiperidine analgesics (Portoghese, Alreja & Larson, 1981), though in the bemidone and ketobemidone (23) series the analogue lacking the m-hydroxyl group is less active (Braenden, Eddy & Halbach, 1955). This point will be further discussed (see page 29)



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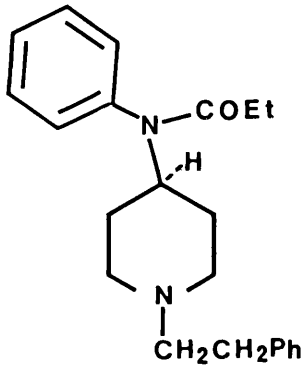
The 4-Anilinopiperidine Analgesics

Fentanyl (24) was the first clinically valuable derivative of the 4-anilinopiperidine analgesics. It has a rapid onset and a short duration of action which makes it particularly suitable for use in surgical analgesia

where it is used in combination with major tranquilisers for operations requiring patient cooperation (neurolept-analgesia).



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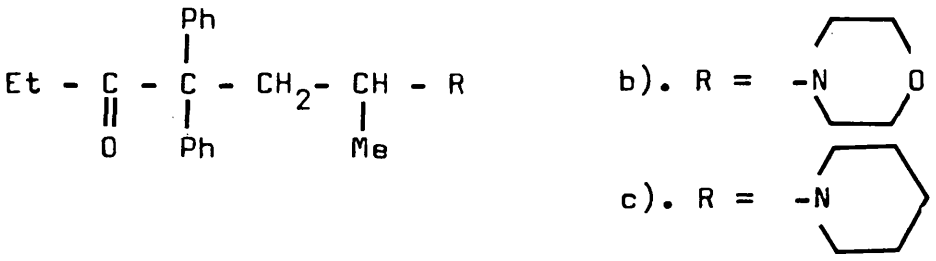
Structure-activity relationships in the 4-anilino-piperidine analgesics were investigated by Casy and co-workers (1969) who highlighted similarities in the behaviour of the group and those of the basic anilides. The N-phenethyl substitution in fentanyl is essential for activity since the N-methyl analogue, for example, was found to be completely inactive in mice, a feature which distinguishes the 4-anilinopiperidine from the 4-phenyl piperidine analgesics. On the other hand, the significant agonist activity of the 1-allyl and the 1-(3-methylbut-2-enyl) derivatives distinguishes them from the fused-ring systems such as the morphine derivatives (see also page 27).

Diphenylpropylamine Analgesics and miscellaneous groups

The 3,3-diphenylpropylamine derivatives were among the early non-fused ring analgesics recognised. The best known example in clinical practice is methadone (25a) which is a strong analgesic in man with potency and duration

of action comparable to those of morphine (Denton & Beever, 1949; Janssen & Eddy, 1960). The side effects of methadone are also similar to those of morphine; tolerance to its therapeutic action develops after repeated administration,



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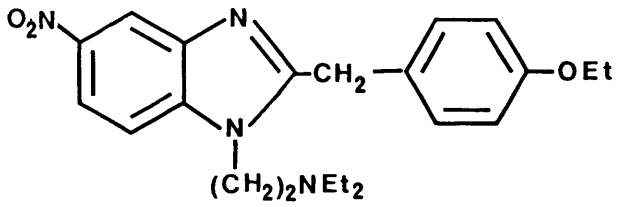
but it sustains addiction at one-quarter of the required dose of morphine, with a longer lasting effect. After withdrawal, physical dependence signs are slow to develop and are less severe than those after morphine withdrawal. For this reason, the most popular clinical use for methadone is in the ambulatory maintenance of narcotic-dependent subjects (Isbell & Fraser, 1953; Freedman et al, 1967). Variations in the basic group of methadone have produced other clinically used analgesics such as the morpholino- (25b, Heptalgin) and the piperidine (25c, Pipanone) derivatives. Many other analogues based on variations of the methadone structure have been prepared, some of which are used clinically, but none of which offers any real advantage over morphine.

A host of other miscellaneous compounds with a variety of structural features, but all bases with aromatic

substituents, have been prepared and evaluated for antinociceptive properties. Among these are benzimidazole derivatives such as etonitazene (26) which is reported to be 1500 times as active as morphine in mice (Eddy,1959), pyrollidine derivatives, for example profadol (Winder et al, 1966), benzylisoquinoline derivatives (Martin et al, 1969; Michne & Albertson, 1969), 3-arylpiperidine (Kugita et al, 1965), and cyclohexane derivatives (Harper et al, 1974), to mention but just a few.



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However, despite the fact that the initial interest generated in the synthetic opiates has led to the preparation of many potent analgesics, even some with improved properties, the original goal of an ideal analgesic, effective for pain relief and yet free from undesirable side effects has remained frustratingly elusive.

Opioid Peptides

The discovery of the endogenous opiate-like peptides was a culmination of research efforts to demonstrate the existence of specific opiate receptor(s) in the body.

All along, indirect evidence had pointed to the existence of such receptors, since the chemical and structural requirements for opiate activity in both naturally ocurring and synthetic opiates were very specific. The first direct evidence for opiate receptor was through stereospecific binding (SSB) studies of nalorphine on the mouse brain (Goldstein, Lowney & Pal, 1971). Further evidence was provided by the discovery in both the brain and gut, of specific receptors that mediate opiate activity (Pert & Snyder,1973). This, however, raised the question of the natural role of these receptors, since it seemed very unlikely that such receptors exist in the body for the sole purpose of receiving exogenous drugs; the implication of this therefore, is the existence of endogenous agents that naturally bind to these receptors.

Endogenous opiate activity was first demonstrated in pig brain extracts and activity, assessed by in vitro procedure, was found to be mediated by two pentapeptides named enkephalins (Terenius & Walstrom,1974; Hughes, 1975). The two peptides, however, differ only in their amino acid residues, these being methionine (27, Met-enkephalin), and leucine (28, Leu-enkephalin) respectively (Hughes, Smith & Kosterlitz,1975; Simantov & Snyder, 1976; Simantov & Snyder, 1976). The enkephalins are rapidly degraded by peptidyl enzymes in the blood and are therefore active only when injected directly to the brain (Graf et al, 1976). Pituitary extracts were also found to have opiate activity (Goldstein, 1976), and the activity resides in three long-

chain polypeptides known as α-, β-, and γ-endorphin (β-endorphin being predominant) all of which are derived from

Tyr-Gly-Gly-Phe-Met(CO_2H) Tyr-Gly-Gly-Phe-Leu(CO_2H)

27 28

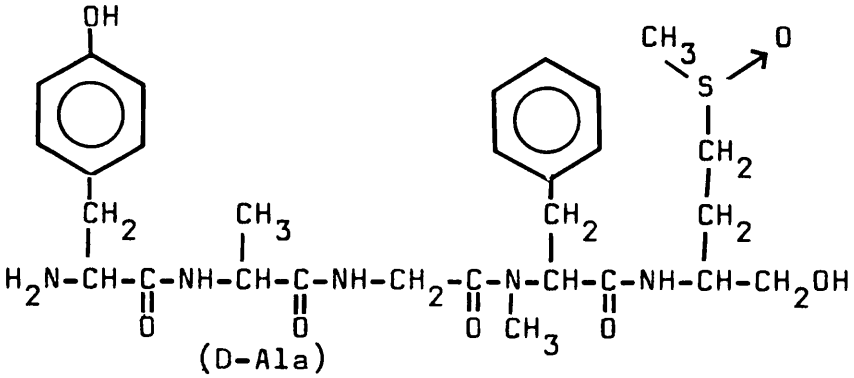
β-lipotropin, a pituitary homone (Li & Chung,1976). β-lipotropin in itself has no opiate activity (Lazarus et al, 1976). The first five residues of β-endorphin are identical with the met-enkephalin sequence, and in all fragments of β-lipotropin examined, only those with this sequence of amino acids (residues 61 - 65) intact had opiate properties (Roemer et al, 1977).

The opiod peptides are similar to morphine in several assay systems. When administered intraventricularly, they elicit analgesia, euphoria, sedation, respiratory depression, emesis, and the loss of the righting reflex in rats(Bloom et al,1976; Belluzi & Stein, 1977). In addition to these actions, the opioid peptides share addictive properties, including tolerance and dependence, and with abrupt discontinuation induce a withdrawal syndrome similar to that of morphine (Bläsig & Herz, 1976; Loh et al, 1976). A considerable number of analogues and derivatives of the enkephalins have been prepared and compared pharmacologically with the parent peptides. Structure-activity relationship studies have demonstrated the importance of the free phenolic and amino groups of the tyrosine residue in opiate activity, since the des-amino-Tyrosine analogues of leu-

and met-enkephalin are inactive (Busher et al, 1976; Morgan et al,1976), and removal of the hydroxyl group led to a marked decrease in activity (Birdsall et al, 1976). Similarly, masking of the tyrosine residue amino acid by N-carbamylation, or the hydroxyl group by O-benzoylation abolished or reduced the opiate properties of β-endorphin (Morgan et al, 1976; Birdsall et al, 1976). The correct absolute stereo-chemistry(L) of the tyrosine residue is also necessary for activity as demonstrated by the lack of opiate properties in receptor binding studies as well as the rat vas deferens assay of (D-Tyr¹)-met-enkephalin (Morin et al, 1976; Coy et al, 1976).

Efforts to stabilise the opiod peptides to peptidyl enzyme hydrolysis include substitution of the amino acid of the D-series in position 2, and preparation of the amide derivatives. For example, the amide of met-enkephalin is reported to be 5 times as active as the parent compound and with a longer duration of action (Lazarus et al,1976). Other major advances in developing a stable synthetic pentapeptide include alteration of the met-enkephalin terminal met-COOH to the corresponding alcohol, which led to increases in potency and duration of action, substitution of Gly^2 by D-Ala, N-methylation of the Phe^4 residue, and oxidation of the methionine sulphide group to sulphoxide, all of which are advantageous. The peptide which incorporates all these variations, $D\text{-}Ala^2$, $MePhe^4$, Met-$(O)^5$-ol (29),showed definite analgesic activity even after oral administration, and on a molar basis was 30,000 and 1,000 times as active

as met-enkephalin and morphine, respectively, in mice following intraventricular injection (Roemer et al, 1977).



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Although, no clinical analgesic based on the endogenous peptides has yet been developed, their discovery has undoubtedly shed a lot of light on our understanding of the opiate receptors and the probable mechanism of opiate mediated analgesia.

Despite the fact that the direct evidence for the existence of the opiate receptor became available only very recently, the design of synthetic narcotic analgesics has all along been pursued in line with the assumption of a definite relationship between chemical structure and biological activity. In this respect, the classical opiate receptor model of Beckett and Casy(1954) set the pattern for correlation in the narcotic analgesic field. The model related the structure of the then known narcotic analgesics to their activity thereby establishing the minimum structural requirements for analgesic activity. The model has, however, been extended and modified to accommodate newer concepts, and classes of analgesics (Bentley,

Cowan & Lewis, 1971; Creese, Feinberg & Snyder, 1976; Galt, 1977).

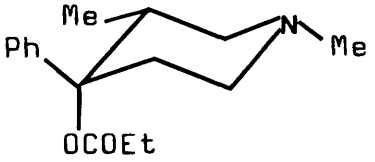
Apart from chemical structure, the stringent stereochemical requirements of the opiate receptor have been known for a long time. The agonist activity of morphine resides only in the laevo-enantiomer (the naturally occuring form of morphine), the dexto-enantiomorph obtained synthetically being almost devoid of any analgesic activity (Goto et al, 1957). Similarly, the agonist activity of racemorphan is due to the laevo-isomer, levorphanol, while the optical antipode (dextrorphan) is devoid of analgesic activity, and examples of pronounced potency variations among enantiomers of several benzomorphan derivatives abound (Tullar et al, 1967). It was therefore evident that the correlation of absolute stereochemistry with analgesic potency was a vital requirement for a thorough understanding of the opiate receptor, its topography, and possibly the mode of interaction with ligands (Larson & Portoghese, 1973). In line with the above, the 4-phenylpiperidine analgesics have received a great deal of attention over the last couple of decades, partly because of the pronounced difference in the analgesic potency of diastereo-isomers obtained from C-alkylation of the piperidine ring, and partly because of the conformational flexibilty inherent in these derivatives.

SECTION TWO

Isomeric Reversed Esters Of Pethidine

The isomeric nature of the 3-methyl derivatives of the reversed ester of pethidine was first studied by Ziering and Lee (1947) who reported potency differences between the diastereo-isomeric pair, examined as racemates. The major isomer, α-prodine whose configuration was proposed as trans 3-methyl/4-OCOEt, was about one-half as potent as morphine, while the minor isomer, β-prodine(cis 3-methyl/4-OCOEt) was about twice as potent as morphine. Potency differences were also noted in isomeric pairs of other 3-alkyl substituted analogues (Ziering, Motchane & Lee, 1957). These results generated a great deal of interest, not only from a potency view point, but also for configurational considerations. Experimental data from other workers confirmed the potency differences, but the veracity of the original configurational assignments remained very controversial (Beckett et al, 1959) until the relative configurations of the prodines were established by X-ray crystallographic studies (Kartha et al, 1960), and substantiated by ^{1}H- and ^{13}C-n.m.r studies (Casy, 1966 & 1968; Portoghese & Shefter, 1976; Jones et al, 1973) as trans 3-methyl/4-Ph for α-prodine (30), and cis 3-methyl/4-Ph for β-prodine (31). (By IUPAC nomenclature (IUPAC, 1970) the configurations are, α: c-3-Me, r-4-OCOEt, β: t-3-Me, r-4-OCOEt).

The effects of 3,5-dimethyl substitution (32) on the reversed ester of pethidine were investigated by



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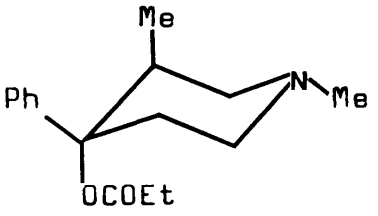
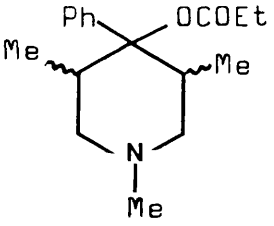


31

(Note: In these and other configurational drawings in this thesis, only one enantiomorphic form is shown for chiral molecules)

Sorokin(1961) who reported an analgesic potency greater than that of morphine for one of the isomers. Stereochemical considerations indicate three possible isomeric



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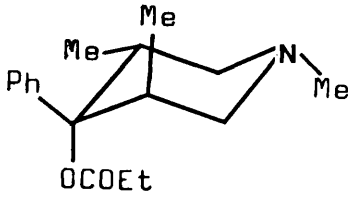
forms, namely, one chiral isomer (33) and two meso-forms (34 and 35). The chiral form (γ-isomer) was found to be



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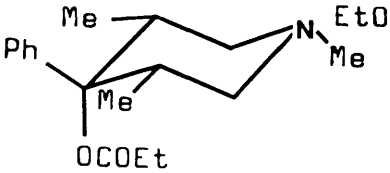

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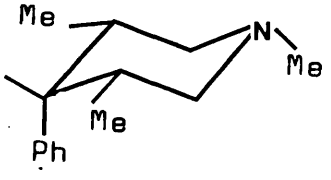
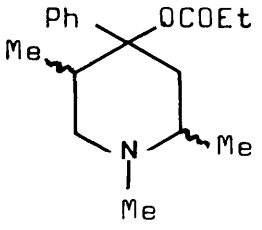


35

active, while the achiral forms were inactive. Evidence confirming the stereochemistry of the γ-isomer was provided by Portoghese and co-workers (1973) who not only resolved it into the optical antipodes, but also determined their absolute configuration. The analgesic activity was due mainly to the (+)-isomer, though the (-)-isomer was found comparable to pethidine in potency.

The promedols, the 2,5-dimethyl derivatives (36), were described by Nazarov and Rudenko (1948) who isolated three of the four possible isomers. The major isomer, named γ-isomer, was found to be twice as active as morphine,

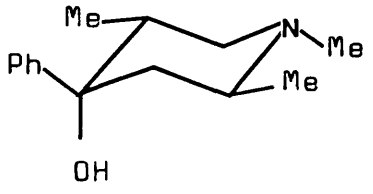


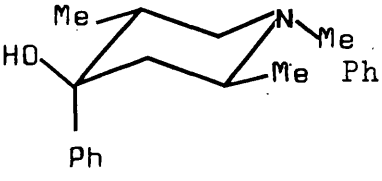
36

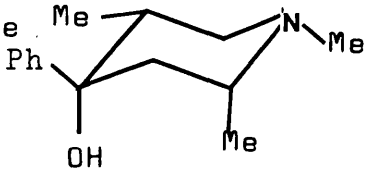
while the two minor isomers (α-and β-) were eight and four times as potent as morphine respectively, in rats (Nazarov, Prostakov & Shvetsov, 1956). The fourth possible isomer (δ-) was later synthesised and reported as having four to six times the activity of morphine in rats (Shvetsov & Kucherov,1959). The γ-isomer is used clinically as an analgesic in Russia.

The stereochemistry of the isomeric 1,2,5-trimethyl-4-phenyl-4-piperidinols, the 4-piperidinol precursors of the promedols, was investigated by Casy and McErlane (1972)

who established the relative configurations of the γ-(37), α-(38) and the β-(39) isomers. Although, designations of the α-, and the β-isomers were interchanged in the Russian and later reports as a result of an abstract error, subsequent X-ray crystallography (deCamp & Ahmed, 1972), and



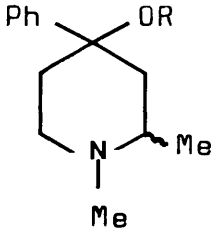




ED_{50} mg/kg (mice hot plate)	1.6	0.18	0.58
	37	38	39

^{13}C-n.m.r studies (Jones, Casy & McErlane, 1973) have confirmed the assigned relative configurations.

As part of the growing interest in the C-alkyl derivatives of the reversed esters, Harper, Beckett and Balon (1960) synthesised the 2-methyl (40) and the 2,6-dimethyl (41) derivatives. They studied the stereochemistry of the



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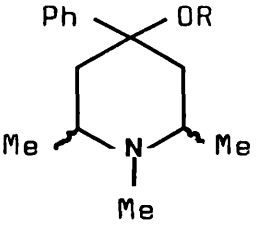
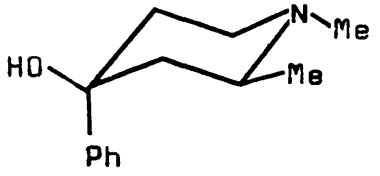
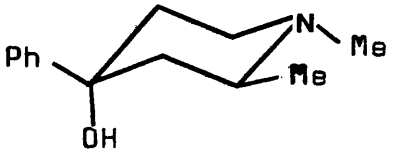


41

1,2-dimethyl-4-phenyl-4-piperidinols (40, R=H) and deduced the relative configuration of the α- (42) and the β- (43)

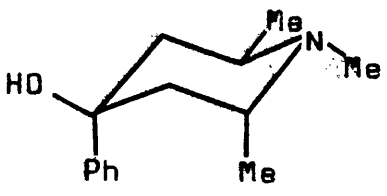
isomers on the basis of their chemical reactivity, pKa, and infra-red (IR) absorption characteristics. These assignments have been confirmed by ^{1}H-, and ^{13}C-n.m.r studies (Casy & McErlane, 1972; McErlane & Casy, 1972), studies which also demonstrated that in the preferred solute conformation ($CDCl_3$ solution), the phenyl group is axially oriented in the α-isomer. Similar stereochemical considera-

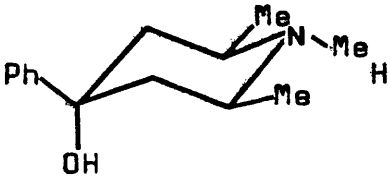


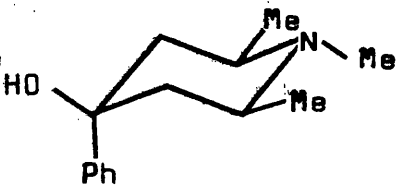


ED_{50} mg/kg	1.32	1.37
	42	43

tions of the isomeric 1,2,6-trimethyl-4-phenyl-4-piperidinols (41, R=H) indicated three possible isomers whose relative configuration were similarly assigned as 44 for the chiral isomer, and 45 and 46 for the two achiral isomers respectively. Spectroscopic evidence confirming the assigned relative configurations were provided by ^{13}C-n.m.r studies



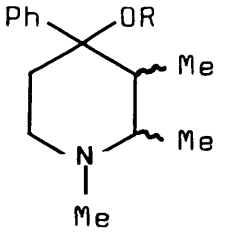




44 45 46

(Jones, Casy & McErlane, 1973), ^{1}H-n.m.r resonances of the acetoxy esters of the corresponding piperidinols (Casy, Coates & Rostron, 1976), and X-ray crystallography (Hayakawa & James, 1973). Analgesic potency tests for the acetoxy esters showed the chiral isomer as the only active form, the two achiral forms being inactive.

One further set of C-methyl substituted reversed esters remainsto be discussed. These are esters of the isomeric 1,2,3-trimethyl-4-phenyl-4-piperidinols (47) reported by Nazarov and co-workers in 1961 and 1962. The four possible diastereoisomers were isolated by Mastryukov and Shvetsov (1961) who also reported the analgesic potency of the propionate esters. The α-isomer was reported equal in activity to morphine, the γ-isomer about 30 times as



47

active, while both the β- and δ-isomers were inactive. The stereochemistry of these compounds has, however, not been studied so as to establish their configurations.

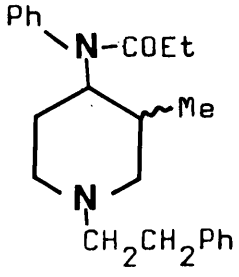
The establishment of the stereochemistry of these isomers forms one of the main aims of this thesis. It will not only provide the required data on the influence of

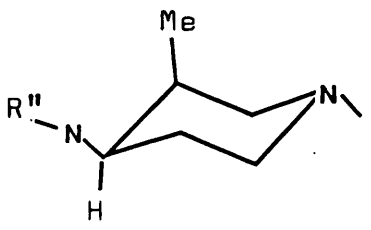
stereochemistry on the opiate activity of the series, but also complete the systematic work on the mono- and di-C-methyl substituted derivatives of the reversed esters of pethidine. The present thesis will therefore be largely concerned with the study of the stereochemistry of the isomeric 1,2,3-trimethyl-4-phenyl-4-piperidinols with the view to establishing their relative configuration and the preferred solute conformations of the pure alcohols as well as those of their corresponding esters.

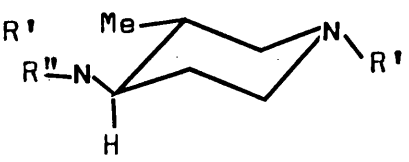
Isomeric C-Alkylsubstituted Analogues Of Fentanyl

The question of whether the 4-anilinopiperidines represent a variant of the 4-phenylpiperidine analgesics such as the reversed esters of pethidine, or a distinct class of narcotic analgesic still remains controversial (Casy et al, 1969; Casy, 1978). Nevertheless, evidence from a comparison of the effect of 3-methyl substitution in the series is in line with the view that they infact are similar.

The synthesis of 3-methyl fentanyl (48) was described by Riley and co-workers (1973) who reported a derivative that was ten times as active as the parent compound







(R'= $-CH_2CH_2Ph$, R"= -COEtPh)

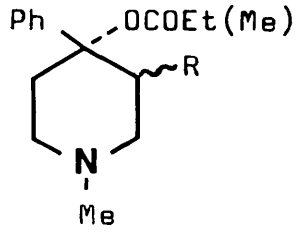
48 49 50

in rats by the tail flick method. The configuration of 48 was however not established. Nevertheless, from the melting point of its hydrochloride salt, and the relative potency, it is probably the cis-diastereoisomer (49) later described along with the trans-isomer (50) by van Bever and co-workers (1975) who readily established their relative configurations from the dimensions of the ^{1}H-n.m.r resonances of the C-4 protons (see page 108). Antinociceptive activity in rats by the tail-withdrawal test showed the cis-isomer to be 8 times more active, and the trans-isomer equipotent with the parent analgesic. Most of the activity of the cis-isomer resided in the laevo-enantiomorph, the dextro-antipode being inactive. This result, therefore, mirrors the stereochemical structure-activity relationships of the 3-methyl pethidines and their reversed esters (the prodines) in which the β-isomer (cis 3-Me/4-Ph) is several times as potent as the α-isomer (trans 3-Me/4-Ph) which in turn is equipotent with the parent compound (Casy et al, 1969; Iorio et al, 1975). The case of 3-methyl substitution in the prodines has, however, been found to be unique since substitution with higher 3-alkyl derivatives such as ethyl, propyl and allyl groups, consistently resulted in isomeric pairs in which the α-isomers(trans 3-alkyl/4-Ph) are more potent than the β-isomers (Table I).

It was considered, therefore, that further evidence about the similarities in the relative modes of uptake of fentanyl- and prodine-like analgesics could be obtained by examining higher 3-alkyl analogues of fentanyl to see if the

receptor preferences for the cis-geometry be reversed as is the case for higher homologues of prodine. This project will also be a subject of this thesis.

Table I: Analgesic activity (ED_{50} mg/kg, s.c. in mice by the hot-plate method) of some reversed esters of pethidine(Iorio,Casy&May,1975)[a]



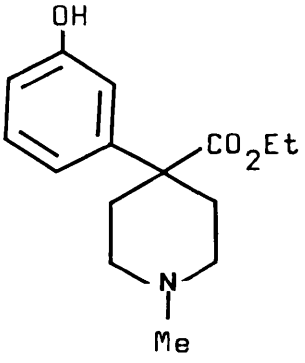
R	α- (trans 3-R/4-Ph)		β-(cis 3-R/4-Ph)	
H	0.85	(3.62)	0.85	(3.62)
Me	0.92	(6.0)	0.18	(0.98)
Et	0.4	(2.1)	3.5	(15.9)
Pr^n	2.0	(10.4)	14.7	(23.4)
Allyl	0.09		11.7	
Bu^n	54.7	(29.3)	12.8	(26.5)
$C_6H_{13}{}^n$	inactive at 80		54.4	

(Note: a acetate data in parentheses)

4-(m-Hydroxyphenyl) Analogues Of The Reversed Ester Of Pethidine

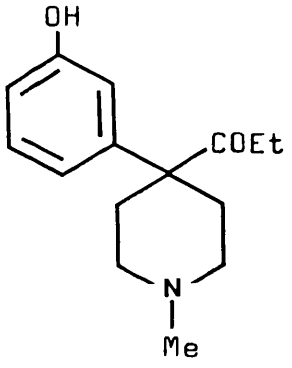
Earlier structure-activity relationship studies of pethidine-type analgesics have shown the detrimental

influence of substituting the 4-phenyl group with ortho- and para-hydroxyl, and para-amino groups on activity (Beckett & Casy, 1962). In contrast however, m-hydroxyl substitution of the phenyl group has led to analogues with enhanced analgesic activity. For example, the m-OH ester, bemidone (51) is 1.5 times more potent than pethidine, while ketobemidone (52) is much more active than the non-phenolic analogue (53). On the other hand, m-hydroxyl



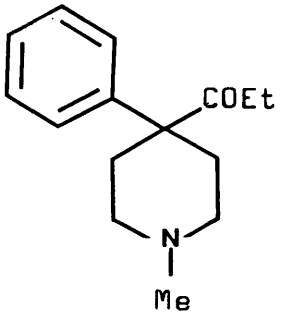
1.5x

51



10x

52

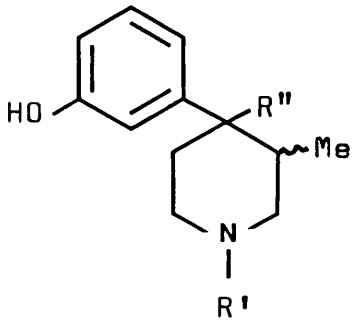


0.5x pethidine (Braenden et al, 1955)

53

substitution of the phenyl group in β-prodine is reported to have transformed the otherwise potent analgesic into an antagonist devoid of any agonist activity (Zimmerman et al, 1978). This unusual antagonist property is claimed to be brought about by the stereochemical placement of the 3-methyl substituent, since all the 1,3,4-trialkyl-4-phenylpiperidine series (54) with reported antagonist properties have the cis-3-methyl/4-phenyl configuration. These results are of particular interest with regards to the effects of stereo-

chemistry on the activities of opiate ligands on the one hand, and the effects of m-hydroxylation of the 4-phenyl



54

group on the properties of the reversed esters of pethidine on the other hand. It will therefore be one of the aims of the present thesis to examine these effects on the activities of some reversed esters of pethidine.

SECTION THREE

Aims And Objectives Of The Present Work

The 2- and 3-monomethyl, and the 2,6-, 2,5-, and 3,5-dimethyl analogues of the reversed esters of pethidine have been thoroughly investigated from both a stereochemical and structure-activity point of view. This is not the case, however, for the 2,3-dimethyl analogues, compounds which are not only potent, but show considerable activity variation amongst the various isomeric forms. One of the main aims of this thesis is to obtain further data on the 2,3-dimethyl analogues with a view to:

i) establishing the relative configuration and the preferred solute conformation for the isomers, and

ii) to relate the stereochemical structure-activity patterns to those of other C-methyl analogues of established stereochemistry.

In addition to the above, since the structure-activity relationships of the 3-methyl analogues of fentanyl mirror to a very large extent those of the 3-methyl analogues of the reversed esters of pethidine, a further aim of the present work is to prepare some higher 3-alkyl analogues of fentanyl, the objectives of which are:

i) to establish the relative configurations and conformations of the diastereoisomers, and

ii) to relate the stereochemical structure-activity pattern to those of the higher 3-alkyl analogues

of the reversed esters of pethidine in order to establish the similarities or otherwise of the relative modes of uptake of the two groups at the analgesic receptor site.

One other aim of the present thesis is to obtain further data on the phenolic derivatives of the reversed ester of pethidine. To this end, work was planned on both the 3-methyl and the 3-desmethyl analogues together with the N-phenethyl derivatives. The objectives of this aspect of the work are;

i) to establish the stereochemistry of the isomeric forms, and

ii) to relate the stereochemistry to their opiate properties in respect of both agonist and antagonist activities.

The work in the thesis therefore entailed;

i) Syntheses;

ii) Separation of isomers;

iii) Configurational and conformational assignments using spectroscopic techniques; and

iv) Pharmacological evaluation.

Another minor objective which developed during the course of the experimental work was the chemistry of the Prins product from a 1-benzyl-4-piperidinol derivative which is described in the appendix.

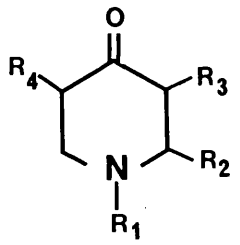
C H A P T E R T W O

DISCUSSION OF EXPERIMENTAL WORK

SECTION ONE

Isomeric 1,2,3-Trimethyl-4-phenyl-4-piperidinols And Their Esters

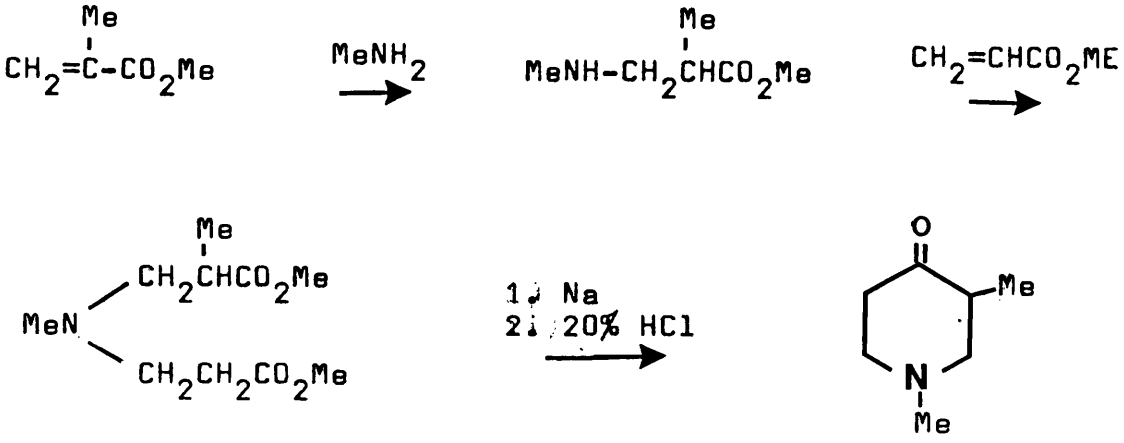
Substituted 4-piperidones (55) are the key intermediates in the syntheses of the reversed esters of pethidine. These piperidones are usually made via the Dieckmann cyclisation of a bis-β-carbalkoxyethylamine with sodium



55

metal or such agents as sodamide and sodium ethoxide, and decarboxylation of the resultant 3-carboxy-4-piperidone. This route could amply be illustrated by Howton's (1945) procedure for the synthesis of 1,3-dimethyl-4-piperidone outlined in Scheme 1.

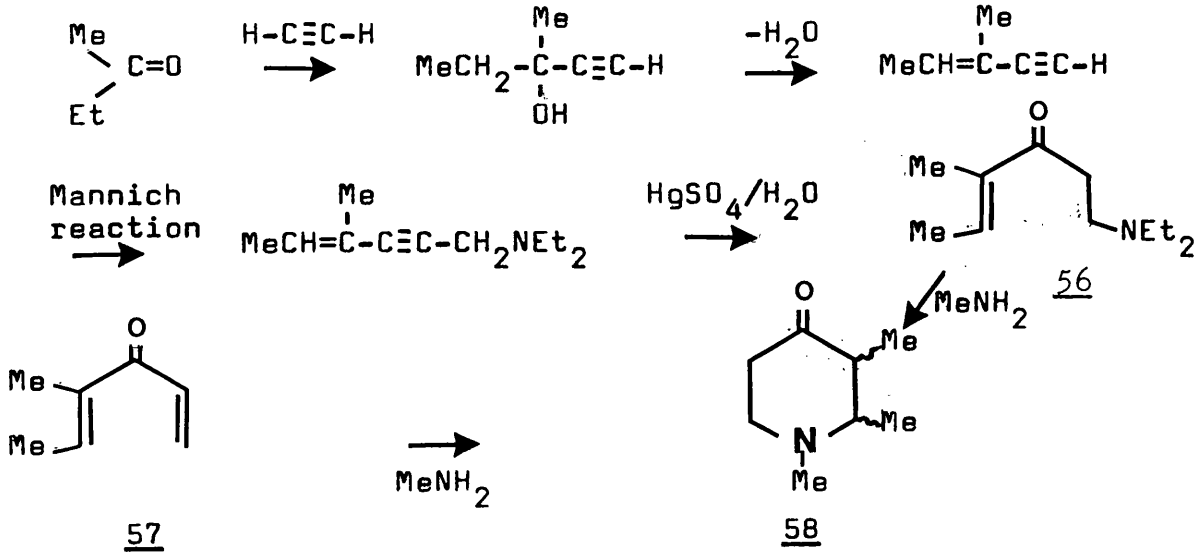
Since the Michael condensation of the amines with the acrylates may be carried out stepwise, the route is easily adapted to the syntheses of various C-alkyl substituted



Scheme 1

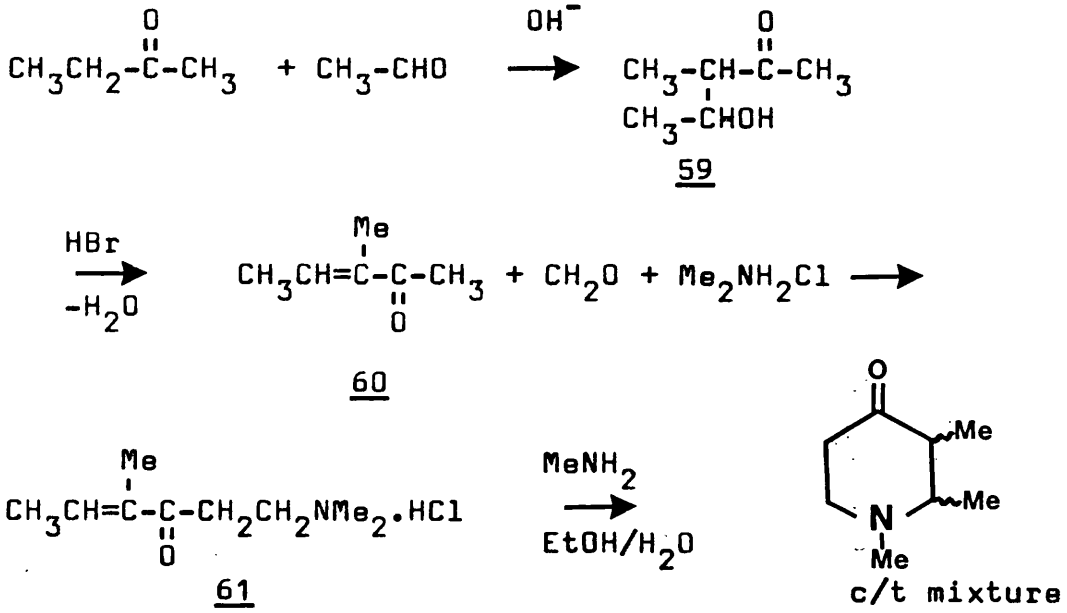
4-piperidones (Ziering, Montchane & Lee, 1957; Harper, Beckett & Balon, 1960). Nevertheless, 1,2,3-trimethyl-4-piperidone (58), the intermediate ketone to the 2,3-dimethyl analogues of the reversed ester of pethidine (see page 50), is not normally synthesised through the Dieckmann cyclisation route since the appropriate intermediate acrylates are not commercially available.

The literature methods (Nazarov & Mistryukov, 1958) for the synthesis of the ketone proceed via cyclisation of a Mannich base (56), or a divinyl ketone (57) with methylamine as outlined in Scheme 2.



Scheme 2

However, full details of the experimental conditions were not available from the literature source. We therefore decided to explore the possibility of synthesising the key Mannich base (56) via an alternative route and hence the desired ketone as outlined in Scheme 3.

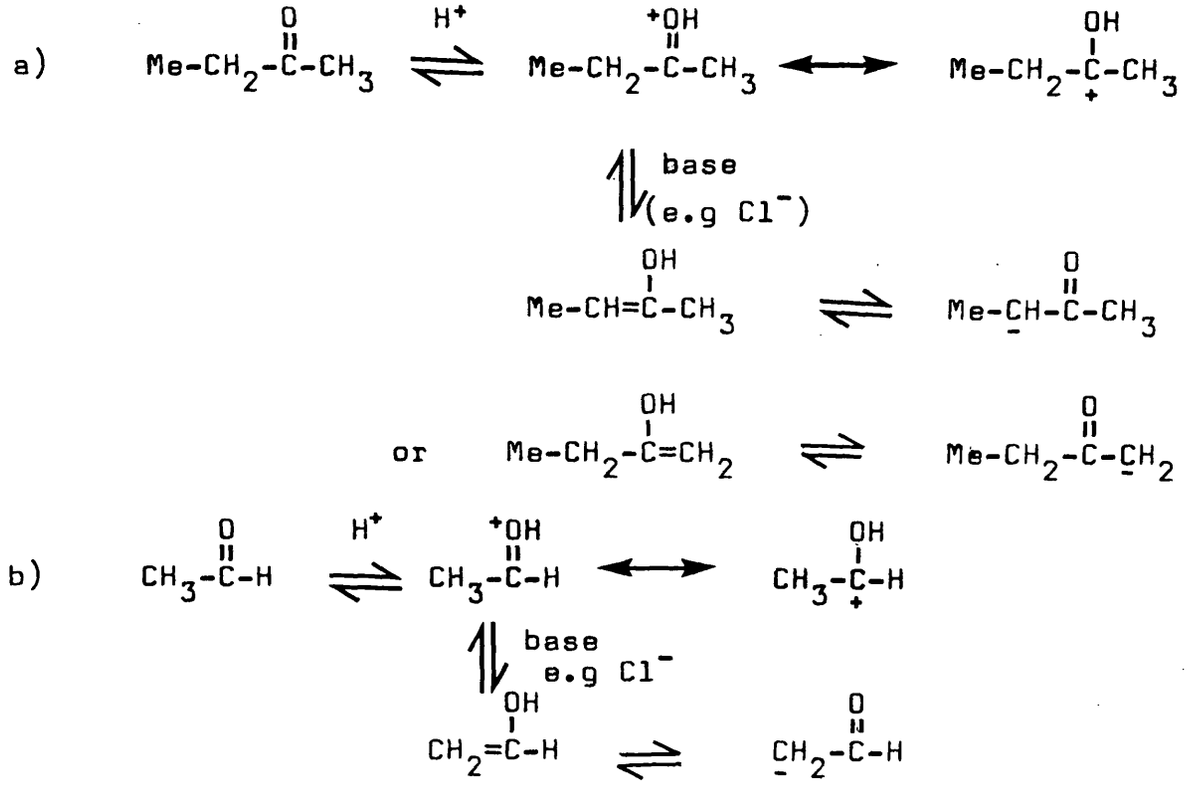


Scheme 3

One literature method (Hinkel et al, 1931) for the synthesis of the intermediate 3-methyl-3-penten-2-one (60), proceeds via an acid catalysed mixed aldol condensation of 2-butanone and acetaldehyde. Yields of the product obtained when this method was employed were poor due to extensive polymerisation of the reactants, especially acetaldehyde, with the formation of crotonaldehyde (strong foul odour).

The mechanism of an acid catalysed aldol condensation can be pictured in terms of an initial protonation of the carbonyl species leading to a reversible generation

of carbonium ions or carbanions - via enols (Scheme 4) - and the subsequent reaction between the carbanions and the carbonium ion species (Nielsen & Houliham, 1968). In the

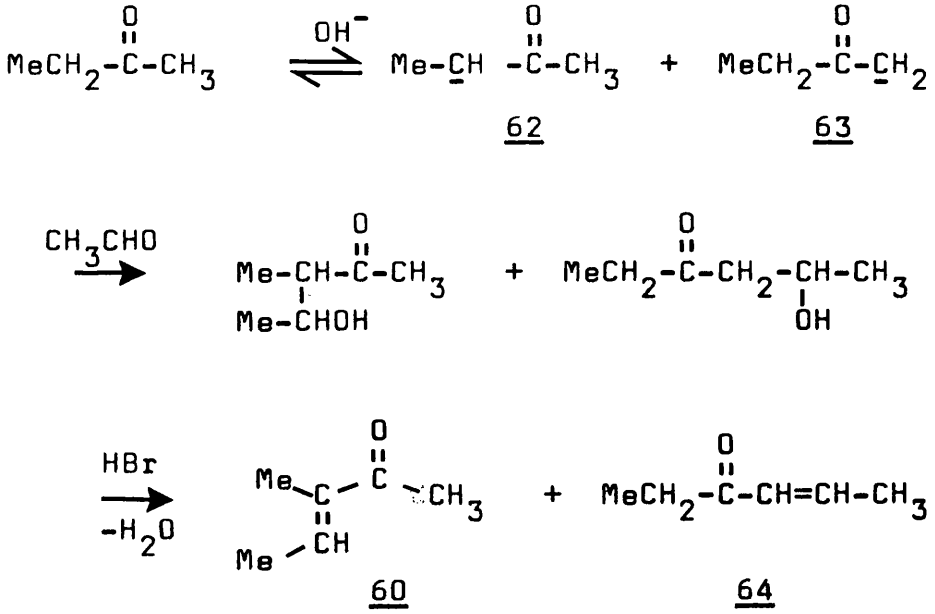


Scheme 4

mixed condensation between butanone and acetaldehyde where two carbonium ions and three carbanions can be generated, the reaction is potentially capable of yielding six different products. The factors governing the ratio of products would therefore be both thermodynamic and kinetic. Acetaldehyde, being less hindered, undergoes self-condensation faster than the bulkier butanone, but the extent of cross-condensation between the two reactants depends on the relative concentration of the species in the reaction medium, hence the need to use excess molar concentration of

butanone.

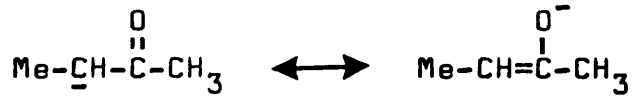
In the base catalysed method (Kyrides, 1933), the mechanism of the reaction involves an initial base abstraction of an α-hydrogen to form a carbanion (Scheme 5). However, since two carbanions are possible from butanone, the reaction is also potentially capable of forming six products. Inspite of this, the desired product (60) was obtained in excellent yields (up to 70%) via the base catalysed method. The technique involves the use of a large excess of butanone (10 moles), and pre-forming the butanone carbanion by stirring it with the base (10% NaOH) at 8-9 °C, a condition under which self-condensation of butanone is minimal, prior to a dropwise addition of acetaldehyde to the stirred reaction medium. In this way, self-condensation



Scheme 5

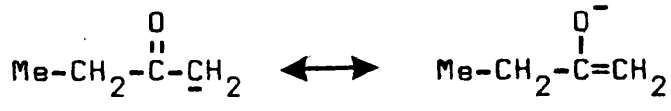
of acetaldehyde is reduced to a minimum. The competing side

reactions are therefore limited to those of carbanions 62 and 63 with acetaldehyde (see page 38), the prepoderance of either of which depends on their relative stabilities. The ^{1}H-n.m.r spectra of the dehydrated product was consistent with structure 60, and no significant absorption due to the alternative ketone (64) where observed (details to follow). This result underscores the relative stability of carbanion 62 over 63. The probable reason for this is the fact that in the mesomeric form, 62b, the double bond



62a 62b

is stabilised by an additional hyperconjugative effect of the α-methyl group, a situation which is absent in the corresponding form of carbanion 63 (63b). The aldol (59,



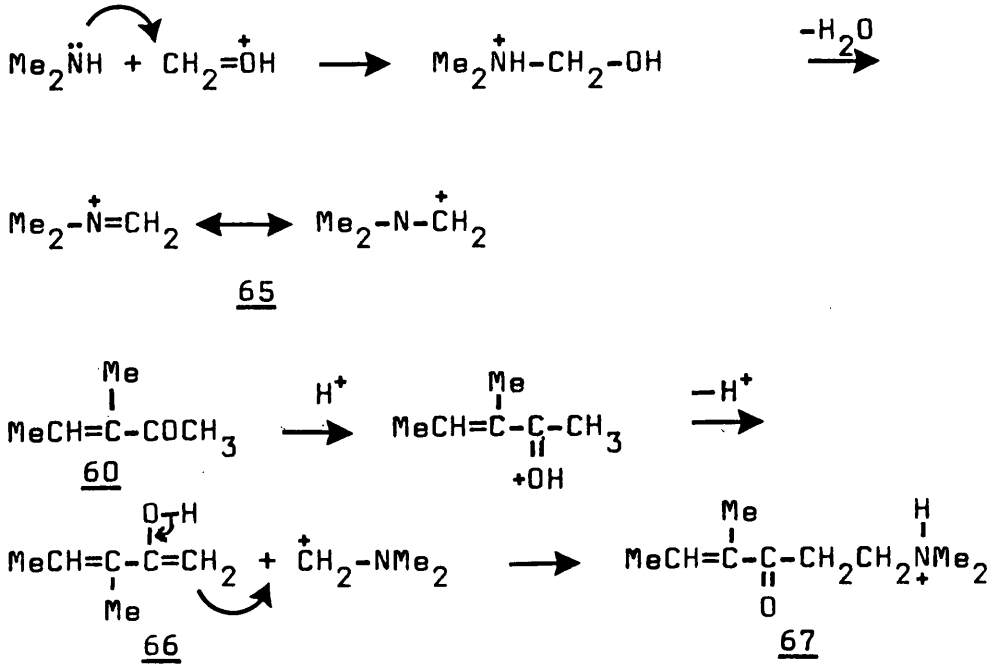
63a 63b

page 36) was not isolated but dehydrated *in situ* with hydrobromic acid.

The IR spectrum of the distilled product showed a strong carbonyl absorption ($\nu_{C=O}$, 1660 cm^{-1}), while its boiling point and melting point of its 2,4-dinitrophenylhydrazone agree with reported values (details in the

experimental section). The ^{1}H-n.m.r spectrum of the ketone (in $CDCl_3$) displayed a vinylic proton resonance (δ 6.8 ppm, quartet), and three methyl proton resonances (δ 1.8, 2.3, singlets; and 1.89, doublets, ppm) in agreement with the assigned structure (60).

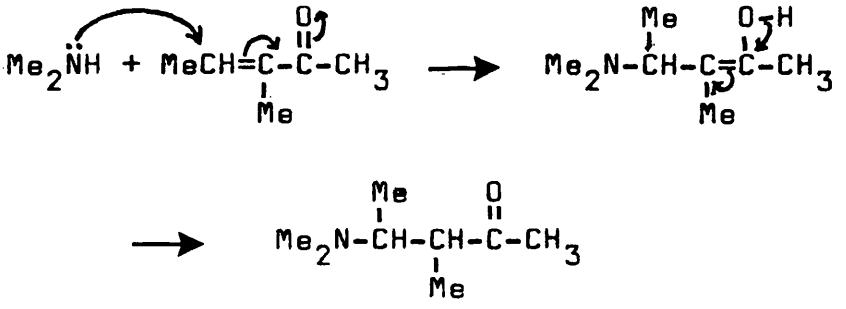
The Mannich reaction is general to compounds which are, or are potentially enolic, such as ketones with α-hydrogen, and certain acetylenes. These compounds react with a mixture of an aldehyde (usually formaldehyde) and a primary or a secondary amine in the presence of acid to give the salt of the aminomethyl derivative. Secondary amines are preferred, since the aminomethyl derivative from a primary amine can still react further to form the bis-aminomethyl derivative. The probable mechanism of the Mannich reaction (Scheme 6) involves an initial reaction of the amine with formaldehyde in the presence of acid to form an adduct which eliminates water to yield an electrophile (65). The acid



Scheme 6

also catalyses conversion of the ketone (60) to its enol tautomer (66) which then reacts with the electrophile to form the amine salt, 67 (Blickie, 1942).

Since 3-methyl-3-penten-2-one (60) has only one kind of α-hydrogen, the Mannich base (67) is the major expected product. Nevertheless, a Michael-type addition of amine to the ketone (68) is a probable competing side reaction. No such amine was however isolated, perhaps because the base is used in its protonated form. The Mannich base (67)



68

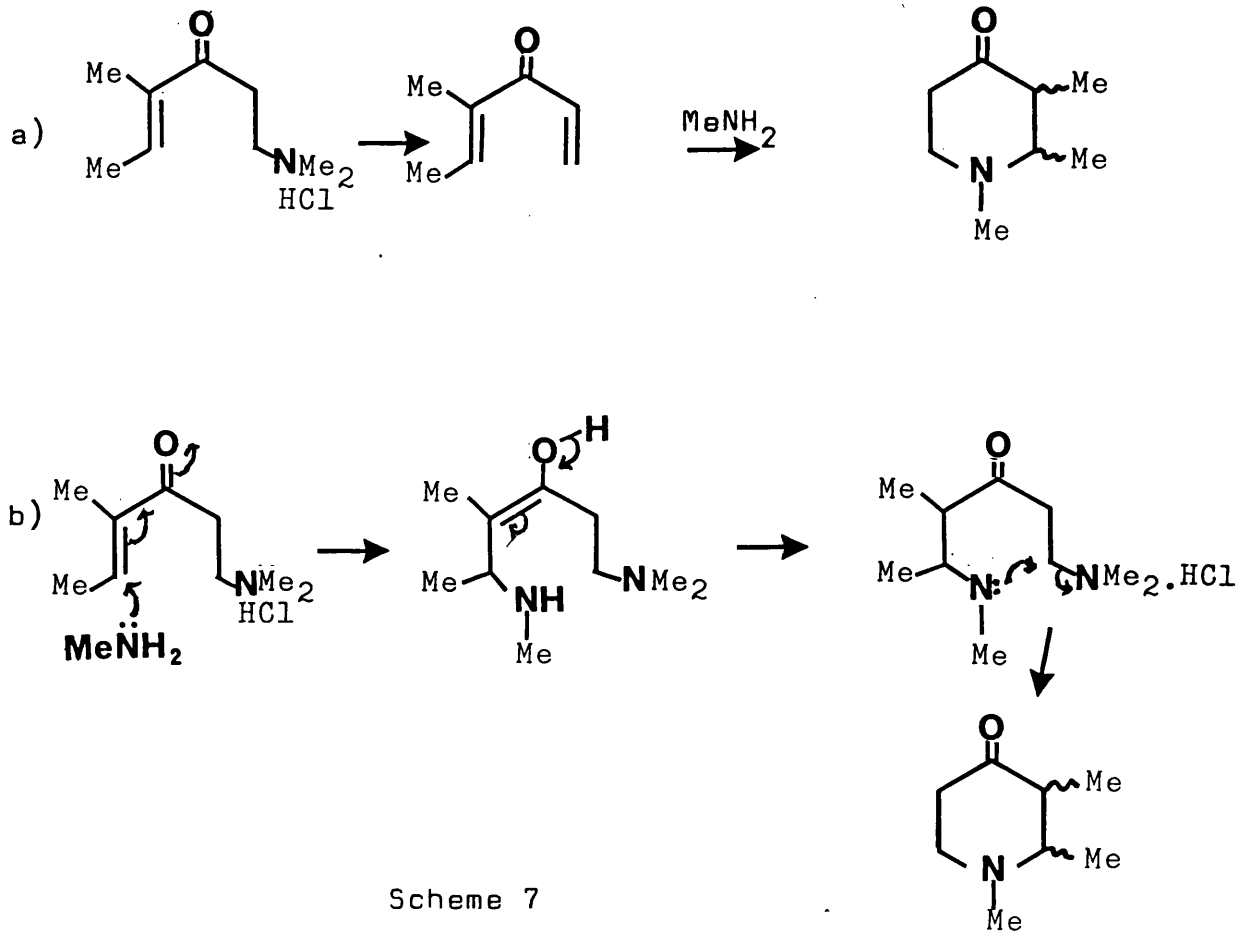
was isolated as the crystalline hydrochloride salt in up to 52% yield. The IR spectrum of 67 showed a carbonyl absorption (ν_{CO} 1650 cm^{-1}, nujol) and the absorption due to the protonated amine ($\nu_{\overset{+}{N}H}$ 2500 cm^{-1}, nujol). Both the ^1H-(δ 6.8 ppm, due to the vinylic proton), and ^{13}C-n.m.r spectra displayed resonances consistent with the structure (67).

The Mannich base was readily cyclised by stirring with excess of methylamine in ethanol and a five molar ratio of water, and the desired 1,2,3-trimethyl-4-piperidone

obtained in yields of up to 60%. In similar reactions without water, the yield of the 4-piperidone was very poor (less than 30%). A similar observation was reported in amine exchange reactions between a primary amine and some 4-piperidone methiodides in which the molar proportion of water added was crucial to the yield of the expected product (Hassan & Casy, 1970). Since methylamine can also react with the carbonyl group of the Mannich base or of the ketone to give an imine, addition of water to the reaction mixture probably facilitates the hydrolysis of any formed imine, thereby improving the yield. It is conceivable to picture the cyclisation of the Mannich base as proceeding via the divinyl ketone (Scheme 7a), because Mannich bases can readily decompose to produce the corresponding olefin. However, since the reaction progresses smoothly, and excellent yields of product are obtained without any application of heat, the mechanism may involve an initial Michael addition of amine to the Mannich base followed by a displacement of the dimethylammonium group (Scheme 7b). This is similar to the mechanism advanced for the amine exchange reaction cited above.

The pure piperidone was a cis/trans isomeric mixture as judged from its ^{1}H- and ^{13}C-n.m.r spectra. The N-methyl protons resonate at δ 2.35 and 2.42 ppm in a ratio of approximately 60:40 judging from their relative intensities, while the C-methyl protons gave a multiplet (δ 0.8-1.2 ppm) due to the overlap of the four pairs of methyl doublets (two pair per isomer). The ^{13}C-n.m.r spectrum

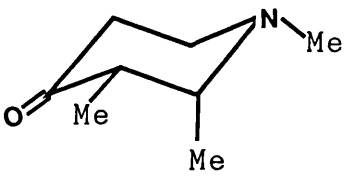
displayed sixteen carbon resonances (eight per isomer), and the intensities of related carbonyl, 2- and 3-methyl



Scheme 7

resonances from a spectrum run with proton decoupling and suppressed Nuclear Overhauser Enhancement (NOE) mode indicated 37-40 % of minor isomer component, close to the value (36 %) established by gas-liquid chromatography (Mistryukov & Smirnova, 1971). The ketone displayed a strong carbonyl absorption at 1702 cm^{-1} in the IR spectrum. ^{13}C-n.m.r chemical assignments, the principle of which will be discussed later on in the thesis, established the minor component as the cis-isomer with a preferred axial 2-methyl

chair conformation(69a), and the major component, trans, with a preferred equatorial methyl chair conformation (69b).

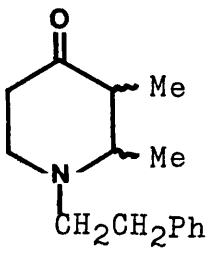


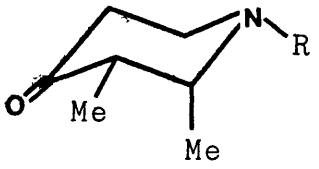
69a

69b

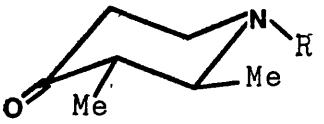
The hydrochloride salt derived from the mixture has the trans configuration, and so also does the methiodide salt (data in Table II).

The N-phenethyl analogue was readily prepared by cyclising the Mannich base (61, page 36) with β-phenethylamine, the full details of which are recorded in the experimental section. The product, like the N-methyl analogue, was also a cis-trans isomeric mixture, but with the components in approximately equal proportions as judged from the relative intensities of their corresponding carbon and proton resonances. The IR spectrum of the mixture displayed a strong carbonyl absorption at 1704 cm^{-1}, while both the ^{1}H- and ^{13}C-n.m.r resonances are consistent with the structure (70). The hydrochloride salt derived from the mixture was isomerically pure, and the ^{13}C-n.m.r chemical shift data of the derived base (Table II, entries 6 and 7) established the isomer as having the cis-configuration with a preferred axial 2-methyl chair conformation





(R= CH_2CH_2Ph)

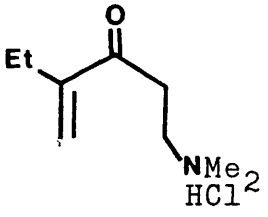


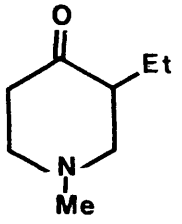
70 70a 70b

(70a), while the other component (data extracted from the spectrum of the mixture) has the trans-configuration with equatorial methyl conformation (70b).

The potentialities of the procedure above as a general synthetic route to 4-piperidones were explored with the syntheses of the 3-ethyl, and the 3-methyl analogues (Scheme 8). The vinyl ketones (71 and 74) were synthesised

a) $EtCH_2-C(=O)-CH_3 + CH_2O \xrightarrow[2.\ -H_2O]{1.\ OH^-} Et-C(=CH_2)-C(=O)-CH_3$ (71)

Mannich reaction →  (72)

$MeNH_2$ →  (73)

b) $MeCH_2-C(=O)-CH_3 + CH_2O \xrightarrow[2.\ -H_2O]{1.\ OH^-} Me-C(=CH_2)-C(=O)-CH_3$ (74)

Table II

^{13}C Chemical shifts (δ ppm) of some 1-methyl-4-piperidones and the N-phenethyl analogue in $CDCl_3$ (TMS standard)[a,b]

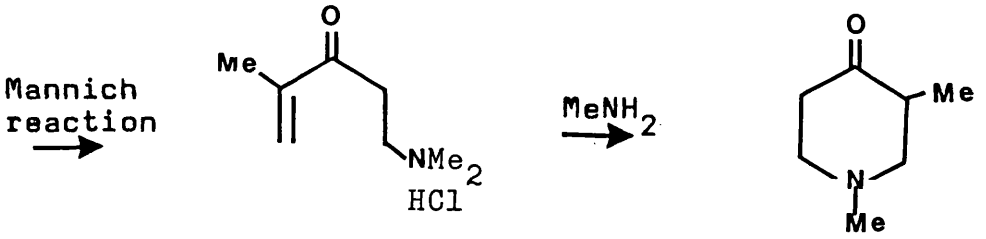
Entry	Compound	Isomer designation	C-2	C-3	C-4	C-5	C-6	1-CH_3 (-CH_2-)	2-CH_3	3-CH_3
1.	1-methyl-4-piperidone(base)[c]	-	55.4	40.89	206.22	40.89	55.4	45.15	-	-
2.	1-methyl-4-piperidone (HCl)	-	52.03	38.39	203 08	38.39	52.03	42.20	-	-
3.	69b (HCl)	trans(major)	65.88	47.29	203.10	38.08	54.07	40.90	16.04	10.94
4.	69b (base)	trans(major)	65.44	49.84	209.55	40.74	55.37	41.50	18.09	11.32
5.	69a (base)[d]	cis (minor)	61.98	48.87	210.68	39.71	49.95	42.02	9.21	11.05
6.	70a (base)	cis	60.67	48.75	210.73	40.25	46.75	55.95	8.61	11.10
7.	70b (base)[d]	trans	61.97	50.65	210.25	39.87	49.78	53.95	16.25	12.78

Note: a Assignments based on off-resonance spectra and chemical shifts of related compounds(Jones et al, 1973; Casy, Iorio & Podo, 1981; Jones & Hassan, 1972)

b Stereochemical assignments based on the similar C-5 and C-6 shifts of the trans piperidone and 1-methyl-4-piperidone, and the relatively high field shifts of the C-6 and 2-CH_3 in the cis base.

c Ref. (Jones & Hassan, 1972)

d Values extracted from the spectum of the cis-trans mixture.



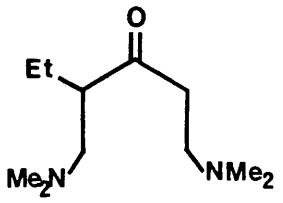
75 76

Scheme 8

via a base catalysed aldol condensation of paraformaldehyde with 2-pentanone and 2-butanone respectively (Landau & Irany, 1947), the details of which are in the experimental section.

The Mannich base (72) could however not be isolated as the crystalline hydrochloride salt. The reaction mixture was therefore treated with methylamine solution, and the cyclised product (73) obtained in about 15% yield (see page 48 for ^{13}C-nmr evidence of structure and purity). The failure of the Mannich base to crystallise appears to be due to the presence of a substantial amount of side-reaction impurities, since a thin-layer chromatography (tlc) analysis of the reaction mixture showed four major spots. These products were, however, not isolated. Nevertheless, it is reasonable to expect the product of a Michael addition of the dimethylamine to the vinyl ketone prior to or after the formation of the Mannich base as one of the major side products. A similar di-amino ketone has been isolated from an analogous reaction (Hassan & Casy, 1970). Such a di-amino ketone (77) would not cyclise to the expected ketone (73, page 46) under

the normal conditions. This view is partly supported by the evidence of a reduced intensities of the vinylic proton resonance (δ 6.05 and 5.80 ppm, br.sing.) in the ^{1}H-nmr



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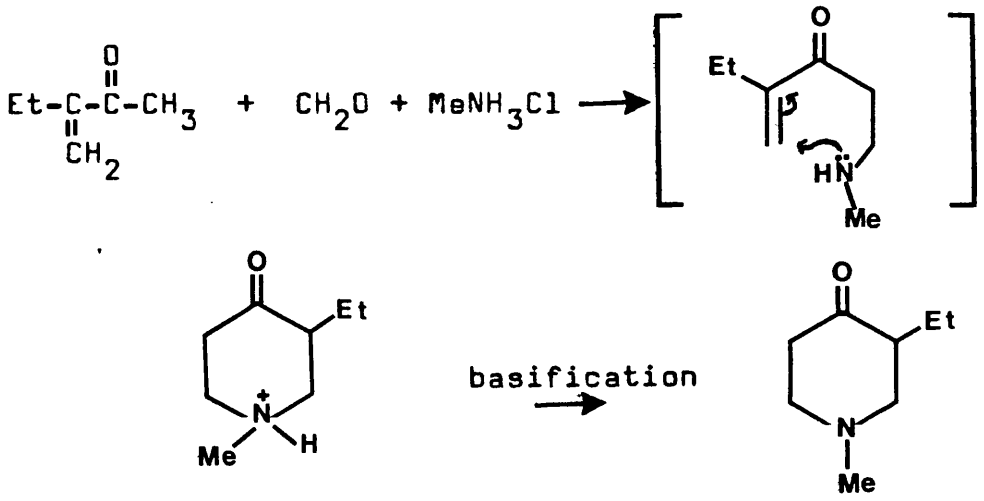
spectrum of the reaction products, and the fact that a one step formation/cyclisation of the Mannich base, made possible by using a primary amine (Scheme 9), gave the expected ketone (73) in up to 25 % yield.



Scheme 9

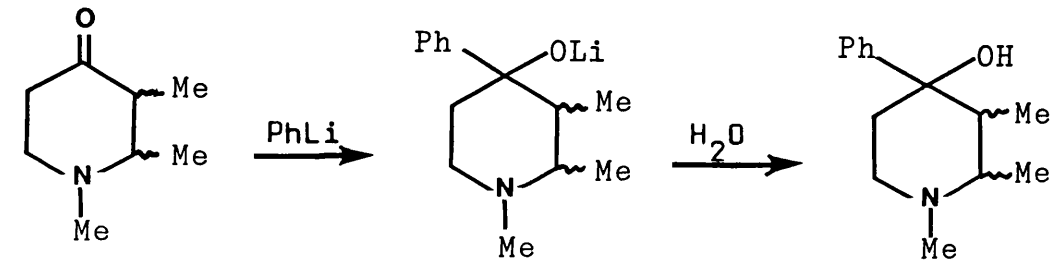
The IR spectrum of the 3-ethyl ketone showed a strong carbonyl absorption at 1705 cm^{-1}, and the ^{13}C-n.m.r

spectrum displayed eight carbon resonances consistent with the structure (details in the experimental section).

A similar difficulty was also experienced with the Mannich base (75), the precursor to the 3-methyl analogue (Scheme 8b, page 46). However, in this case, we managed to isolate some crystalline form of the Mannich base, which displayed the vinylic proton resonances (δ 6.05 and 5.80 ppm, br. singlets) and other resonances consistent with the structure. The yield of the Mannich base hydrochloride (75) was however very low. Nevertheless, cyclisation of 75 with methylamine in the usual way proceeded smoothly to give the 3-methyl ketone (76, 60 % yield). which formed a hydrochloride salt with melting point similar to that reported by Howton (1945). The IR spectrum showed a strong carbonyl absorption at 1705 cm^{-1}. The ^{1}H-n.m.r resonances, a doublet (δ 0.96 ppm, 3-CH_3) and a singlet (δ 2.35 ppm, N-CH_3), are also consistent with the structure.

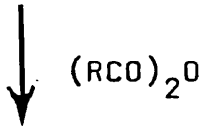
Treatment of the 1,2,3-trimethyl-4-piperidone with phenyllithium gave an adduct which when decomposed with water or acid anhydrides gave isomeric mixtures of the 4-piperidinol and the corresponding esters respectively (Scheme 10). Separation of the diastereoisomers was first attempted by fractional crystallisation of the hydrochloride salts of the propionate and acetate esters following the success of this technique in the separation of the prodines (Ziering, Montchane & Lee, 1957), but in this

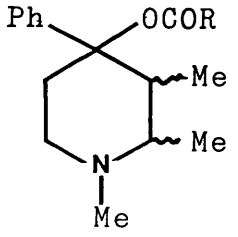
case only one pure form corresponding to the β-isomer (see page 56 for assignment of configuration) could be isolated in either of the esters. However, fractional



c/t mixture

78





a) R = Et

b) R = Me

79

Scheme 10

crystallisation of the isomeric piperidinols (78) from toluene afforded the pure α-, and β-alcohols with melting points in accord with reported values (Mistryukov & Shvetsov, 1961). The γ-isomer was isolated as the hydrochloride salt from an acidified mixture of the residues.

The hydrochloride salts of the propionate and the acetate esters were readily made by refluxing the isomer-

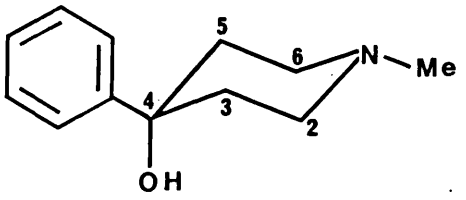
ically pure alcohols with propionyl or acetyl chloride in toluene.

Stereochemical Studies Of The Isomeric 1,2,3-Trimethyl-4-phenyl-4-piperidinols And Their Esters.

Evidence of the stereochemistry of the 4-piperidinols (78) were first sought from n.m.r data, following previous studies of related 2-, 3-monomethyl, 2,5-, 2,6-, and 3,5-dimethyl-4-phenyl-4-piperidinols (Jones, Casy & McErlane, 1973; Casy, Iorio & Podo, 1981; Jones, Beeman,Casy & McErlane, 1973; Hanish & Jones, 1976; Casy, Coates & Rostrum, 1976). The ^{1}H-n.m.r spectra of the isomeric alcohols were too similar for any direct stereochemical deductions to be made from the chemical shift data. The bulk of the stereochemical information was therefore derived from the ^{13}C-n.m.r data, and supplemented with ^{1}H-n.m.r and IR studies.

The most general method for ^{13}C-n.m.r assignments is by the aid of off-resonance spectra and chemical shift correlations with spectra of closely related compounds of established stereochemistry. The main principle behind the use of ^{13}C-n.m.r data for stereochemical assignments is based on the fact that the effects of a substituent on the chemical shifts of the parent compound depends not only on the nature of the substituent, but also on its spatial orientation in relation to other carbon atoms in the molecule. These substituent effects are

significantly noticeable on the immediate (α-carbon), as well as on distant carbon atoms in the molecule, especially the γ-carbon. 1-Methyl-4-phenyl-4-piperidinol (80), with a preferred equatorial 4-phenyl chair conformation, may be regarded as the parent compound from which the 2,3-dimethyl analogues (78, page 50) are derived.



80

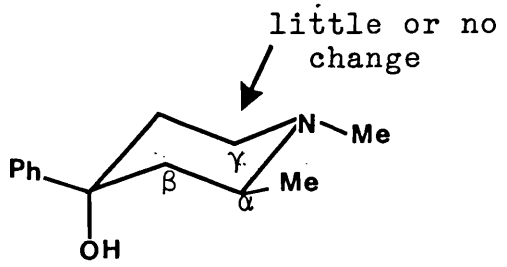
The complete proton-noise decoupled ^{13}C-n.m.r spectrum of this model compound (together with the off-resonance spectrum) was recorded in order to assign the basic chemical shifts of the various carbon atoms in the molecule. The spectrum displayed four carbon resonances in the aliphatic(alicyclic) region, made up of a singlet, a quartet, and two triplets as shown from the off-resonance spectrum. The singlet was assigned to C-4 (quaternary carbon), and the quartet to the N-methyl carbon. Of the two triplets, the lower field signal (δ 51.69 ppm) was assigned to C-2 and C-6 (the two positions being chemically and magnetically equivalent, as are C-3 and C-5) because, being adjacent to nitrogen, they are more deshielded than C-3 and C-5 which were therefore assigned the

page 58,

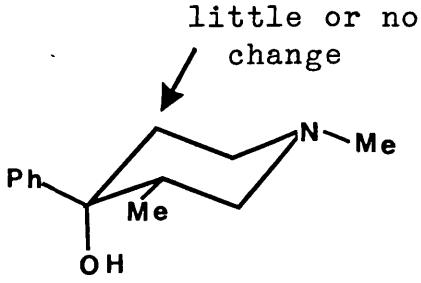
resonance at δ 38.36 ppm (Table III, entry 1). The aromatic region showed four carbon resonances (the two ortho-positions are chemically and magnetically equivalent, and so are the two meta-positions) which in the off-resonance are made up of a singlet, and three doublets. The singlet (δ 149.02 ppm) was assigned to the quaternary carbon(C-q). An unequivocal assignment for the chemical shifts of the o-, m- and p-positions of the phenyl group could not be made, and since these shifts were of no stereochemical significance to the present work, individual assignments to these positions were not made.

Generally, substituent effects due to methyl groups on the chemical shifts of a parent molecule are such that the α- and β-carbons are deshielded, while the γ-carbon is shielded. This γ-effect on the chemical shifts is of particular stereochemical significance in conformational studies of 6-membered alicyclic compounds. This is based on the fact that if an equatorial methyl substituent is inserted in positions 2 or 3 of 1-methyl-4-phenyl-4-piperidinol (81), for example, very little or no change (in some cases) is expected in the chemical shifts at C-6 and C-5 respectively. On the other hand, insertion of an axial methyl group at these positions (82) produces a large upfield shift (about 4-7 ppm) at C-6 and C-5 respectively due to the γ-gauche effect of the axial substituents (Dalling & Grant, 1967). The γ-effect has been rationalised (Grant & Paul, 1964) in terms of non-bonded

interactions between closely neighbouring hydrogen atoms in hydrocarbons, in which case the C-H bonds of the interacting hydrogens suffer steric polarisation such that

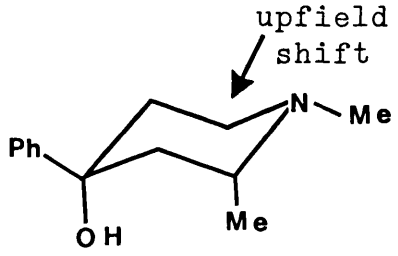


a.

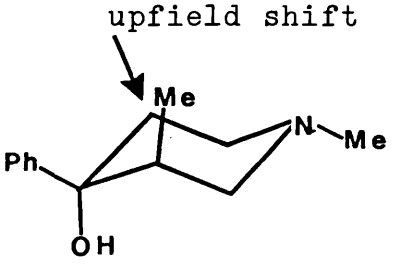


b.

81



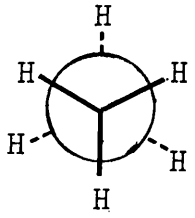
a.



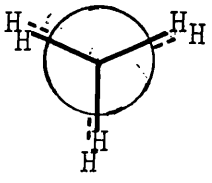
b.

82

the electron density at the carbon atoms is changed (partially increased) because of the non-bonded repulsion of hydrogens on the γ-carbons in gauche or eclipsed orientations. The γ-gauche effect therefore causes a



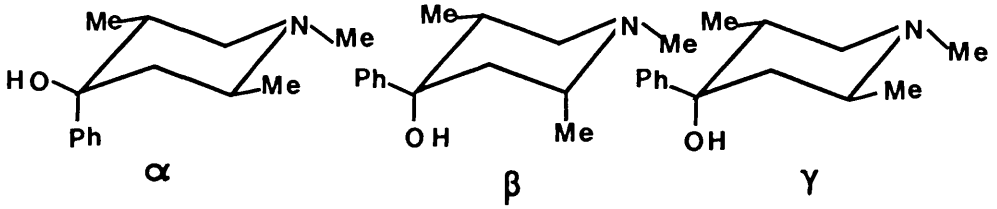
gauche



eclipsed

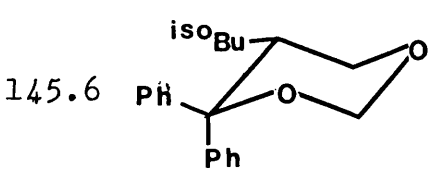
mutual change in the chemical shifts of the two interacting carbon nuclei. Typical examples of effects of such interactions can be found in the C-5 chemical shifts of α-(81b), and β-(82b) prodinols (δ 39.44, and 31.50 ppm, respectively, and 38.36 ppm for the desmethyl compound).

Another diagnostic shift for stereochemical assignments in the model compound under consideration is the chemical shift of the quaternary carbon (C-q) of the phenyl group. When the phenyl group is axially oriented, the C-q shifts are upfield (2-4 ppm) of those of equatorial phenyl groups. This upfield shift in the C-q value is probably due to steric polarisation of the axial C-q carbon. Some examples taken from compounds of established stereochemistry are given in 83-85 (Jones, Beeman, Casy & McErlane, 1973; Bernaert et al, 1974; Geneste & Kamenka, 1975).



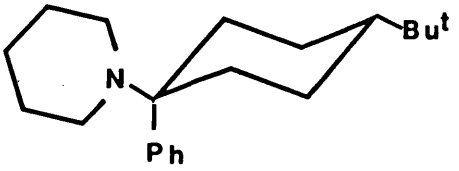
The promedols	C-q shift(ppm)
α	144.9
β	147.4
γ	147.2

83



143.8

84



130.5

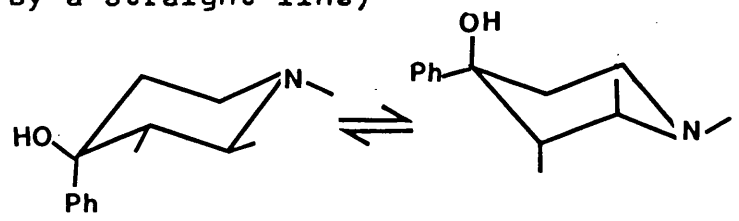
(eq-Ph isomer, 132.9)

85

The ^{13}C-n.m.r chemical shifts of the α-, β-, and γ-1,2,3-trimethyl-4-phenyl-4-piperidinols together with those of the unsubstituted parent alcohol (80, page 52) in $CDCl_3$ and DMSO-d_6 are given in Table III. The reaction of phenyllithium with isomeric 1,2,3-trimethyl-4-piperidone (Scheme 10, page 50) would produce four diastereoisomeric alcohols of relative configurations 86 to 89 as shown in Scheme 11(page 57).

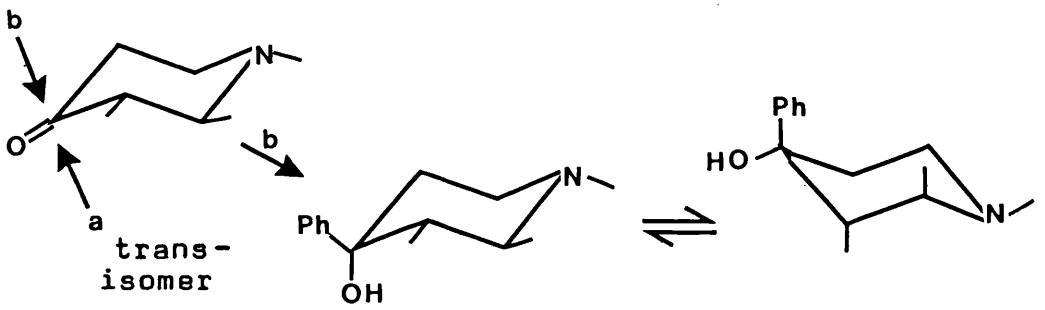
The chemical shifts of the 2- and 3-methyl groups of the β-isomer (Table III, entry 2, page 58) are typical of equatorial methyl groups in 4-piperidinols (Jones, Casy & McErlane, 1973; Casy, Iorio & Podo, 1981). This assignment is supported by similar shifts for C-5 and C-6 in the spectra of the β-alcohol and the parent alcohol (Table III, entries 1 and 2), that is, these positions are not sterically compressed. The C-q shifts of the β- and α-isomers are similar and are both to lower field of the γ-isomer C-q shift both in $CDCl_3$ and DMSO-d_6. Considering the fact that in all the probable chair conformations

(Note: In order to simplify the following configurational formulae, methyl group orientation is denoted by a straight line)



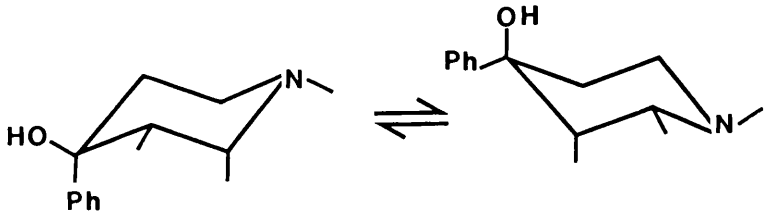
86

a → (a) (b)



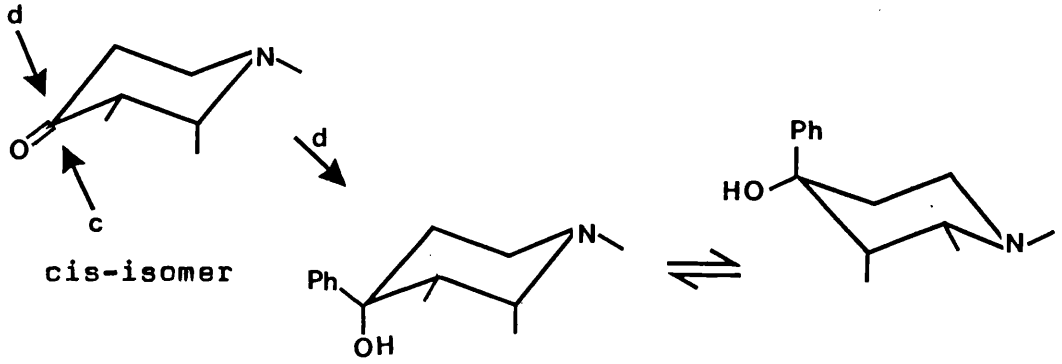
87

(a) (b)



88

c →



89

(a) (b)

Scheme 11 (a, b, c, and d =PhLi/H_2O)

Table III. ^{13}C- Chemical shifts of some 1-methyl-4-phenyl-4-piperidinols in $CDCl_3$[a] and DMSO-d_6[b] (TMS standard).

Entry	Compound*	Isomer designation	C-2	C-3	C-4	C-5	C-6	1-CH_3	2-CH_3	3-CH_3	C-q
1.	80	-	51.69	38.36	70.09	38.36	51.69	46.29	-	-	149.0
			(51.36)	(38.00)	(69.35)	(38.00)	(51.36)	(46.06)	-	-	(150.0)
2.	78 (base)	β	60.95	45.07	74.98	40.47	52.39	43.33	17.33	12.02	148.00
			(60.19)	(44.75)	(73.68)	(39.55)	(51.84)	(42.80)	(17.12)	(12.08)	(149.2)
3	78(base)	α	59.00	42.80	75.03	39.87	45.45	42.47	7.64	11.76	147.90
4.	78 (base)	γ	63.38	49.14	75.47	31.04	51.98	41.93	19.02	16.74	145.68
			(61.05)	(46.43)	(73.14)	(34.94)	(47.78)	(42.58)	(16.04)	(15.17)	(147.84)
5.	80 (HCl)[d]	-	51.58	35.95	69.30	35.93	51.53	44.16	-	-	146.7
6.	78 (HCl)	γ	64.09	45.56[f]	73.46	31.75	45.56[f]	41.50	16.20	15.76	145.62
7.	78 (HCl)[d]	γ	63.88	45.14[g]	73.58	31.87[g]	45.14[g]	41.50	15.8[g]	15.8[g]	145.24

(* Compound 78 is 1,2,3-trimethyl-4-phenyl-4-piperidinol, while compound 80 is 1-methyl-4-phenyl-4-piperidinol).

Table III contd

Footnotes:

a Footnote a of Table II applies.

b Values in parentheses.

c Quaternary carbon of 4-phenyl group; other phenyl resonances were near δ 128, 126, and 125 in all cases.

d In D_2O with internal dioxan (δ 67.4)

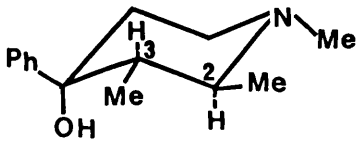
e In 50:50 methanol-D_2O with TMS as standard.

f Coincident resonances which form broad signals in proton-noise decoupled, and broad multiplets in the off-resonance spectra.

g Broad singlets.

---

for the isomeric 2,3-dimethyl-4-piperidinols (86 to 89, page 57), only one of the possible isomers is expected to have a high population of axial phenyl chair (86) in the most stable conformation, it is therefore reasonable to expect both the α- and β-isomers to have equatorial phenyl groups. This therefore implies that the β-configuration is 87, with a preferred 2,3-diequatorial methyl/equatorial 4-phenyl chair conformation (87a). If this is the preferred conformation, the 2- and 3-carbon protons (90) are expected to be axially oriented to one another. In this respect, evidence from the vicinal coupling constant (^3J values) of the two protons is necessary to confirm the stereochemistry of the 2- and 3-methyl groups.



90

It has been established that the magnitude of vicinal coupling constants (^3J values) largely depends on the dihedral angle (ϕ) between the two protons. ϕ is the angle between the plane containing the C-C-Ha bonds, and that containing the C-C-Hb bonds. The relationship between ϕ and ^3J values can be represented pictorially as shown in figure 1. It means therefore that the ^3J values are largest when the vicinal protons are trans-coplanar ($\phi = 180^o$), slightly less when they are cis-coplanar ($\phi = 0^o$), and almost zero when the protons are at right angles.

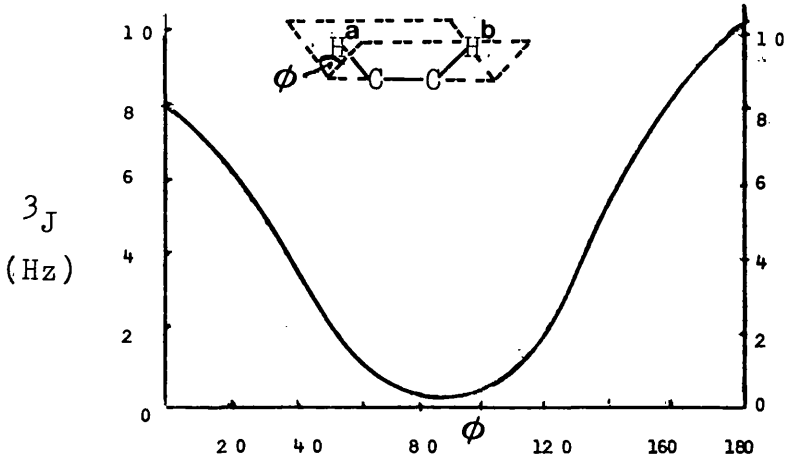


Fig. 1: Relationship between the dihedral angle, ϕ, and vicinal coupling constants.

One of the most important consequences of this relationship is that the order of magnitude of diaxial, axial-equatorial, and diequatorial coupling constants ($^3J_{aa}$, $^3J_{ae}$, and $^3J_{ee}$ respectively) in a six-membered ring chair system can be predicted from the angular relationships of the protons. Thus $^3J_{aa}$ values generally fall within 8-14 Hz, while $^3J_{ae}$ and $^3J_{ee}$ values fall within 1-6 Hz (Sternhell, 1969).

The C-2 and C-3 protons (2-H and 3-H respectively) in the 1,2,3-trimethyl-4-phenyl-4-piperidinols, in addition to being coupled to one another, are also coupled to the 2- and 3-methyl protons, giving rise to multiple signals. Spin decoupling experiments were therefore needed to resolve these ring protons in order to extract their ^3J values. ^{1}H-n.m.r spin decoupling experiments carried out at 100MHz by double irradiation of the methyl proton signals could not resolve the 2-H and 3-H signals adequately. However, a successive double irradiation at 220MHz resolved the 2-H and 3-H signals into doublets (fig. 2) with coupling constants (^3J = 10 Hz) typical of axially related vicinal protons (Sternhell, 1969; Casy, 1971).

The 3-CH_3 chemical shift in the α-isomer is similar to the values in the β-isomer and related 4-piperidinols with equatorially oriented 3-CH_3 groups. On the other hand, the 2-CH_3 chemical shift showed a large upfield shift (by about 9.0 ppm) compared to the corresponding

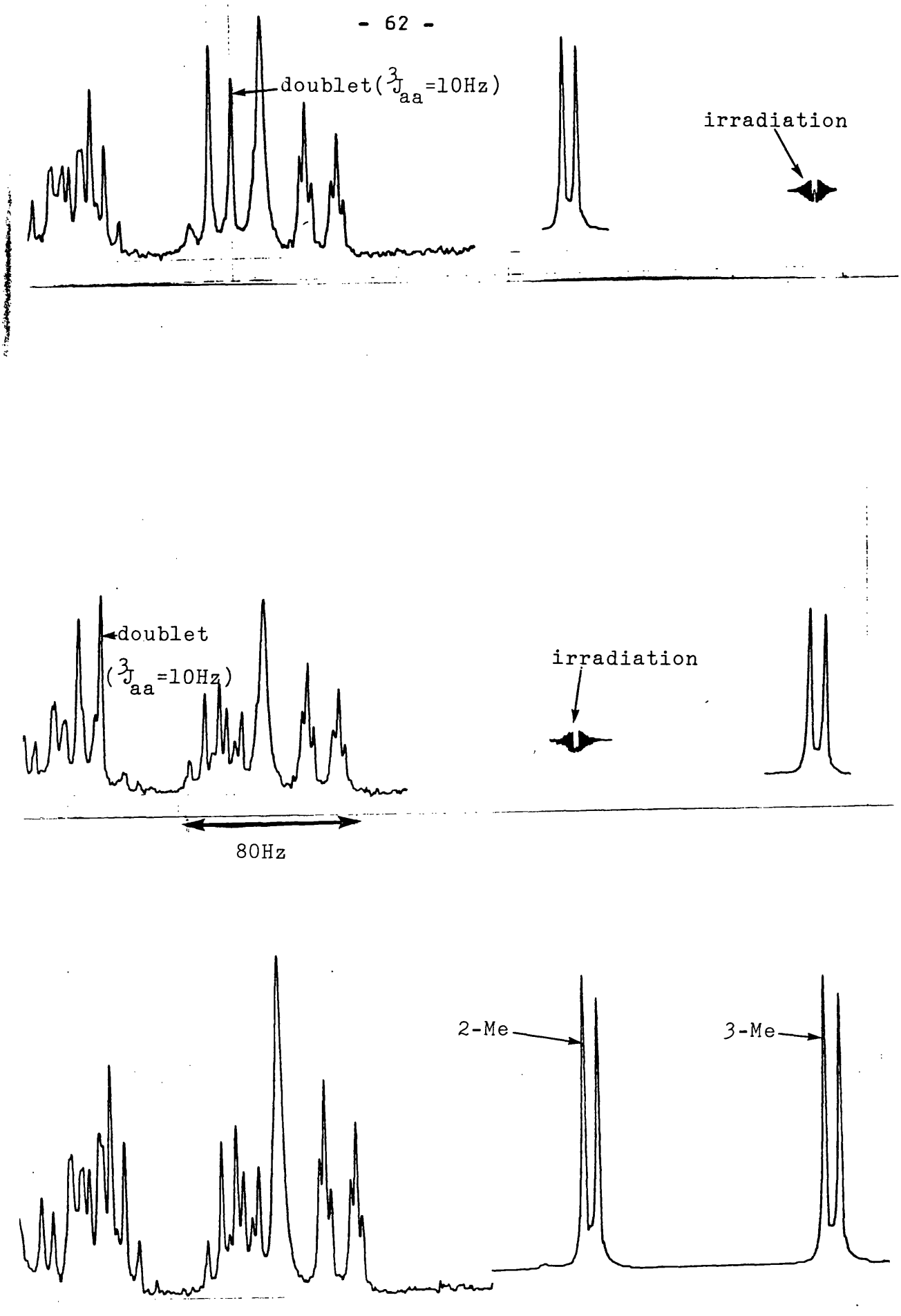
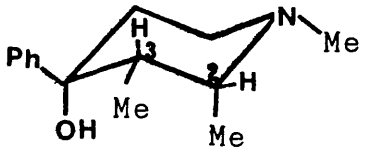


Fig. 2. Parts of the 'H-n.m.r Spectrum and the Spin Decoupled Spectra of β-1,2,3-trimethyl-4-phenyl-4-piperidinol as base in $CDCl_3$ (220MHz).

shift in the β-isomer (Table III, entries 2 and 3). Such upfield shifts have been described in situations when an α-methyl group has an antiperiplanar relationship with a nitrogen lone pair of electrons (Casy, Iorio & Podo, 1981). This result suggests an axial 2-methyl chair for the α-isomer. This inference was supported by the C-6 shift which was 7.0 ppm upfield of that of the β-isomer in accord with the anticipated γ-shielding influence of an axial 2-methyl substituent. In such a conformation (91), the 2-H and 3-H would be equatorially, and axially oriented respectively. A knowledge of the coupling constant between these ring protons, therefore, would

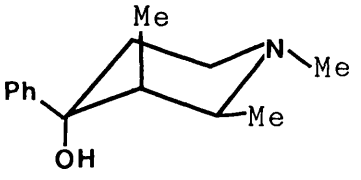


91

be valuable in establishing the preferred conformation of the α-isomer as a solute. A spin-decoupling experiment carried out at 220MHz resolved the 2-H and 3-H signals into pairs of doublets with a coupling constant of 4-5 Hz. This value is typical of axial-equatorial vicinal couplings in support of 91 as the α-configuration and preferred solute conformation in $CDCl_3$ and DMSO-d_6.

The 2-CH_3 chemical shift of the γ-isomer was similar

to those of the β-isomer and related compounds with equatorial 2-methyl substituents. That the 2-CH_3 in the γ-isomer base is equatorially oriented was supported by the similarity in its C-6 shift and those of the β-isomer and the parent compound (Table III, entries 1, 2 and 4). The 3-CH_3 chemical shift was to lower field of the corresponding values for the α-, and β-isomers. This was interpreted in terms of an axial 3-methyl/equatorial 4-phenyl chair conformation (92), since a γ-antiperiplanar oxygen in such piperidinol conformations have been shown to deshield the axial 3-methyl group (Casy, Iorio & Podo, 1981). This interpretation was supported by an upfield



92

shift of about 5.0ppm at the C-5 position in accord with a γ-shielding influence of the axial 3-methyl orientation. A similar spin decoupling experiment to those carried out for the α- and β-isomers, established the coupling constant between 2-H and 3-H as 6.03 Hz, which is an intermediate value between a true axial-axial, and axial-equatorial couplings. This, however, suggests a departure of the preferred conformation from a true chair, a view

strongly supported by the significant upfield shift in the C-q value of the γ-isomer compared to those of the parent compound, the α-, and the β-isomers (Table III, entries 1, 2, 3, and 4).

Infra-red Dilution Studies Of The Isomeric 4-Piperidinols

One other important possible solute conformation of the 1,2,3-trimethyl-4-phenyl-4-piperidinols not taken into account by the ^{1}H- and ^{13}C-n.m.r interpretation of the preceding section, is the possibility of a boat conformation stabilised by intra-molecular hydrogen bonding. For this reason, it was considered necessary to study the extent of intra-molecular hydrogen bonding in the different isomers as solutes in carbon tetrachloride.

The principle behind these studies relies on the fact that as solute in a non-polar solvent, such as CCl_4, both inter-molecular and intra-molecular hydrogen bonds are formed in compounds capable of forming such bonds. However, as the solution becomes more dilute, the extent of inter-molecular hydrogen bonding is decreased, and is virtually non-existent when the solution is sufficiently dilute (usually $4\text{-}5 \times 10^{-3}$ molar), whereas intra-molecular hydrogen bonding is not affected by dilution (Aaron, 1979). What is therefore observed in the IR spectrum at such dilutions is the free hydroxyl absorption ($\upsilon(f)$ ca. 3600 to 3590 cm^{-1}), and the intra-molecularly bonded O-H absorption ($\upsilon(b)$ ca. 3600-3200 cm^{-1}) for compounds capable of forming them (Williams & Fleming, 1973).

At 2.5×10^{-3} molar solution in CCl_4, both the α- and β-isomers showed a sharp free O-H absorption at 3600 cm^{-1}, with virtually no absorption due to intra-molecular hydrogen bonding. On the other hand, the spectrum of the γ-isomer showed a sharp broad intra-molecular hydrogen bonding absorption band at 3320 cm^{-1} (fig. 3). The ratio of the free to bonded O-H group as determined by weighing the area of paper under the absorption intensities (Aaron, 1979), was 14:86. These results indicate that both the α- and β-isomers exist in the preferred chair conformation shown by the high population of the free O-H groups, whereas the boat conformation is preferred for the γ-isomer, being intra-molecularly hydrogen bonded up to 86 %. A similar study of the promedols established the ratio of free to intra-molecularly bonded O-H in the α-, β-, and the γ-isomers as 73:27, 81:19, and 98:12 respectively (Staniforth, 1974).

The n.m.r data, including the 2-H and 3-H coupling constants (^3J = 6.03 Hz) are therefore in accord with the stereochemistry (93a), in which the 3-CH_3 is pseudo-axial and therefore shields C-5 by steric polarisation, while the 2-CH_3 is too remote from C-6 to cause any significant change in its chemical shift. However, the C-5 and C-6 shifts of the γ-base in DMSO-d_6 were both upfield relative to those of 1-methyl-4-piperidinol (Table III, entries 1 and 4), evidence that the 2,3-diaxial methyl chair (86b, page 57) makes a significant contribution to

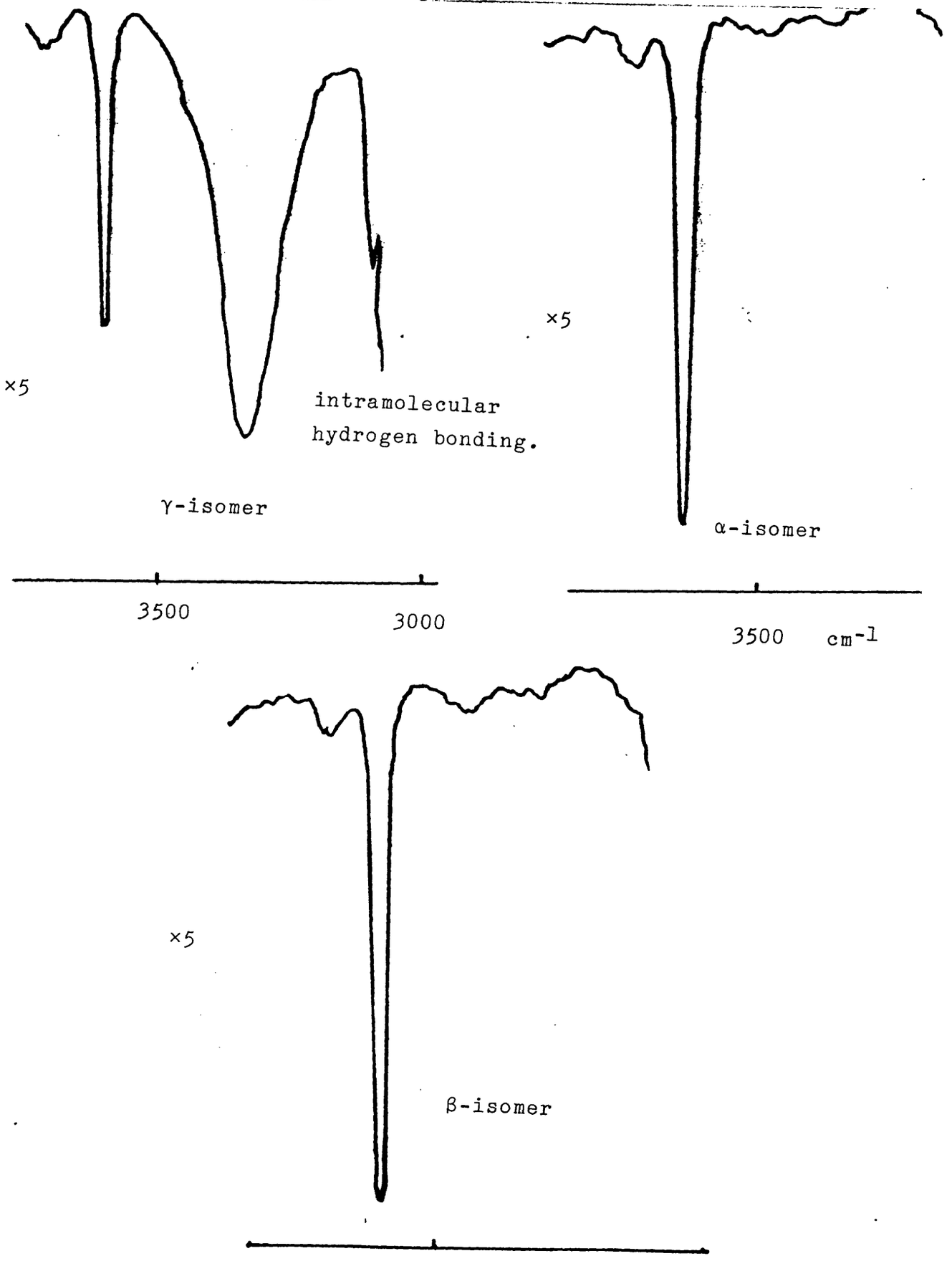
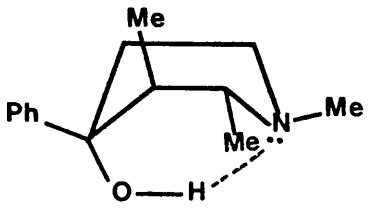
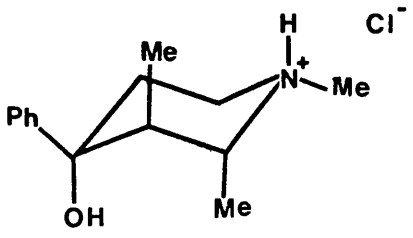


Fig. 3. Part of the IR Spectra of some 1,2,3-trimethyl-4-phenyl-4-piperidinols in CCl_4 (2.5×10^{-3} molar, 0.5cm cell).

the conformational equilibrium in a solvent capable of forming strong hydrogen bonds with the 4-hydroxyl group and disrupting the intra-molecular hydrogen bonding.



93a



93b

This is supported by the fact that the O-H chemical shift of the γ-alcohol (^{1}H-n.m.r) was about 2 ppm to lower field of the corresponding α- and β-signals in $CDCl_3$, whereas all three resonances were near 4.7 ppm in DMSO-d_6. The fact that the chemical shift variations in C-6 and C-5 are not merely solvent effects is evident from the similar shifts of the β-isomer and 1-methyl-4-phenyl-4-piperidinol (Table III, entries 1 and 2) in the two solvents concerned.

The effects of N-protonation on the conformational equilibrium of the γ-alcohol was sought from the ^{13}C-nmr spectrum of the hydrochloride salt. Some difficulty was however experienced in obtaining the complete spectrum since in polar solvents (necessary for reasons of solubility) several of the resonance lines were broad, and the off-resonance multiplets, ill-defined. Such problems are however common and are frequently encountered when recording the spectra of piperidines with charged nitrogen

as in hydrochloride and methiodide salts, and are thought to be due to the quadrupolar effects of ^{14}N (Abraham & Loftus, 1979; Casy, 1982). The best results were obtained with a methanol-D_2O mixture (the latter provided the lock signal) and overnight runs. Although epimeric mixtures of hydrochlorides have been detected by n.m.r in related compounds from the duplication of the N-Me and other signals, especially in conformers with preferred axial phenyl piperidine chairs (Jones, Casy & McErlane, 1973; Jones, Beeman, Casy & McErlane, 1973), no such evidence was found in the spectra of the present series. In addition to this, the ^{13}C-n.m.r N-Me chemical shifts were typical of α-methyl piperidines with equatorial N-Me groups (Jones & Hassan, 1972).

The C-5 and C-6 shifts of the γ-isomer hydrochloride salt were upfield of those of the desmethyl standard by about 5 ppm (Table III, entries 5, 6, and 7) in accord with the γ-shielding influence of axial methyls at C-2 and C-3. The chemical shifts of the 2- and 3-Me groups were both at lower field of the corresponding shifts of the α- and β-isomers in accord with axial orientations in similar compounds (Casy, Iorio & Podo, 1981), evidence for a preference for the diaxial methyl chair (93b, page 67) as the solute conformation once the strong OH-N interaction is abolished by N-protonation. The lower field shift for the C-methyl resonances is probably due to the mutual deshielding influences of the two anti-periplanar

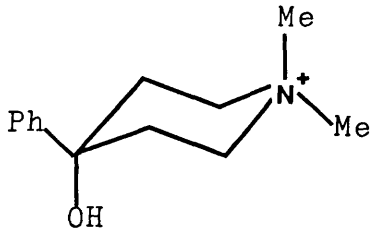
methyl groups (Tsuda, 1973), detail of which will be given later.

The n.m.r data on the quaternary salts of the isomeric 1,2,3-trimethyl-4-phenyl-4-piperidinols corroborate the configuration assignments, the details of which are given in the sub-section that follows.

Configurational And Conformational Studies Of The Methiodide Salts Of The Isomeric 1,2,3-Trimethyl-4-phenyl-4-piperidinols.

The stereochemistry of the isomeric 4-piperidinol methiodides was studied as an aid to the assignment of their relative configurations (evidence of preferred conformations were also obtained). The ^{13}C-n.m.r chemical shifts of the methiodide salts together with those of related 4-piperidinols are given in Table IV in which the methiodide salt of 1-methyl-4-phenyl-4-piperidinol (94) represents the parent member of the series.

Of the two N-methyl resonances of this and other N,N-dimethylpiperidinium salts, that at higher field was assigned to the axial substituent on the grounds that the



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(Note. The iodide anion is omitted in this and subsequent quaternary salt formulae).

axial substituent is more subject to steric polarisation

Table IV. ^{13}C Chemical shifts of methiodides of 1-methyl-4-phenylpiperidine and some 1-methyl-4-phenyl-4-piperidinols in DMSO-d_6[a].

Entry	Compound	Isomer[b] designation	C-2	C-3	C-4	C-5	C-6	C-q[c]	C-2'	C-3' (C-5')	C-1' (eq)	C-1' (ax)
1a.	1-methyl-4-phenyl piperidine	-	60.79	26.06	37.38	26.06	60.79	142.75	-	-	54.50	46.10
1b.	1a in $CDCl_3$	-	62.78	27.62	38.08	27.62	62.78	142.42	-	-	56.55	48.32
2.	94 (desmethyl)	-	57.97	32.23	67.07	32.23	57.97	146.87	-	-	55.95	46.37
3.	98 (2-Me)	β	63.10	38.73	68.42	32.29	60.35	146.76	14.36	-	53.04	40.63
4.	99 (2-Me)	α	64.80	38.50	68.63	32.20	57.80	144.65	15.82	-	51.20	46.40
5.	100a (3-Me)	α	63.0	34.13	69.90	33.80	57.70	144.90	-	10.73	55.85	47.29
6.	100b (3-Me)	β	63.87	37.92	69.89	27.79	58.40	144.48	-	15.76	55.53	51.25
7.	102 (2,5-diMe)	γ	62.90	41.8[d]	71.19	34.46	65.40	144.98	13.98	10.63	53.21	41.8[d]
8.	103 (2,5-diMe)	β	63.90	39.20	71.19	34.46	58.24	145.63	16.98	10.90	52.29	50.61
9.	104 (2,5-diMe)	α	65.99	43.50	71.46	36.74	66.80	142.81	15.28	12.41	53.26	42.20
10.	105 (2,3-diMe)	β	68.26	(40.3)	71.56	34.08	60.08	146.00	(12.19)	11.70	54.01	(41.9)
11.	106 (2,3-diMe)	α	69.24	36.19	71.40	34.18	52.71	145.95	12.08	10.73	53.0	46.68
12.	107 (2,3-diMe)	γ	69.57	(43.34)	71.78	35.00	60.78	143.50	(13.27)	(12.89)	53.40	(42.64)

Table IV contd.

Footnotes: a values in ppm from TMS; values in parentheses may be interchanged.

b Literature designations.

c Other aromatic carbon resonances fall in the range of 124-128 ppm.

d Coincident signals within solvent resonances.

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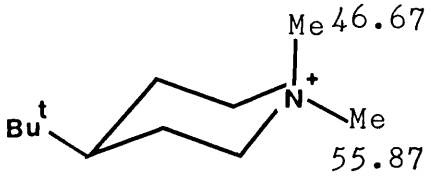
than the equatorial group. This arguement is supported by a comparison of the spectra of the methiodide (95) and the trideuteromethiodide (96) of 4-t-butyl-1-methylpiperidine (anchored by the bulky t-butyl substituent). The



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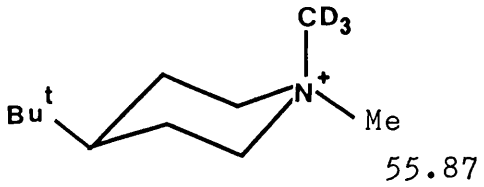

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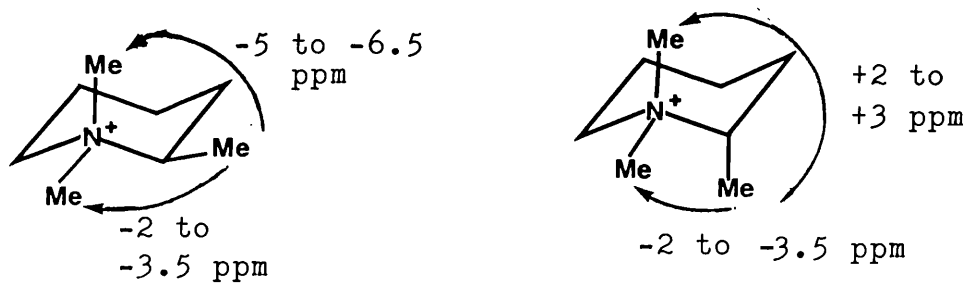
higher field resonance of 95 was absent in the spectrum of 96. The higher field signal was therefore assigned to the axial N-methyl substituent since N-methylation is known to prefer an axial course of attack (Stein et al, 1968; Mckenna, 1970).

The interpretation of the preferred conformations

in the substituted 4-piperidinols were based upon the aspects of stereochemical shift relationships outlined below, some of which have been explained earlier.

a). Influence of α-methyl (2-Me) on N,N-dimethyl chemical shifts.

Studies of simple mono- and di-C-methyl derivatives of N,N-dimethylpiperidinium iodides have shown that an α-equatorial-methyl group shields both the N-methyl carbons, with greater effects upon the axial N-methyl group (97a), while α-axial-methyl shields the equatorial N-methyl carbon, but deshields the axial atom (97b; Tsuda, 1973).



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The upfield shift of the N-methyl resonances can be rationalised on the basis of steric compression resulting from the γ-gauche interactions between the 2-Me and the N-methyl groups, but the basis of the antiperiplanar Me/Me deshielding is as yet unknown. Similar shielding influences of α-methyl substituents have also been noticed in the N-methyl proton resonances of piperidinium salts (Tsuda et al, 1974).

b). The Influence Of 2- or 3-Methyl Substituents On The Chemical Shifts Of C-5 and C-6 Positions.

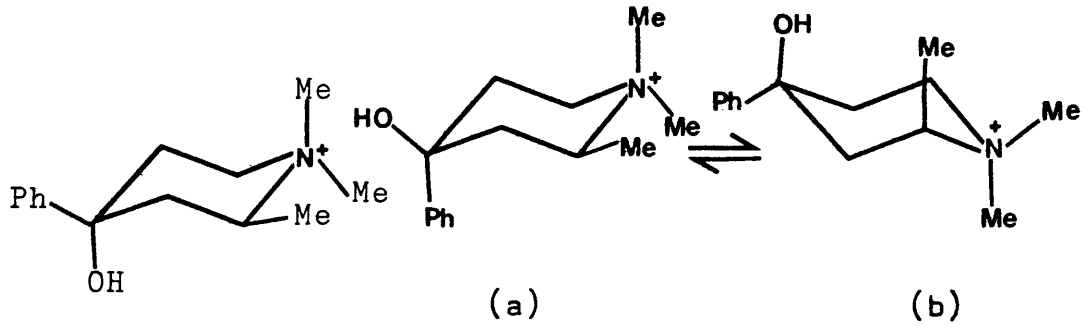
An upfield shift of the C-5 in the 3-methyl, or the C-6 in the 2-methyl-4-piperidinol derivatives relative to the desmethyl analogue is evidence for a preferred axial orientation of the methyl substituents due to the γ-shielding effects on such positions.

c). Chemical Shifts Of The Aromatic Quaternary Carbon (C-q) Of The 4-Phenyl Substituent.

As an extension of the γ-shielding principle as explained earlier (page 55), the C-q resonance of phenyl six-membered ring alicyclic compounds is 2 to 4 ppm to higher field in the preferred axial than in the equatorial phenyl conformers (see examples 83 to 85, page 55).

Applying these principles to the ^{13}C-n.m.r data of the methiodide salts of related 4-piperidinols of established stereo-chemistry, the conclusions outlined below were reached, and these formed the model on which the stereochemical deductions for the isomeric 1,2,3-trimethyl-4-phenyl-4-piperidinols were based.

In the β-isomer of the 2-methyl derivative (t-2-Me, r-4-OH), the equatorial 4-phenyl (eq-4-Ph) chair (98) is clearly favoured as shown by the upfield shift of both N-methyl carbon resonances relative to those of the desmethyl standard, and the absence of any significant change in the chemical shift of C-6 (Table IV, entries 2 and 3). In the α-isomer (c-2-Me, r-4-OH), however, if the axial



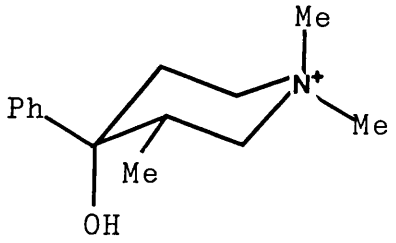
(a) (b)

98 99

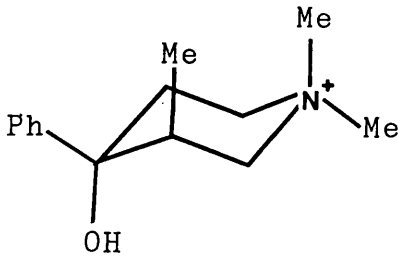
4-phenyl (ax-4-Ph) chair (99a) is markedly preferred, as it is for the base (Jones, Casy & McErlane, 1973), N-methyl shifts close to those of the β-methiodide would be expected. It would also be expected that contributions from the inverted chair conformation (99b, eq-4-Ph) move the axial N-methyl (ax-N-Me) resonance (40.6 ppm in the β-salt) downfield, and the equatorial N-methyl (eq-N-Me) upfield (53.0 ppm in the β-salt). Hence the observed shifts of 46.4 and 51.2 ppm (Table IV. Entry 4) were interpreted in terms of contributions from both conformers. The upfield shift of the α-C-6 resonance relative to the β-C-6 resonance, further supports a contribution from eq-4-Ph chair in which the 2-Me group is axial (99b). Evidence for a significant ax-4-Ph chair population is given by the relative C-q shifts for the α- and β-isomers (higher field for the α-isomer), and the fact that N-methyl shifts typical of N,N-dimethylpiperidinium salts with highly preferred ax-2-Me substituents (for example as in β-2,5-dimethyl analogue, see below) are not observed.

The preferred solute conformation of the 3-methyl analogue bases were unaltered after N-methylation as judged

from the chemical shifts of the methiodide salts; both the α-(c-3-Me, r-4-OH), and the β-(t-3-Me, r-4-OH) methiodides favour eq-4-Ph chair conformations (100a and 100b, respectively) judging from their similar C-q shifts.

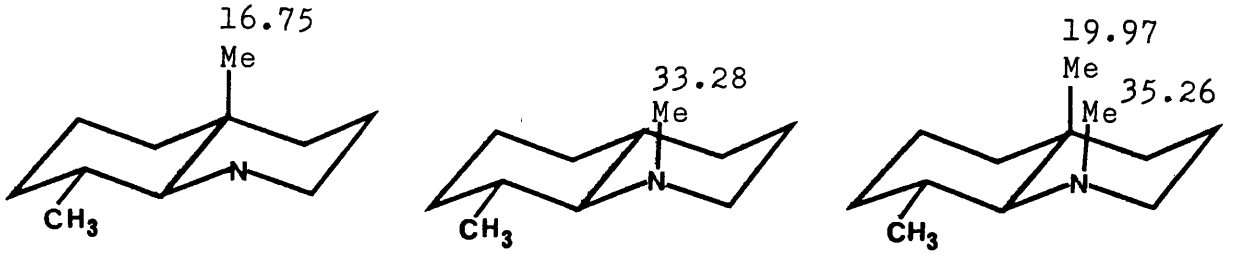


100a



100b

The upfield shift for C-5 in the β-isomer relative to the desmethyl standard is indicative of axial methyl orientation, while the C-5 shift of the α-isomer supports an equatorial methyl substituent. The N-methyl resonances of the α-isomer are close to those of the desmethyl compound (Table IV, entries 2 & 5), and the unusually low field position of the ax-N-Me resonance of the β-isomer (51.2 ppm) can be attributed to a deshielding influence on the axial carbon by the opposed methyl at C-3. Such 1,3-syn-diaxial deshielding is not without precedence [cf. methyl shifts of the substituted trans-decahydroquinolines 101a-101c (Eliel & Pietrusiewicz, 1979)]. The 3-Me shift is also reciprocally affected as seen by comparison with the 3-Me chemical shift (δ 14.4 ppm) of the β-hydrochloride salt in DMSO-d_6 (Jones, Casy & McErlane, 1973). The eq-4-Ph chair (100b) is thus preferred inspite

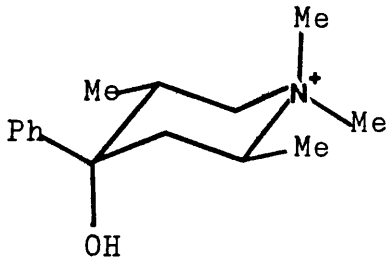


(a) (b) 1,3-syn-diaxial (c) interaction

101

of the unfavourable syn-diaxial interactions. In eq-4-Ph chair conformations of α-2,5- and γ-2,3-dimethyl analogues, syn-diaxial interactions are augumented by energy-raising interactions of an additional axial methyl group (at C-2), and in each case the inverted (ax-4-Ph) chair is preferred (see below).

The 2,5-dimethyl analogue (promedol alcohols) methiodides provided another set of examples for stereochemical studies. The γ-isomer methiodide (t-2-Me, c-5-Me, r-OH) clearly has a favoured eq-4-Ph chair conformation(102), judging from the N-methyl shifts, close to those of the β-2-methyl salt (98), and the chemical shifts of C-3, C-6, C-2' and C-5', close to or not to higher field of appropriate congeners with equatorial C-methyl substituents.



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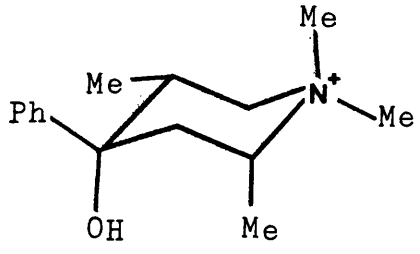
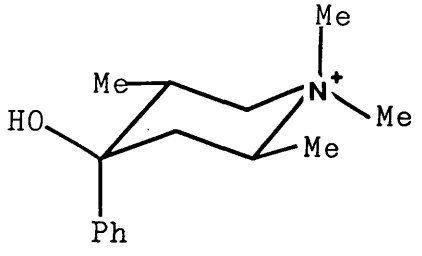


103

Data for the β-methiodide (c-2-Me, c-5-Me, r-OH) likewise support an eq-4-Ph chair conformation (103) with the 2-Me axially oriented (the ε-6 shift is about 7.4 ppm upfield of γ- and α-C-6 shifts), and the 5-Me substituent, equatorial. The N-methyl resonances relative to those of the standard are consistent with shielding influences due to an axial methyl adjacent to nitrogen, eq-N-Me being shielded (γ-gauche effect) and the ax-N-Me, deshielded (antiperiplanar Me/Me deshielding). The 2-Me carbon, as is to be expected, is also reciprocally deshielded judging from the chemical shift (16.9 ppm) at lower field than that of the corresponding hydrochloride salt (13.1 ppm in $CDCl_3$; Jones, Beeman, Casy & McErlane, 1973), allowing for solvent effects which are probably very small as can be seen from the data on N,N-dimethyl-4-phenyl-4-piperidinium iodide in $CDCl_3$ and DMSO-d_6 (Table IV, entries 1a and 1b).

The preferred ax-4-Ph conformation of the α-isomer base (c-2-Me, t-5-Me, r-4-OH) is retained in the methiodide (104) as judged from the C-q shift which is 2-3 ppm



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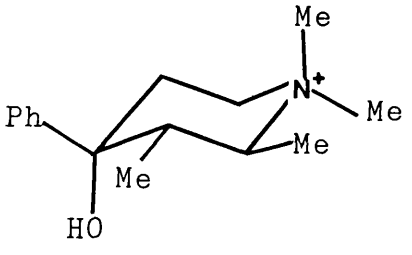
to higher field of the corresponding β- and γ-shifts. The

C-3, C-6, C-2' and C-5' chemical shifts are close to those of piperidines with preferred equatorial 2- and 5-methyl substituents, while the similarities in the shifts of the N-methyl resonances of the γ-isomer and β-2-methyl analogue (Table IV, entries 3 & 7), underscores the fact that the 2-Me is equatorially oriented in the α-salt.

In the 2,3-dimethyl analogues, the data for the β-isomer support an eq-4-Ph chair conformation (105). The similarities in its N-methyl chemical shifts and those of γ-2,5-dimethyl and β-2-methyl analogues compared to those of the desmethyl standard are indicative of equatorial 2-methyl influence, while the chemical shift of C-5 and C-6 are also in accord with equatorial 2- and 3-methyl substitution.



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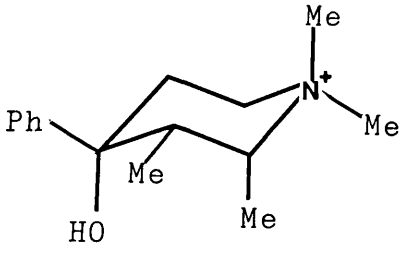

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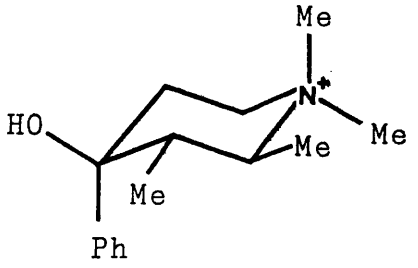
Corresponding data for the α-isomer are consistent with an ax-2-Me, and eq-4-Ph chair conformation (106). The α-C-6 shift is 7-8 ppm to high field of those of the β- and γ-isomers, while the N-methyl resonances are close to those of the β-2,5-dimethyl analogue (Table IV, entries 8,10,11 & 12), which reveal a pronounced deshielding of

the axial N-substituent. The chemical shift of C-5 is similar to that of α-prodinol methiodide (100a) and is therefore consistent with eq-3-Me, while the higher field position of the C-2' carbon (12.1 ppm) relative to the corresponding C-2' carbon of the β-2,5-dimethyl analogue (16.9 ppm) can be explained on the basis of a γ-gauche interaction with a vicinal methyl at C-3 in support of 106. The C-q shift of the γ-isomer, 2.5 ppm to higher field of the corresponding α- and β-resonances, indicates an axial 4-phenyl orientation. This fact coupled with the chemical shifts of C-5, C-6, C-2', and C-3' which are similar to those of the β-isomer having equatorial methyl substituents, is indicative of a preferred ax-4-Ph chair conformation (107) for the γ-isomer. The chemical shifts of



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the N-methyl substituents (also near those of the β-methiodide) are also in accord with the assigned conformation in which the syn-diaxial interactions are avoided.

These stereochemical deductions on the quaternary salts were also corroborated by their proton chemical shifts (Table V). The N-methyl signals in the model compound, N,N-dimethyl-4-phenyl-4-piperidinol methiodide(94,

Table V. ^{1}H-n.m.r Chemical shifts of methiodides of 1-methyl-4-phenylpiperidine and some 1-methyl-4-phenyl-4-piperidinols in DMSO-d_6 (ppm, TMS standard)

Entry	Compound	Isomer designation	eq-N-Me	ax-N-Me	2-Me	3-Me (5-Me)	OH
1a	1-methyl-4-phenylpiperidine	-	3.19	3.19	-	-	-
1b	1a in $CDCl_3$	-	3.65	3.43	-	-	-
2.	94	-	3.27	3.27	-	-	5.59
3.	98 (2-Me)	β	3.23	3.05	1.30	-	5.49
4.	99 (2-Me)	α	3.21	3.13	1.49	-	5.40
5.	100a (3-Me)	α	3.38	3.32	-	0.59	5.46
6.	100b (3-Me)	β	3.32	3.32	-	0.77	5.58
7.	102 (2,5-diMe)	γ	3.24	3.17	1.29	0.57	5.37
8.	103 (2,5-diMe)	β	3.17	3.44	1.64	0.59	5.31
9.	104 (2,5-diMe)	α	3.27	3.12	1.38	0.74	5.49
10.	105 (2,3-diMe)	β	3.25	3.16	1.34	0.60	5.34
11.	106 (2,3-diMe)	α	3.18	3.42	1.48	0.60	5.34
12.	107 (2,3-diMe)	γ	3.26	3.05	1.34	0.77	5.49

page 69), overlapped to form a broad singlet in DMSO-d_6, a result attributed to the greater accessibility of the equatorial group to solvation whence eq-N-Me protons will be more shielded by the solvent than the axial methyl protons (Tsuda *et al*, 1974). This is also supported by

the data on N,N-dimethyl-4-phenylpiperidinium iodide, a salt soluble in both $CDCl_3$ and DMSO-d_6, in which the two methyl protons had a shift of 3.65 and 3.43 ppm for equatorial and axial N-methyl protons, respectively, in $CDCl_3$, while both methyl protons overlap to form a singlet (3.19 ppm) in DMSO-d_6 (Casy & McErlane, 1972; Table V, entries 1 & 2).

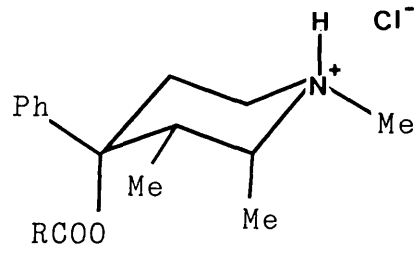
Isomers with preferred conformations in which the 2-Me is equatorial, show eq-N-Me shifts close to the model value, while the ax-N-Me protons are shielded whereas in isomers with axial 2-methyl substituents, eq-N-Me protons are shielded while the ax-N-Me protons are deshielded. It is interesting to note that both axial and equatorial 3-methyl substituents have small deshielding influences on the two N-methyl protons as seen from the data on the prodinol methiodides (Table V, entries 2,3 and 4). The chemical shifts of the hydroxyl group are also of qualitative value in stereochemical assignments for these piperidinol methiodides; lower field values are seen for members of isomeric salts having the OH function in orientations most accessible to solvation, namely the methiodides of β-prodinol (OH hindered by eq-3-Me in the α-salt), and the α-2,5-, and γ-2,3-dimethyl analogues (Table V, entries 3, 9, and 12) both of which have equatorial hydroxyl groups in the preferred conformations (104, and 107 respectively).

In previous stereochemical studies of C-alkyl substituted 4-piperidinols, X-ray crystallography has proved a very useful technique for substantiating, and confirmation of the assigned stereochemistry (Hayakawa & James, 1973; Portoghese et al, 1973; Kartha, Ahmed & Barnes, 1960; Ahmed, Barnes & Masironi, 1963). In the light of this, it was considered necessary to have the X-ray crystallographic analyses of the isomeric 1,2,3-timethyl-4-phenyl -4-piperidinol samples done as a final check on their deduced stereochemistries. The samples, α- and β-isomers as crystalline bases, and the γ-isomer as the crystalline hydrochloride salt, were kindly analysed by Dr F.R. Ahmed of the National Research Council of Canada, Ottawa, who has been associated with similar analyses of the configuration of related 4-piperidinols (Kartha, Ahmed & Barnes, 1960; Ahmed, Barnes & Masironi, 1963). The analyses confirmed the deduced configurations for the α- and β-bases, and the γ-hydrochloride. The result also showed that the preferred solid conformations of the α- and β-bases are similar to their preferred solute conformations (91 and 90 respectively, pages 63 and 60), whereas the γ-isomer exists in the diaxial methyl chair conformation (93b, page 68) in the solid hydrochloride salt form.

Conformational Studies Of The 1,2,3-Trimethyl-4-phenyl-4-piperidinol Esters.

The conformational preference of the protonated 4-piperidinol esters were investigated next. ^{13}C-n.m.r

data for the acetate and propionate ester hydrochlorides together with those of the reversed ester of pethidine model compound and α-prodine standards are given in Table VI, page 85. The chemical shift results support equatorial phenyl chairs as preferred conformations for all the three salts as solutes in $CDCl_3$. This conclusion was based on the lack of any significant upfield shifts of β-C-5 and C-6 signals as anticipated if there were any departure from the preferred conformation of the precursor 4-piperidinols. The pronounced upfield shift of C-6 in the α-isomer, in comparison to the corresponding shifts of the standard compounds in addition to the high field position of the α-2-Me signal, is evidence for the eq-4-Ph chair conformation (108). The γ-esters displayed



7.6 ppm (R=Me)
8.07 ppm (R=Et)

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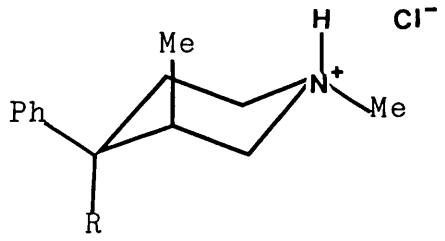
upfield shifts of about 5.0 ppm at both C-5 and C-6 (Table VI, entries 7 & 8) in accord with axial orientations of the methyl substituents at C-2 and C-3 positions. The 2- and 3-methyl chemical shifts are both to lower field of the corresponding α- and β-resonances. One way

Table VI. ^{13}C Chemical shifts (δ, ppm) of esters of 1,2,3-trimethyl-4-phenyl-4-piperidinols and related standard compounds as hydrochloride salts in $CDCl_3$(TMS stand.)[a,b]

Entry	Compound[e]	Isomer designation	C-2	C-3	C-4	C-5	C-6	1-Me	2-Me	3-Me	C-q[c]
1.	1-methyl-4-phenyl-4-propionoxypiperidine.	-	50.49	32.83	77.31	32.83	50.49	43.34	-	-	141.61
2.	Prodine[d]	α	56.65	40.36	81.53	30.48	50.56	43.60	-	11.98	139.53
3.	79-(a)	β	62.84	45.94	83.16	30.39	51.74	41.50	14.79	11.92	139.82
4.	79-(b)	β	62.63	45.76	83.43	30.28	51.57	41.53	14.74	11.81	139.78
5.	79-(a)	α	60.51	40.79	82.56	29.80	45.67	42.31	7.64	11.65	139.28
6.	79-(b)	α	60.51	40.61	82.72	29.63	45.34	42.20	8.07	11.65	139.12
7.	79-(a)	γ	61.16	44.80	81.70	25.25	46.35	41.17	16.09	15.22	141.02
8.	79-(b)	γ	61.22	44.91	82.13	25.25	45.96	41.23	16.14	15.22	140.85

Footnotes: a. Footnote a of Table I applies. b. Acyloxy resonances; OCOEt 172.1-172.7 (CO), 28.44-28.88 ($-CH_2-$), 9.05-9.37 (-Me); OCOMe 168.6-169.5 (CO), 22.1-22.3 (-Me).[2] c. Quaternary carbon of 4-phenyl group; other aromatic resonances were near δ 128, and 125 in all cases. d. 1,c-3-dimethyl-4-phenyl-r-4-propionoxypiperidine. e. Compound 79 is a 1,2,3-trimethyl-4-phenyl-4-piperidinol ester ; (a) propionate ester, (b) acetate ester.

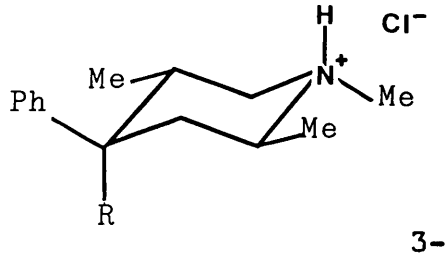
of interpreting the downfield shift of the 3-methyl signal is by the γ-anti-deshielding influence of oxygen on the axial 3-methyl group as illustrated by the 3-methyl chemical shifts of β-prodinol and the analogue lacking the 4-hydroxyl group (109a and 109b, respectively; Jones, Casy & McErlane, 1973). On the other hand, the absence



3-Me chemical shifts.
a). 16.2 ppm (R=OH)
b). 12.5 ppm (R=H)

109

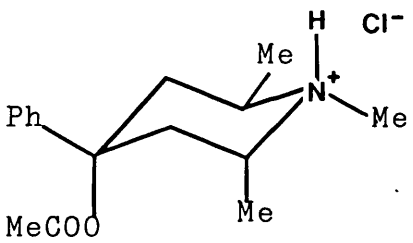
of a γ-gauche interaction with oxygen (ester group), present in the equatorial methyl orientation, as illustrated by a comparison of the 3-Me shifts of γ-promedol (110a) and the analogue lacking the 4-hydroxyl group (110b, Casy, Iorio & Podo, 1981), may well have contributed, to a large extent, to the downfield shift of the axial 3-methyl group.



3-Me chemical shifts.
a). 12.0 ppm (R=OH)
b). 17.2 ppm (R=H)

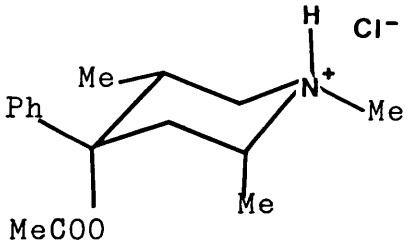
110

In the same vein, the significantly lower field shift of the 2-methyl group in the γ-isomer, compared to the α-2-methyl shift (Table VI, entries 5,6,7&8) is probably due to the absence of a mutual γ-gauche shielding influence of the vicinal 2- and 3-methyl sbstituents as occurs in the α-2,3-dimethyl esters (cf chemical shift data of 108, 111 and 112) in addition to the antiperiplanar Me/Me deshielding influences as explained on page 73.



13.33 ppm

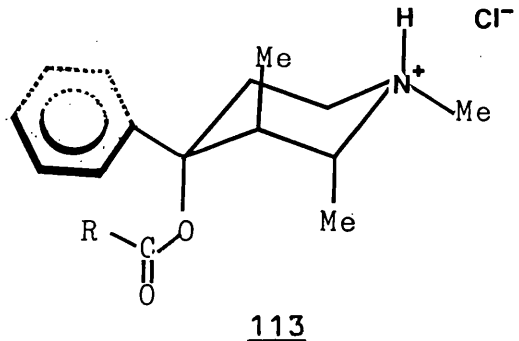
111



11.33 ppm

112

The diaxial methyl chair (113) was also supported by ^{1}H-n.m.r data as the preferred conformation for the γ-ester hydrochloride salt in D_2O. In this conformation,



113

the 2-H and 3-H being equatorially oriented towards one

another, only small ^3J values plus possible long range couplings are expected. Successive double irradiation of the 2- and 3-methyl protons revealed the 2-H (δ 3.6ppm) and the 3-H (δ 2.6 ppm) signals as broad singlets ($W_{\frac{1}{2}}$=5 Hz), as a result of the small coupling between them. It was therefore of interest to resolve the ring protons in order to study their coupling patterns, since six-membered alicyclic derivatives with preferred antiperiplanar methyls are rare. A 400MHz ^{1}H-n.m.r Fourier transform spectrum of the hydrochloride salt in D_2O was recorded in order to extract all the ^3J values. A triplet of doublets (δ 3.58 ppm, ^3J 12-13 Hz, 3-4 Hz; axial 5- or 6-H), and a doublet of triplets (δ 3.42 ppm, ^3J 12-13 Hz, 3-4 Hz; equatorial 6-H) of equal intensity were resolved (evident but poorly defined in the 220MHz spectrum). Hence all the vicinal couplings have magnitudes typical of cyclohexane or piperidine chairs.

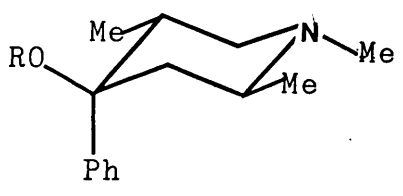
The stereochemical deductions were further corroborated by the acyloxy resonances of the γ-isomer which are to higher fields of the related α- and β-signals as shown in Table VII. In the α- and β-esters, the free rotation of the phenyl group is hindered by the equatorial 3-Me and hence the orientation of the ring is such that the acyloxy protons do not stay for long in the shielding zone of the ring. In contrast, the γ-ester with the axial 3-Me orientation (113) has more freedom in the rotation of the phenyl group, therefore, there is a higher proportion of conformers in which the acyloxy group lies in

the shielding zone of the ring, hence the acyloxy signals are to higher field of those of the α- and β-esters (Iorio, Casy & May, 1975).

Table VII: ^{1}H-n.m.r chemical shifts (δ, ppm) of the acyloxy protons of the isomeric 1,2,3-trimethyl -4-phenyl-4-propionoxypiperidine in $CDCl_3$(TMS STD)

Entry	Isomer designation	$-OCO\underline{CH_2}-$	$-OCOCH_2-\underline{Me}$
1.	α	2.55	1.26
2.	β	2.64	1.20
3.	γ	2.40	1.08

It is of interest, however, to note that in the 2,5-dimethyl analogues of γ-78 (page 50) of similar configuration, the axial phenyl chair conformation (114)



114

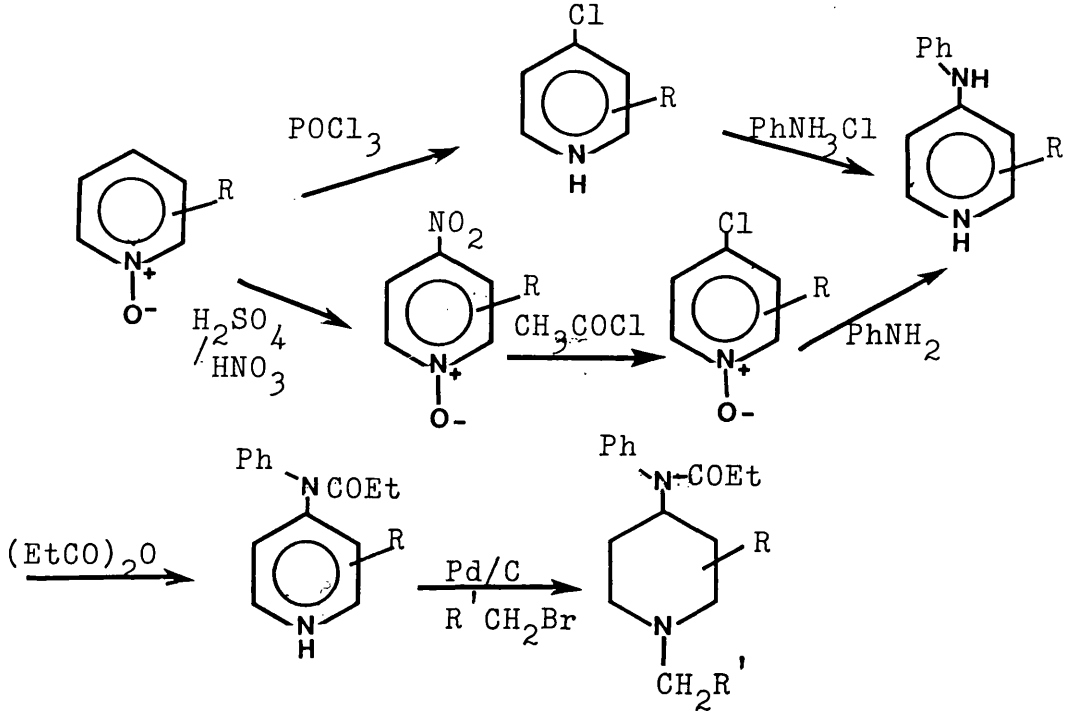
is preferred (Jones, Beeman, Casy & McErlane, 1973). The determining factor for the preferred conformation in the γ-2,3-dimethyl analogue must therefore be the avoidance of the additional dimethyl gauche interaction, which is absent in the 2,5-dimethyl derivative, since the Me-C-N-Me gauche interaction is present in both types of compounds.

SECTION TWO

Fentanyl Analogues

The most general route to syntheses of fentanyl analogues proceeds via 1-substituted 4-piperidones with formation of the Schiff base with aniline, followed by reduction, and subsequent acylation of the anilino moiety (Janssen, 1962; Casy et al, 1969; van Bever et al, 1974) as illustrated by the synthesis of 1-methyl-4-(N-phenyl propionamido)piperidine(117, Scheme 12). The main synthetic problem involved in this route therefore concerns the syntheses of the intermediate ketones.

An alternative route to the alkyl substituted analogues, however, proceeds via the appropriate 4-anilinopyridines (Riley, Hale & Wilson, 1973; Scheme 11) made

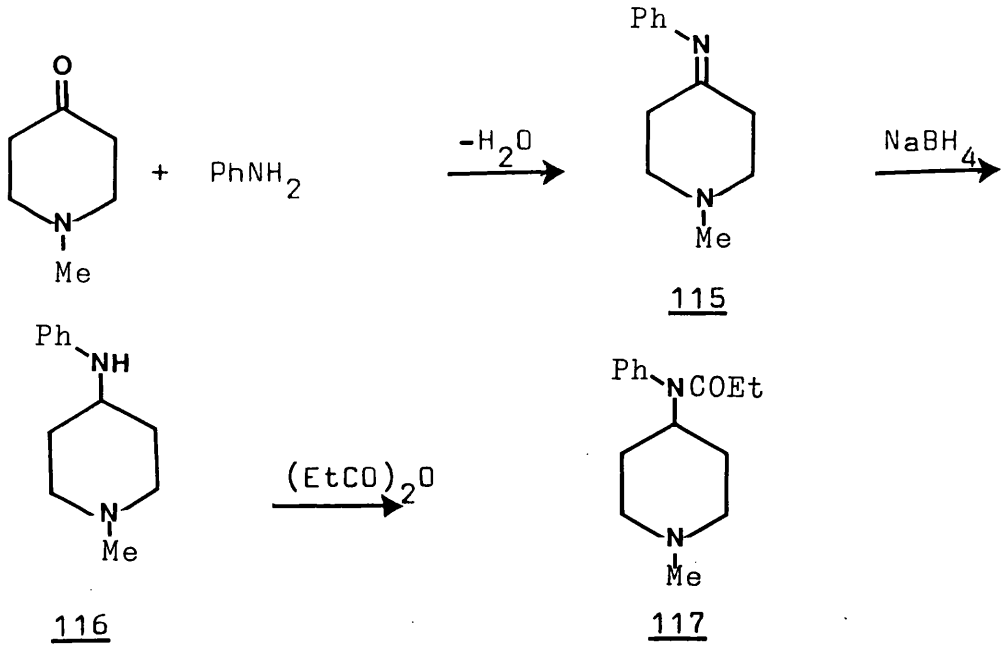


Scheme 11

by nucleophilic displacement of chloride from the appropriate 4-chloropyridine N-oxide or 4-chloropyridine hydrochloride. Acylation of the 4-anilinopyridine, followed by alkylation and reduction, leads to the desired analogue. Nevertheless, apart from the usual problem of availability of the appropriate C-alkyl pyridine starting material, the method suffers from an additional disadvantage of being unsuitable for the synthesis of analogues with easily reducible functional groups such as an allyl substituent.

1-Methyl-4-(N-phenylpropionamido)piperidine Synthesis.

The synthesis of the N-methyl analogue of fentanyl (required as a CMR standard) exemplifies the general procedure employed for all the analogues prepared during the course of the present work.



Scheme 12

Formation of the Schiff base (115) was catalysed

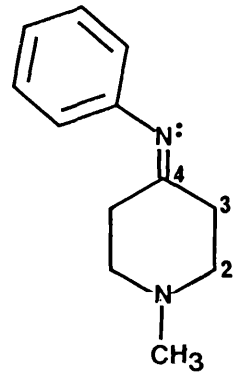
by p-toluene sulphonic acid (p-TsOH) or zinc chloride, and the reaction, being reversible, was driven essentially to completion by azeotropic removal of water to give the product in up to 90 % yields (details in the experimental section).

The IR spectrum of the Schiff base displayed a strong absorption band at 1660 cm^{-1}, characteristic of the imine group. The characteristic feature of the ^1H-n.m.r spectrum of the Schiff base was the aromatic protons which appeared as two groups of multiplets centred at δ 6.65 ppm (2H), and 7.15 ppm (3H) respectively. On reduction of the Shiff base to the anilino derivative (116), the lower field signals (δ 7.15 ppm) integrated for two protons, while the higher field signals (δ 6.65 ppm) integrated for three. This splitting of the aromatic proton signals into two groups of multiplets, however, appears to be due to the influence of the nitrogen lone pair of electrons, since in the derivatives where the lone pair is unavailable such as the dihydrochloride salt of the reduced base (116) and the acylated derivative (117), the aromatic protons resonated as a single group of multiplet at δ 7.5 ppm, and a broad singlet at 7.3 ppm respectively. The ^{13}C-n.m.r spectrum of the Schiff base displayed five carbon resonances in the aliphatic region (i.e different chemical shifts for C-2 and C-6, C-3 and C-5) because of the unsymmetric nature of the compound due to the imine geometry (118). Also of interest was the low field chemical shift of C-4 (δ 172.5 ppm),

characteristic of the Schiff base.

Reduction of the Schiff base was readily accomplished by heating the solution in methanol with sodium borohydride ($NaBH_4$) for 30 minutes. Other reducing agents such as Lithium aluminium hydride ($LiAlH_4$), or catalytic hydrogenation over Raney Nickel (RaNi) catalyst, are equally suitable. Treatment of the reduced product (116) with propionic anhydride in toluene under reflux conditions afforded the desired fentanyl analogue (117), which on conversion to the hydrochloride salt had a melting point in accord with the reported value (Casy et al, 1969).

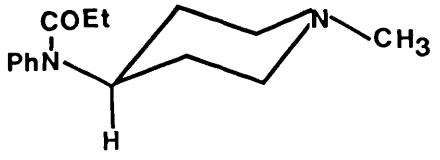
Characterisation of the final product was mainly by IR and Nmr spectroscopy. The IR spectrum of the base(117, neat) showed a strong carbonyl absorption at 1660 cm^{-1},



118

characteristic of the amide group in all the subsequent N-propionamido derivatives studied. The amide carbonyl chemical shift (δ 174 ppm) was also a characteristic feature of the ^{13}C-n.m.r spectra. As mentioned earlier, the aromatic protons resonance was a broad singlet, an indica-

tion of a freedom of rotation of the phenyl group along the C-N bond. The most characteristic aspect of the ^{1}H-nmr spectrum on the other hand, was the C-4 proton resonance, which was separated from the other ring protons and appeared as a multiplet centred at δ 4.4 ppm. Analyses of the coupling pattern of this proton (4-H) was of immense value in the stereochemical assignments of the 3-alkyl substituted derivatives, the basis of which will be discussed later (see page 108). Evidence for the preferred conformation (119) for the N-methyl analogue has been provided by the

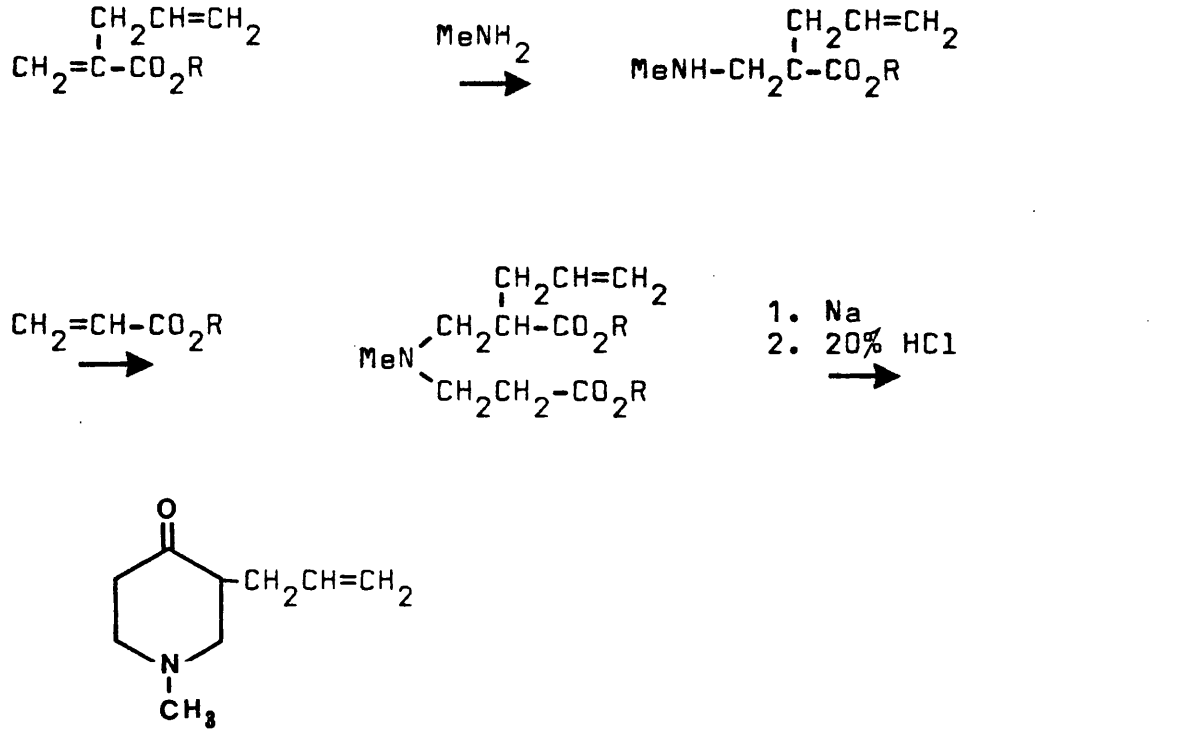


119

width of the 4-H signals (36 Hz) which is evidence for an axial 4-H, since the width of the corresponding signal of the other conformer in which the 4-H is equatorial will be much smaller (Casy et al, 1969).

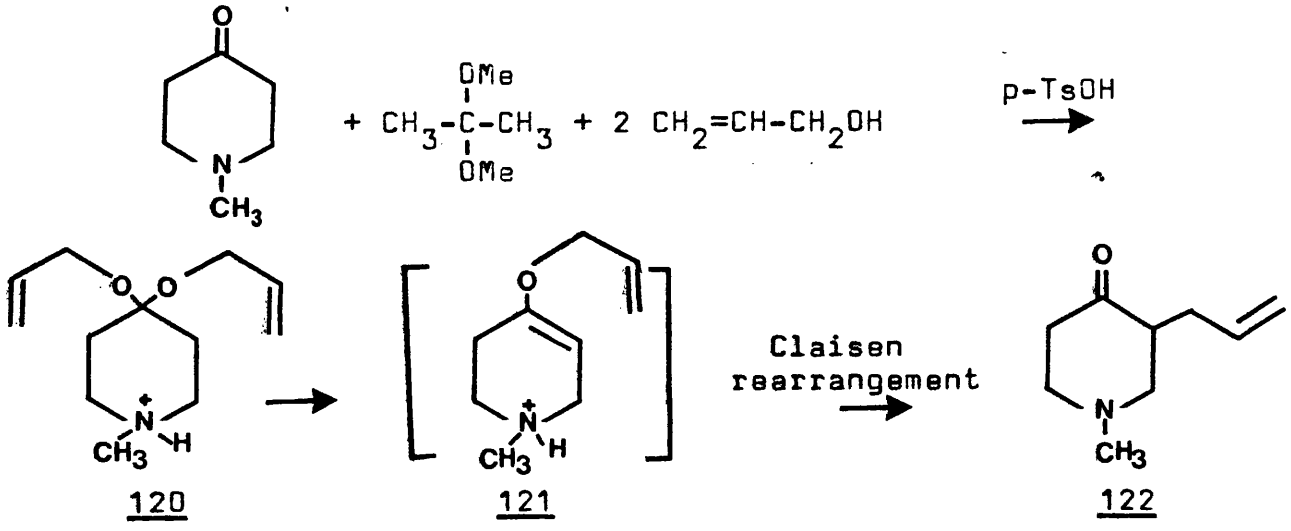
1-Methyl-3-allyl-4-piperidone Synthesis

This ketone was the key intermediate to the 1-methyl-3-allyl analogue of fentanyl. The synthesis of the ketone via the Dieckmann route (Scheme 13) was reported by Ziering et al (1957). However, because this procedure is lengthy



Scheme 13

and tedious in addition to the fact that the key starting material (α-allyl acrylate ester) is not readily available, we decided to employ the alternative route developed by Bell and Portoghese (1973) as outlined in Scheme 14.



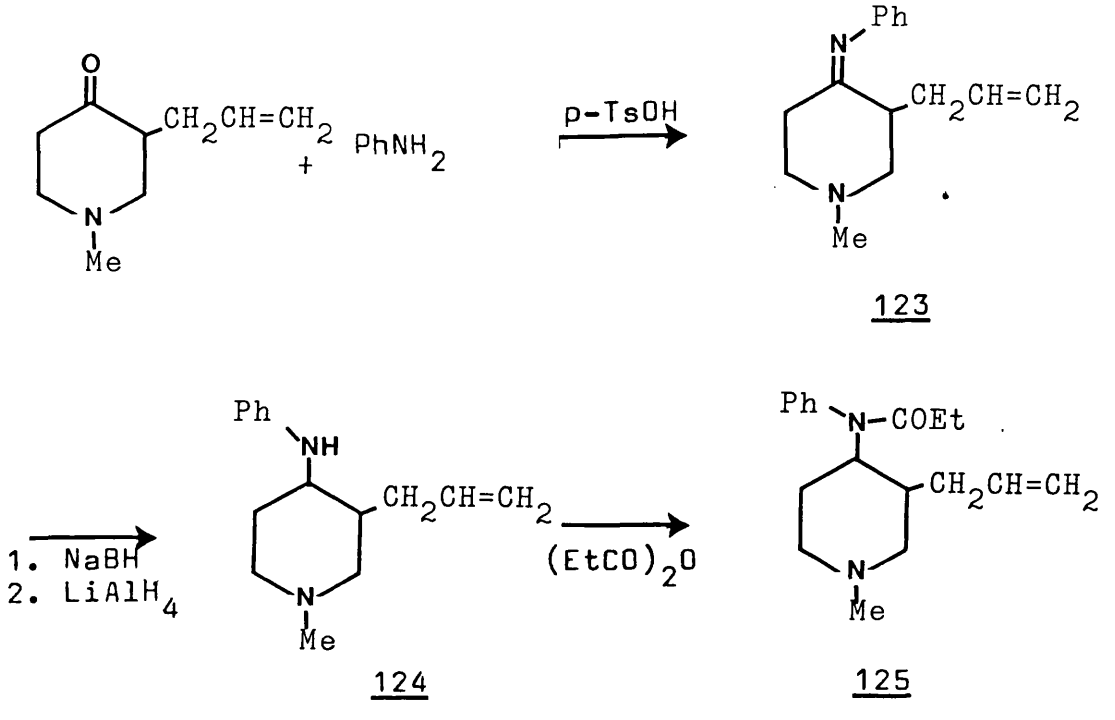
Scheme 14

A ketal exchange between acetone diallyl ketal (formed *in situ* from 2,2-dimethoxypropane and allyl alcohol) and 1-methyl-4-piperidone in the presence of *p*-TsOH yields the diallyloxy tosylate (120), which on thermal elimination of one mole equivalent of allyl alcohol produces the allyl vinyl ether (121). The allylvinyl ether is then allowed to undergo an *in situ* Claisen rearrangement to the 3-allyl ketone (122). With a slight modification of the reaction conditions (mixture of cyclohexane and toluene was used instead of benzene) the yield of the diallyloxy ketal (120) was increased by up to 22 %. However, attempts to increase the yield of the ketone (122) by carrying out the rearrangement step at a higher temperature (xylene substituted for toluene as solvent), since elevated temperatures are known to increase the yield of Claisen rearrangement reactions (Tarbell, 1944), were unsuccessful. Charred and tarry products were produced which led to very low yields. The reaction was therefore carried out in toluene with improvised equipment (details in the experimental section), and the course of the rearrangement followed by the disappearance of the allyl vinyl ether absorption at 1670 cm^{-1}. The IR spectrum of the product (122) showed a strong carbonyl absorption at 1705 cm^{-1}. The ^1H-n.m.r spectrum of the ketone showed the allylic proton resonances at δ 5.05 (doublet, 1H), 5.2(br. singlet) and 5.7 ppm (multiplet, 1H), and the ^{13}C-n.m.r spectrum displayed the correct number of carbon signals consistent with the structure.

Attempts to prepare the corresponding N-benzyl and N-phenethyl ketones via the same procedure were unsuccessful. The corresponding N-benzyl-4-diallyloxy ketal analogue could not be isolated. Although the corresponding N-phenethyl analogue was isolated as the crystalline tosylate salt, the quantity was not enough to give a reasonable yield of the rearranged product. Since the starting ketones were in short supply, this variant was not pursued further. An alternative synthetic route was therefore explored for the intermediate ketone needed for the synthesis of the N-phenethyl-3-allyl analogue of fentanyl.

1-Methyl-3-allyl-4-(N-phenylpropionamido)piperidine.

The procedure employed for the synthesis of this analogue is as outlined in Scheme 15. Reduction of the Schiff base (123) with $NaBH_4$ led predominantly to one major



Scheme 15

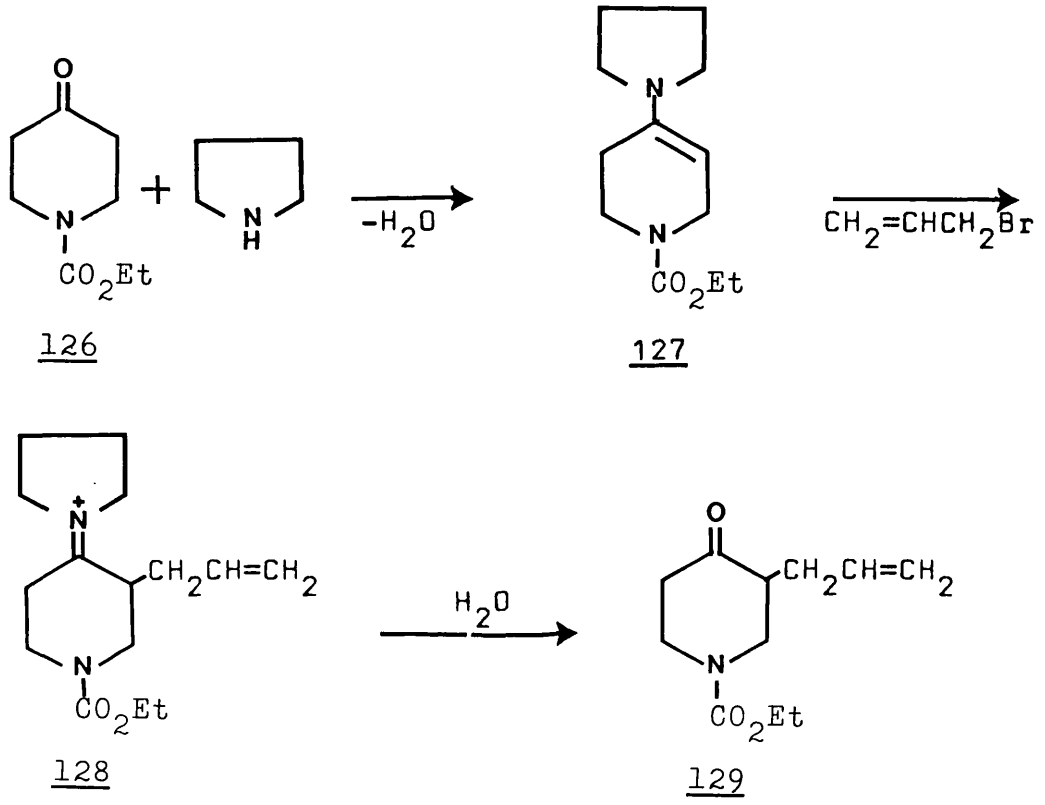
isomer, with the other isomer present in a very small proportion in the reaction mixture, as shown from the relative intensities of the corresponding resonances in the ^{13}C-n.m.r spectrum of the total product. Attempts to increase the proportion or selectively produce the minor isomer by reducing the Schiff base with $LiAlH_4$ were not successful, since the latter method gave similar isomeric proportions of the product as the sodium borohydride method. The choice of methods of reduction was however limited by the presence of the allylic double bonds. One other reducing agent that could be used however, is sodium metal in ethanol (Riley et al, 1979), but this was not tried.

Acylation of the anilino derivative (124) with propionic anhydride in toluene under reflux conditions gave the final product (125) from which the major isomer was isolated as the hydrochloride salt, while attempts to isolate the minor isomer from the mother liquor by fractional crystallisation of the salts or by chromatographic methods were unsuccessful. The stereochemistry of the product is discussed later (see page109). The N-phenethyl analogues were made by replacing the nitrogen substituent of the N-carbethoxy analogue of 125 by a phenethyl group (see page105). Since N-carbethoxy-3-allyl-4-piperidone was the key intermediate to this analogue, an account of its synthetic procedure will therefore be given here.

Synthesis Of The N-carbethoxy-3-allyl-4-piperidone Via The Enamine Route.

Alpha-alkyl substituted derivatives of most ketones

can often be readily synthesised via alkylation of the corresponding enamine, which, unlike the base catalysed alkylation, rarely produce poly-alkylated derivatives (Stork et al, 1963). The procedure for the synthesis is as outline in Scheme 16.

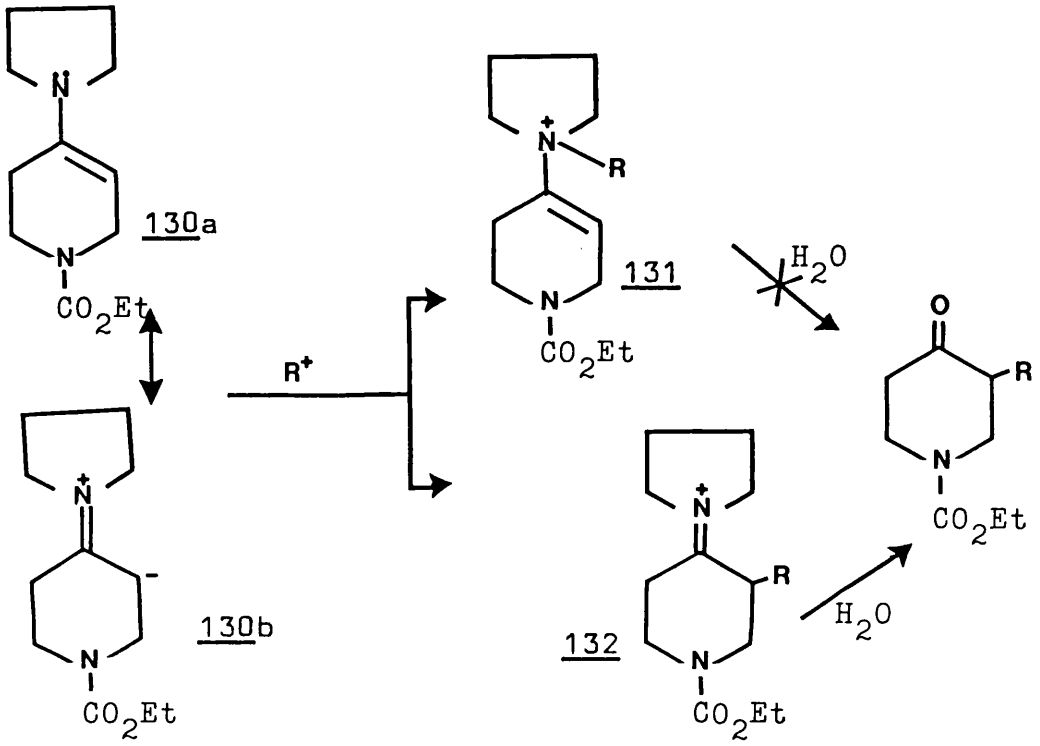


Scheme 16

Pyrollidine reacted readily with N-carbethoxy-4-piperidone in the presence of p-TsOH catalysis to produce the enamine (127) and water. However, since the reaction is reversible, azeotropic removal of water from the reaction medium ensured that the reaction was driven essentially to completion and the enamine obtained in up to 85 % yield. The enamine had to be used immediately

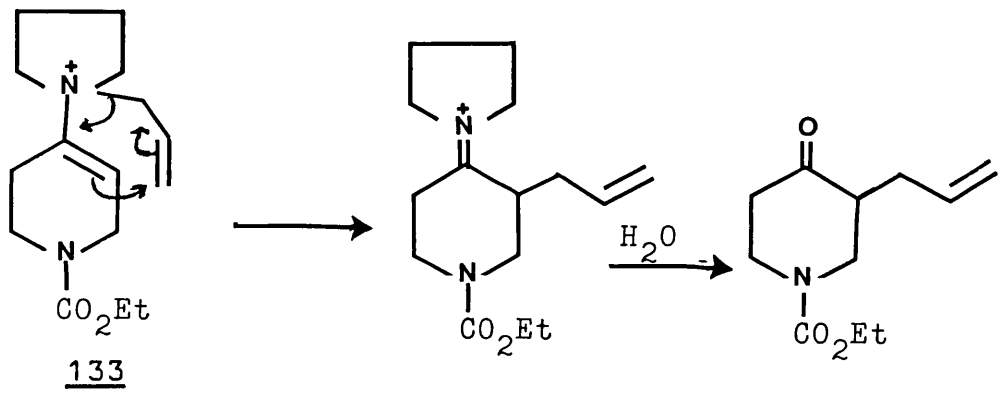
because of its sensitivity to moisture.

In the ^{1}H-n.m.r spectrum of the enamine, the vinylic proton, at about δ4.05 ppm, was masked by the methylene resonance of the propionyl ester (quartet, δ4.15 ppm), and the C-2 ring protons which resonated in about the same region. Nevertheless, the ^{13}C-n.m.r spectrum displayed the correct number of carbon resonances consistent with the structure (details in the experimental section). Alkylation of the enamine was effected by treating it with allylbromide in acetonitrile under reflux conditions. In this respect, the 1-carbethoxy group, apart from the ease of removal, serves the additional purpose of rendering the piperidine ring nitrogen non-basic thereby preventing its quaternisation by the alkylating agent. C-alkylation at the 3-position occurs because the electronic disposition in the enamine is such that the β-carbon carries an appreciable negative charge, as exemplified by the resonance structures , 130a and 130b, and may therefore act as a nucleophile. Such a C-alkylation produces the iminium ion (132) which is readily hydrolysed to the corresponding ketone (Scheme 17). However, electrophilic attack on the amine nitrogen leading to the N-alkylated derivative (131) is also probable. Unlike the iminium ion, the enammonium ion (131) formed by N-alkylation cannot be readily hydrolysed to the corresponding ketone, and being water soluble, often accounts for the poor yields of neutral ketone derived from these reactions. This not withstanding, the allyl ketone was obtained in excellent yields (up to 70%)



Scheme 17

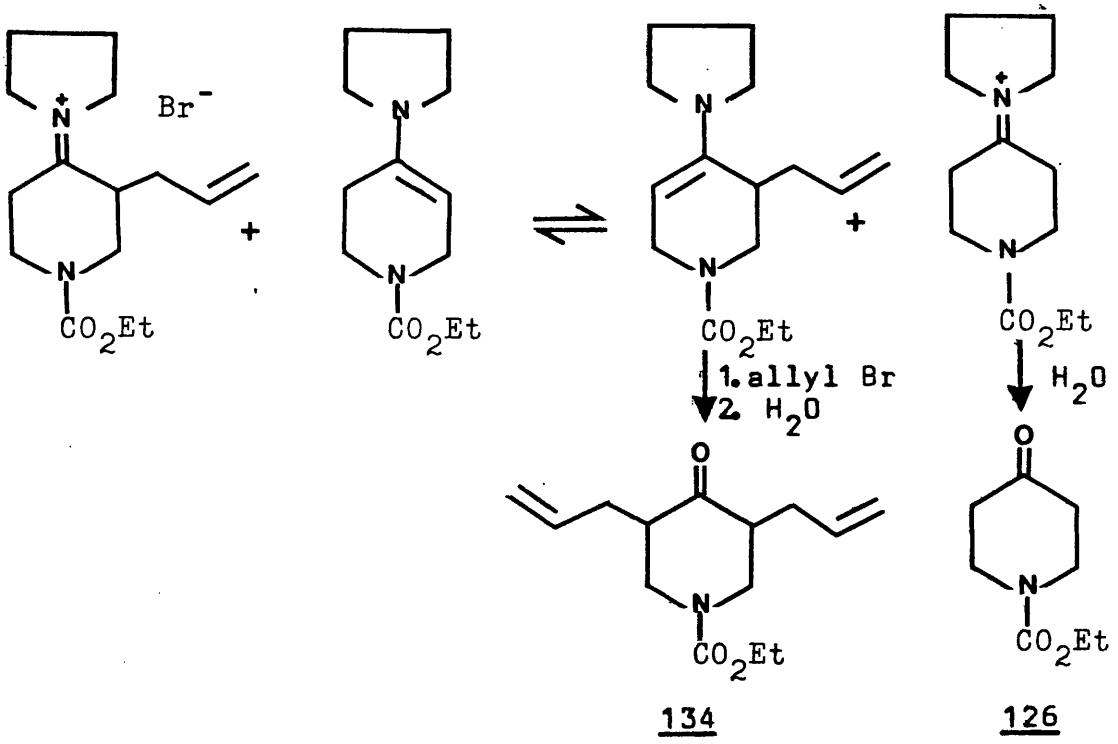
contrary to prediction. The result can, however, easily be accounted for by the fact that the initial N-alkylated product (133) can undergo a Claisen rearrangement to the C-alkylated product (Brannock & Burpitt, 1961) which can then be hydrolysed to the corresponding ketone as illustrated in Scheme 18. This explanation is reinforced by the



Scheme 18.

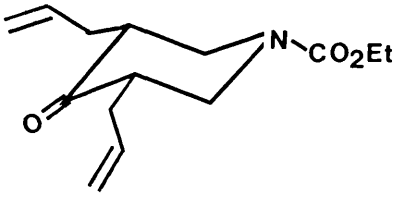
fact that a similar alkylation of the enamine with ethyl iodide gave a yield of less than 15 % of the 3-ethyl ketone analogue.

Chromatographic analysis of the total distilled allyl ketone showed three major products which on separation by column chromatography were made up of the expected 3-allyl ketone (129), an isomeric mixture of the 3,5-diallyl analogue (134), and the starting des-allyl ketone (126). The same pattern of product ratio was obtained in repeated trials with varied reaction time and ratio of reactants. This was puzzling at first. However, the alkylated iminium salts have been known to react with the original enamine to form a new enamine which can then react with the alkylating agent (House, 1972).as illustrated in Scheme 19.



Scheme 19

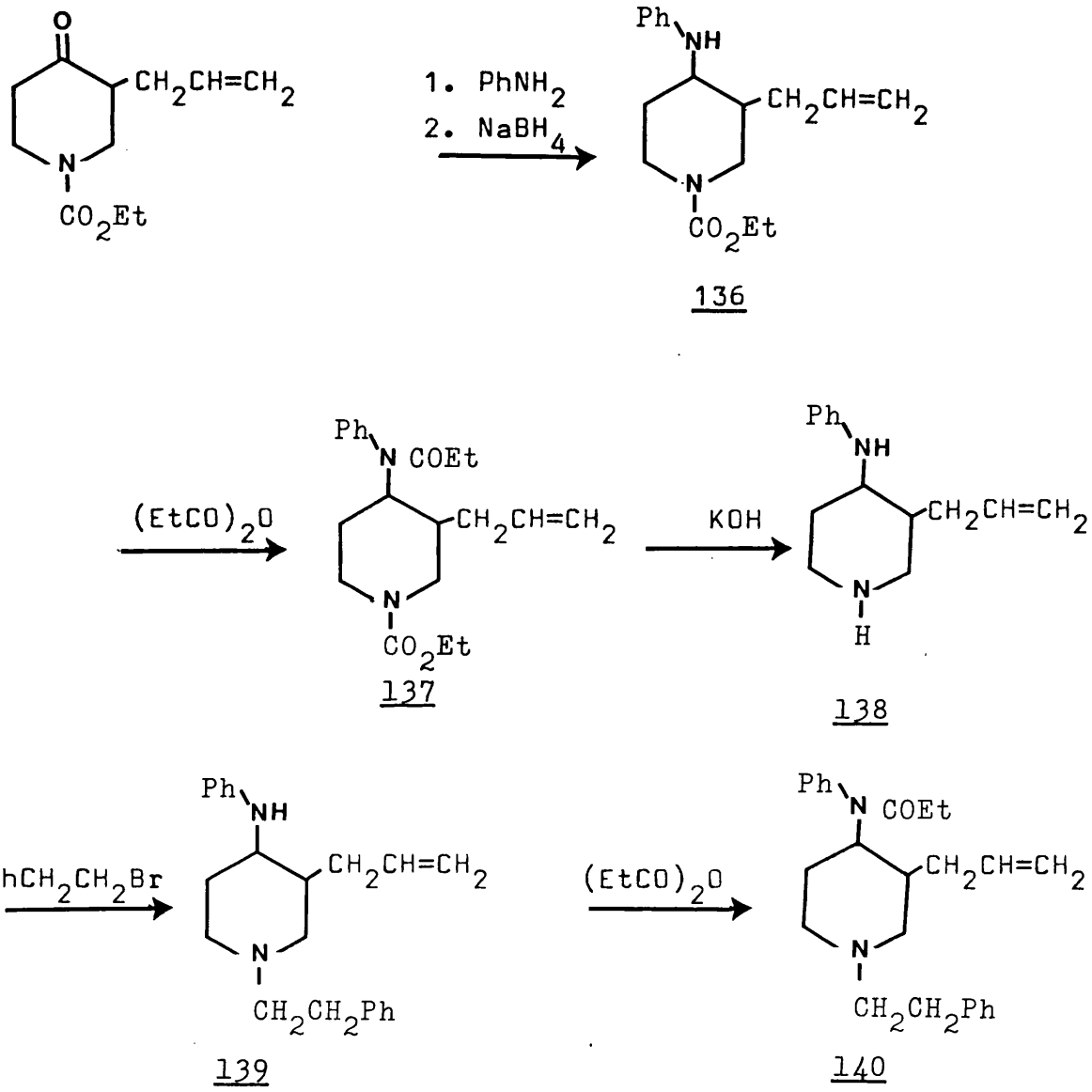
Hydrolysis of the reaction mixture therefore yields as neutral products, the starting ketone, the mono-, and the dialkylated ketones. Since the 3,5-diallyl ketone (134) exists in two isomeric forms, attempts were made to establish their configurations. ^{13}C-n.m.r spectrum of the major isomer showed it has the symmetrical cis-configuration (135) as judged from the chemical shifts of the ring carbons; there were only two such resonance signals, one at δ 49.19 ppm (a doublet) due to the C-3 and C-5, and the other at δ 49.19 ppm (triplet) due to the C-2 and C-6 (the coincidence of the two resonances was apparent from the Off-resonance spectrum).



135

1-Phenethyl-3-allyl-4-(N-phenylpropionamido)piperidine.

The 1-phenethyl-3-allyl analogue of fentanyl was synthesised via the 1-carbethoxy-4-piperidone as outlined in Scheme 20. Reduction of the Schiff base with $NaBH_4$ (as usual) gave a diastereoisomeric mixture of the corresponding anilino derivative (136), but with only a fractio-



136 137 138 139 140

Scheme 20

nal proportion of the minor isomer. The mixture was then acylated in the hope of separating the resulting isomeric derivatives by fractional crystallisation following the success of such methods in the separation of isomers in the corresponding 3-methyl analogue (van Bever et al, 1974). The product (137) was a semi-solid oil from which the major

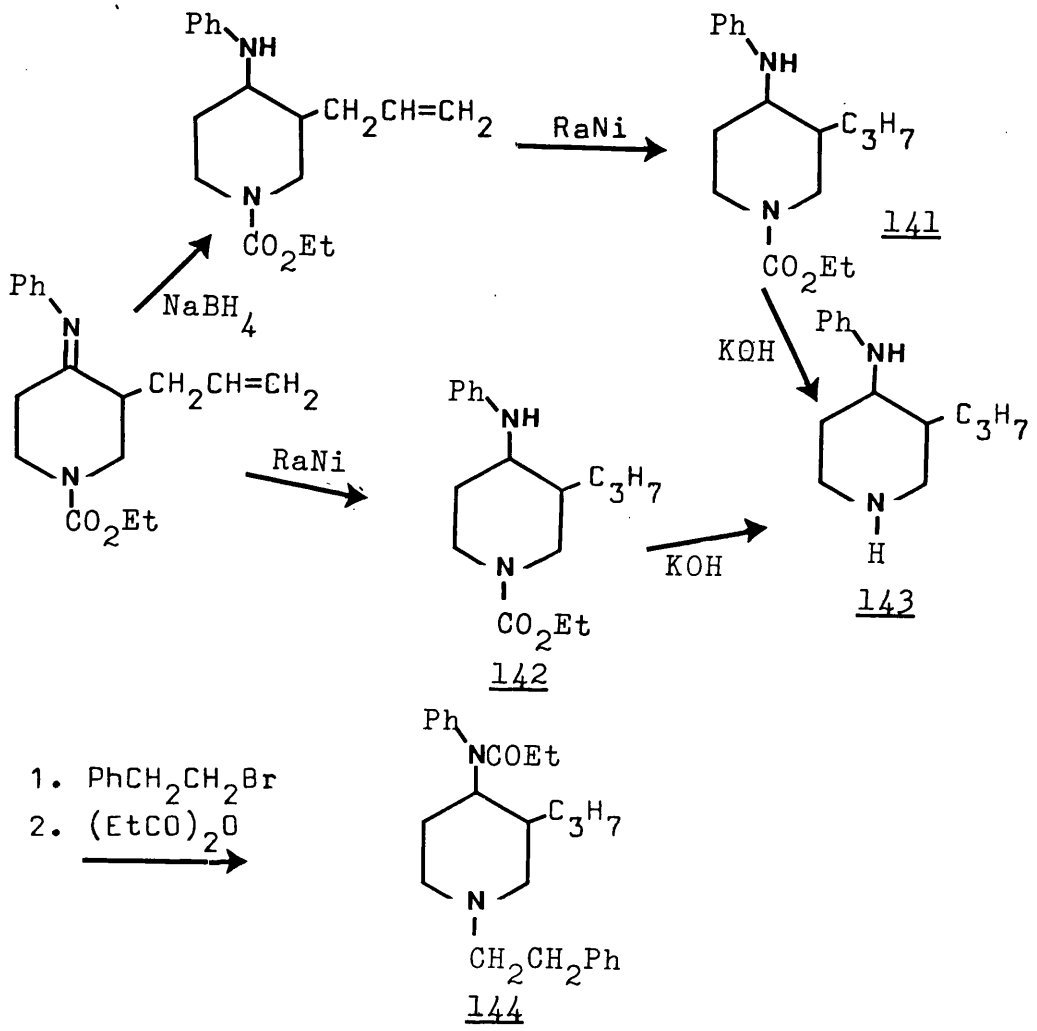
isomer was isolated by fractional crystallisation from n-hexane. Further attempts to isolate the minor isomer from the mother liquor proved unsuccessful. This is not surprising since the workers referred to above worked with 248g of product(compared to the 20g we had to work with) and were able to isolate only 29g of the minor isomer, i.e less than 10 %.

Selective removal of the 1-carbethoxy group from 137 could not be achieved. On treating the compound with potassium hydroxide in isopropanol under reflux conditions (Hermans, Verhoeven & Janssen, 1970), both the 1-carbethoxy and the N-propionamido groups were cleaved to give 138. The 1-phenethyl derivative was readily formed by refluxing 138 with β-phenethyl bromide in acetonitrile in the presence of sodium carbonate (to remove liberated HBr), and the product isolated as the hydrochloride salt. Propionylation of the 1-phenethyl derivative (139) in the usual way gave the desired analogue (140) which was isomerically pure.

1-Phenethyl-3-propyl-4-(N-phenylpropionamido)piperidine.

The 3-propyl analogues were readily made by reducing the allylic bond in the corresponding anilino derivative of the 3-allyl analogue. The procedure for the synthesis was, therefore, essentially the same as for the 3-allyl derivatives except in the choice of reducing methods for the Schiff base precursor as outlined in Scheme 21.

In an analogous reduction of the Schiff base from



Scheme 21

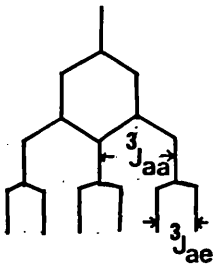
cyclohexanone derivatives and aniline to the corresponding cyclohexylamines, Bull and co-workers (1967) reported that the minor isomer of the cis-trans mixture obtained by catalytic hydrogenation over RaNi catalyst became the major isomer when the Schiff base was reduced by $NaBH_4$. We therefore decided to employ the same technique in the hope of

producing both isomers in reasonable yields. However, a reversal of the isomeric proportions envisaged for the catalytic reduction as compared to reduction by $NaBH_4$ was not achieved. Although the proportion of the minor isomer was slightly increased, catalytic reduction of the Schiff base over RaNi still gave the same major isomer as the $NaBH_4$ method. The reduced amines (141 and 142) were solids, and the major isomer was isolated by fractional crystallisation from n-heptane. The residue from the combined mother liquors was purified by a repeated passage through a chromatographic column of silica gel, and the minor isomer eventually isolated as the oxalate salt; full details are given in the experimental section. The individual isomers were converted to the corresponding fentanyl analogues (144) by the normal method.

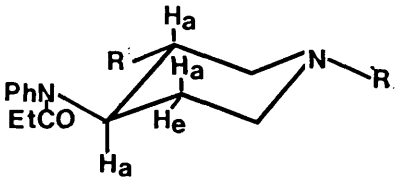
Stereochemistry Of The Fentanyl Analogues.

Stereochemical assignments of all the 3-alkyl substituted fentanyl analogues were based on evidence from ^1H- and ^{13}C-n.m.r spectroscopy. The C-4 proton (4-H) resonance, being isolated from other ring proton resonances, provided valuable information on the relative orientation of groups at the 3- and 4-positions in the molecule through its coupling patterns (Trager, Vicenzi & Huitric, 1962; van Bever et al, 1974). Assuming a piperidine chair conformation in which the 4-(N-phenylpropionamido) substituent is equatorial, the C-4 proton is axially oriented. In the trans-

isomer, therefore, where the 3-alkyl group is equatorially oriented (145), 4-H would be adjacent to two axial and one equatorial protons. Hence the coupling pattern in the trans-isomer is expected to be a triplet of doublets, arising from the C-4 axial hydrogen coupled to two adjacent axial hydrogens to give a triplet ($^3J_{aa}$ 8-14 Hz), each of which



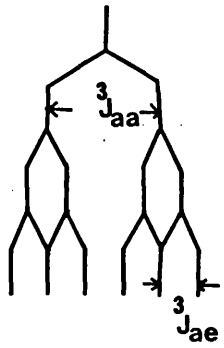
triplet of doublets
(assuming the two J_{aa} values to be equal or close)



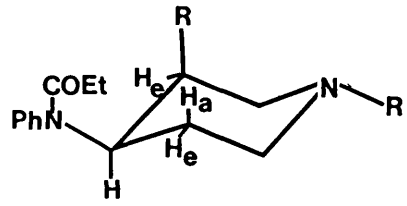
145

would again be split into a narrow doublet by the adjacent equatorial hydrogen ($^3J_{ae}$ 0-6 Hz). On the other hand, a doublet of triplets is expected from the cis-isomer (146) in which the C-4 proton would be coupled to one axial proton to give a doublet ($^3J_{aa}$ 8-14 Hz), each component of which would again be split into narrow triplets ($^3J_{ae}$ 0-6 Hz) by the two adjacent equatorial protons.

A 220 MHz spectrum of the major isomer from 1-methyl-3-allyl-4-(N-phenylpropionamido)piperidine as a base in $CDCl_3$ showed the C-4 proton resonance as a sextet (fig. 4), made up of a doublet of triplets, the coupling constants

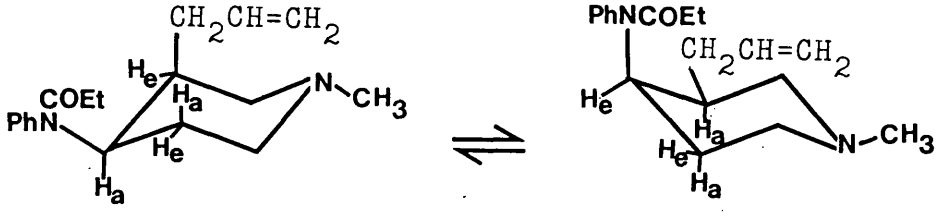


doublet of triplets



146

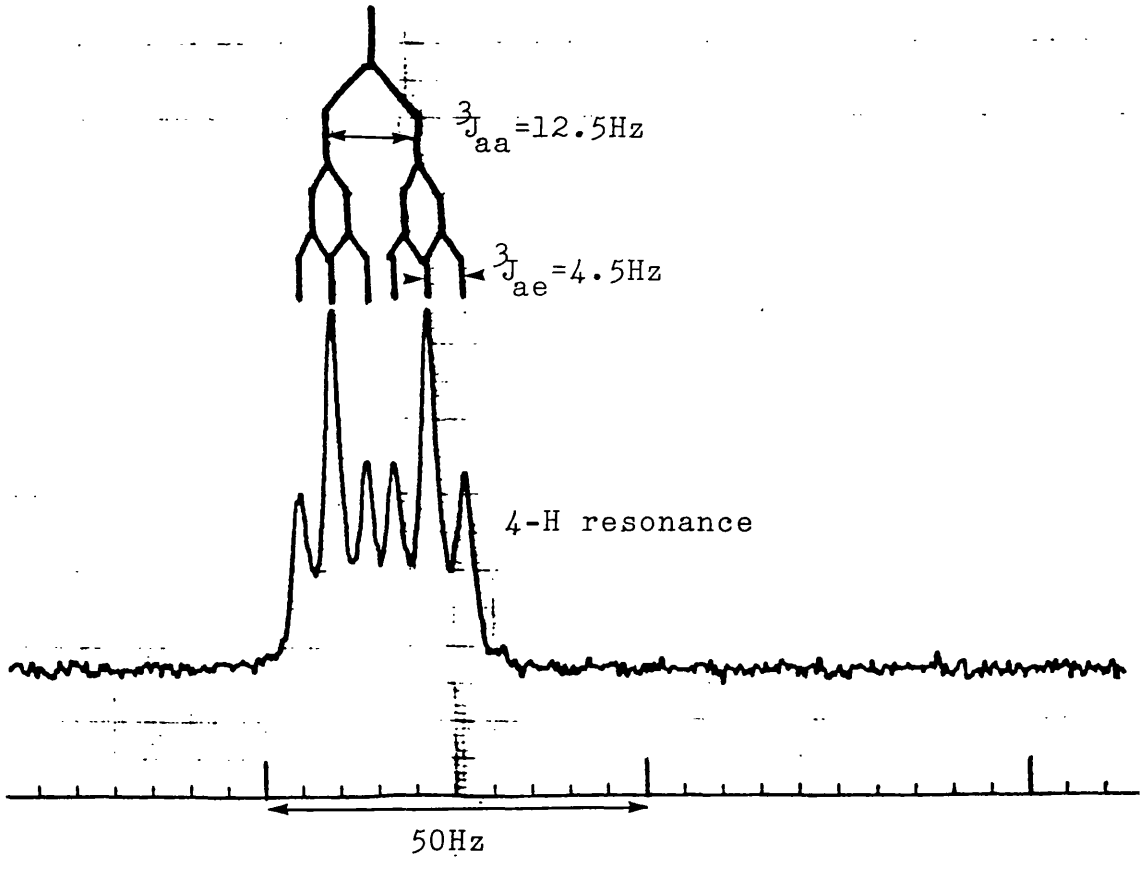
($^3J_{aa}$ 12.5 Hz, $^3J_{ae}$ 4.5 Hz) of which are typical of axial-axial, and axial-equatorial vicinal proton couplings respectively (Sternhell, 1969). Hence the major isomer has a cis-configuration, with a preferred ax-3-allyl/eq-4-NCOEtPh chair conformation (147a) as solute in $CDCl_3$. These values are in accord with the ^3J values ($^3J_{aa}$ 12.5 Hz, $^3J_{ae}$ 5.0 Hz) reported for the cis isomer of the corresponding 3-methyl analogue (van Bever et al, 1974). The deduction that 147a is the preferred solute conformation of the cis-compound is further reinforced by the consideration that in



147a ⇌ 147b

the inverted chair conformation (147b) in which the 4-H is equatorially oriented, only narrow vicinal couplings typical of eq-ax ($^3J_{ae}$ 0-6 Hz), and eq-eq ($^3J_{ee}$ 0-6 Hz)

Fig. 4. Part of the 220MHz ^{1}H-n.m.r Spectrum of cis-1-methyl-3-allyl-4-(N-phenylpropionamido)piperidine as base in $CDCl_3$.



are possible, both of which are considerably smaller than the observed ax-ax coupling.

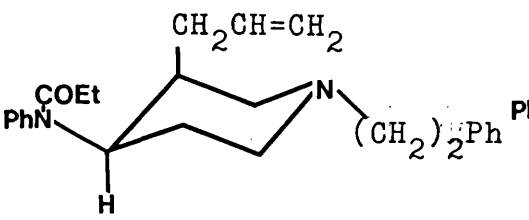
The ^{13}C-n.m.r chemical shift data on the two isomeric forms of 125 (page 98; data on the minor isomer obtained from the spectrum of the mixture) showed an upfield shift of about δ 3.4 ppm in the C-5 carbon resonance of the major isomer as compared to that of the des-3-allyl parent compound (Table VIII, entries 2 & 3). This is in accord with the cis-configuration in which the 3-allyl substituent is axially oriented, thereby causing a shielding of the C-5 carbon through steric polarisation (γ-gauche effect). On the other hand, the chemical shift of C-5 in the minor isomer is similar to that of the parent compound (Table VIII, entries 2 &4) indicating a trans-configuration. The mutual shielding influence of the γ-gauche interaction in the cis-isomer is evident from the high field resonance position of the 3-CH_2- fragment of the substituent, compared to that of the trans-isomer (Table VIII, entries 3 & 4).

From a similar analyses of the C-4 proton coupling pattern in the 'H-n.m.r spectra of the other analogues, it was evident that the major isomer from the 1-phenethyl analogue (140, page 105) has a cis-configuration with a preferred ax-3-allyl/eq-4-NCOEtPh chair conformation (148, doublet of triplets, $^3J_{aa}$ 12.5 Hz, $^3J_{ae}$ 4.5 Hz), and that the major isomer from the 1-phenethyl-3-propyl analogue(144) also has a cis-configuration with a preferred ax-3-allyl/eq-4-NCOEtPh chair conformation (149, doublet of triplets, $^3J_{aa}$ 12.5 Hz, $^3J_{ae}$ 4.5 Hz). These deductions are supported

Table VIII. ^{13}C Chemical shifts (δ, ppm) of some 1- and 3-substituted 4-(N-phenylpropionamido)piperidines (Fentanyl analogues) as bases in $CDCl_3$ (TMS standard).

Entry	Compound	Substituents 1-R	Substituents 3-R	Isomer	C-2	C-3	C-4	C-5	C-6	1-CH_3 (1-CH_2-)	3-CH_2-
1.	Fentanyl	$PhCH_2CH_2$-	H	-	53.19	30.71	52.49	30.71	53.19	60.42	-
2.	117	Me	H	-	55.31	30.66	51.95	30.66	55.31	46.04	-
3.	125	Me	CH_2=$CHCH_2$	cis	57.95	36.83	57.64	27.24	56.07	46.48	31.15
4.	125	Me	CH_2=$CHCH_2$	trans[a]	60.51	38.30	51.73	30.50	55.20	45.93	34.8
5.	137	EtOCO-	CH_2=$CHCH_2$	cis	45.51	37.27	58.02	26.38	43.31	-	29.53
6.	140	$PhCH_2CH_2$-	CH_2=$CHCH_2$	cis	55.04	36.89	58.34	27.35	54.12	60.07	30.95
7.	144	$PhCH_2CH_2$-	C_3H_7-	cis	55.63	36.89	58.50	27.35	54.01	60.02	29.7
8.	144	$PhCH_2CH_2$-	C_3H_7-	trans	58.72	38.72	56.01	30.66	53.03	60.45	32.50

Footnote: a Chemical shifts extracted from the spectrum of the cis-trans mixture.



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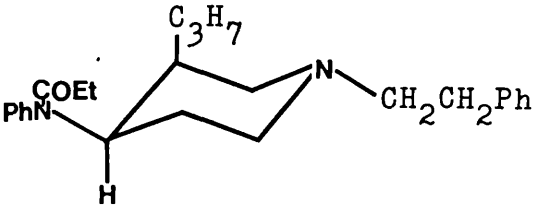

149

by the upfield shift in the chemical shifts of their C-5 carbons, compared to that of the parent compound (Table VIII, entries 1, 6 & 7). The C-5 chemical shift of the precursor 1-carbethoxy analogue (137, page 105) is also upfield (Table VIII, entry 5) in accord with the cis-configuration of the final product.

On the other hand, the C-4 proton resonance of the minor isomer from the 3-propyl analogue (144, page 107), was a triplet of doublets (fig. 5) with coupling constants ($^3J_{aa}$ 11.5 Hz, $^3J_{ae}$ 4.5 Hz) typical of axial-axial and axial-equatorial vicinal couplings respectively, indicating a trans-configuration with a preferred eq-3-propyl/eq-4-NCOEtPh chair conformation (150). The ^{13}C-n.m.r chemical

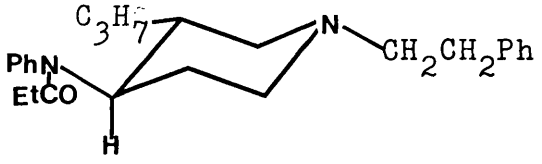

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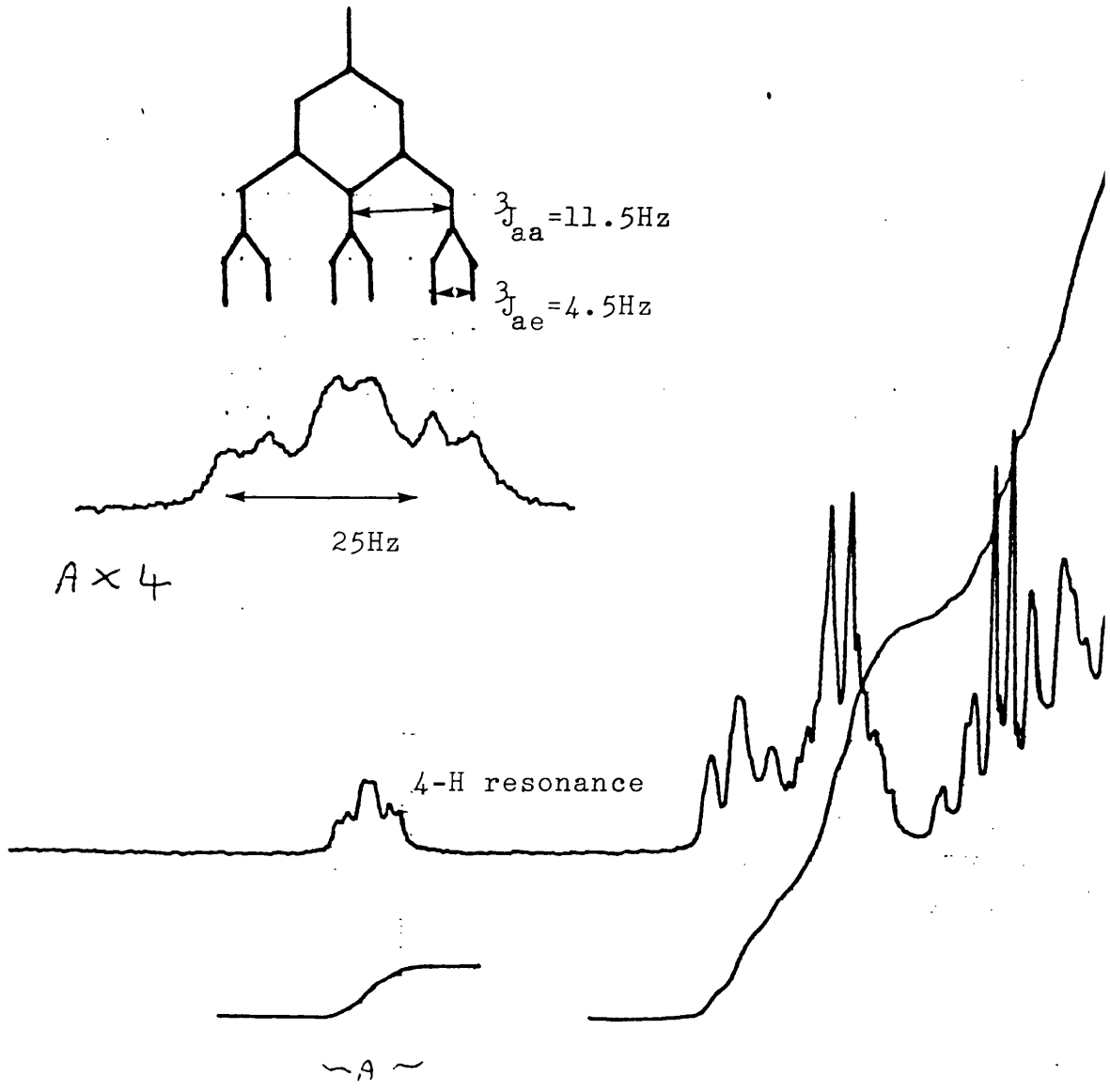
Fig. 5. Part of the ^{1}H-n.m.r Spectrum of trans-1-phenethyl-3-propyl-4-(N-phenylpropionamido)piperidine in $CDCl_3$ (100MHz).

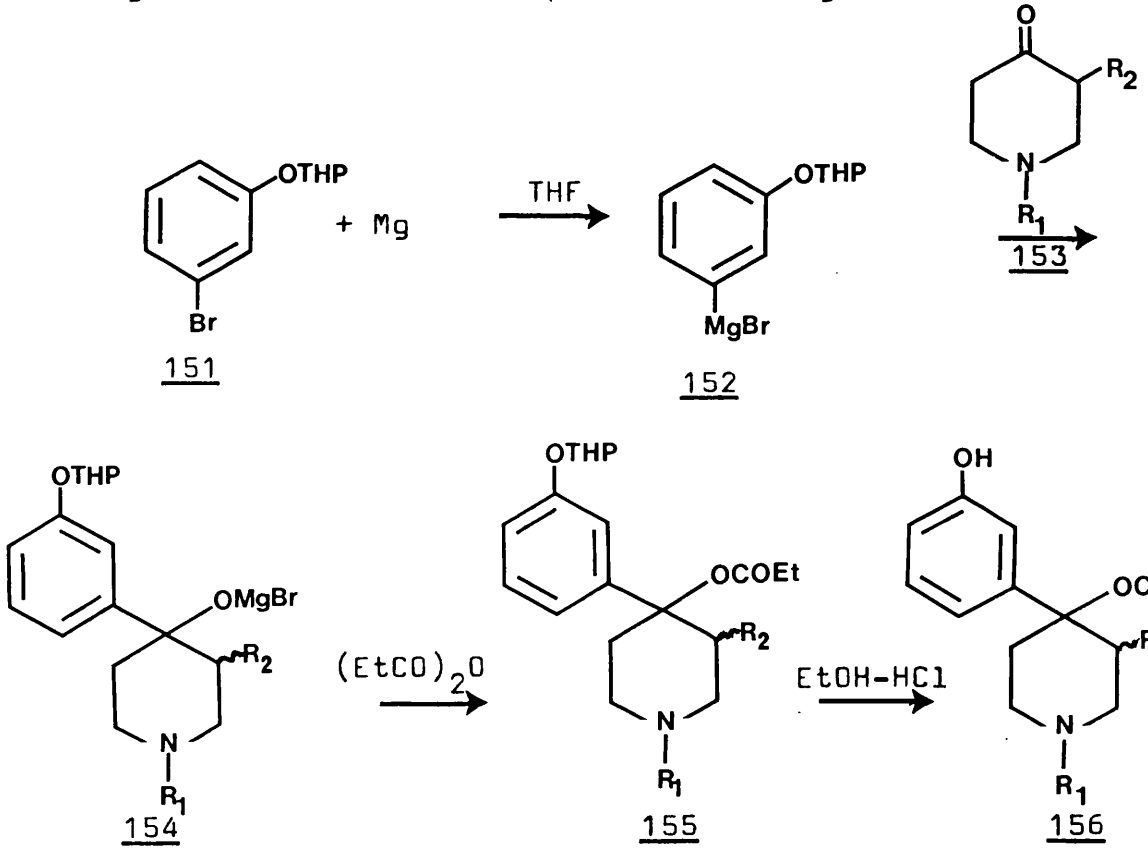


shift of C-5 is similar to that of the parent compound (Table VIII, entries 1 & 8) in accord with an equatorial 3-propyl substituent.

SECTION THREE

Phenolic Analogues Of Reversed Esters Of Pethidine.

The general procedure employed in the syntheses of the 4-(m-hydroxyphenyl) analogues of the reversed esters of pethidine is as outlined in Scheme 22. The organometallic compounds of halogenated phenols cannot be prepared by a direct reaction with metallic lithium or magnesium as in the non-phenolic analogues because of



R_1= Me, $PhCH_2CH_2$-

R_2= Me, H.

(Note: THP=Tetrahydropyran,
THF=Tetrahydrofuran)

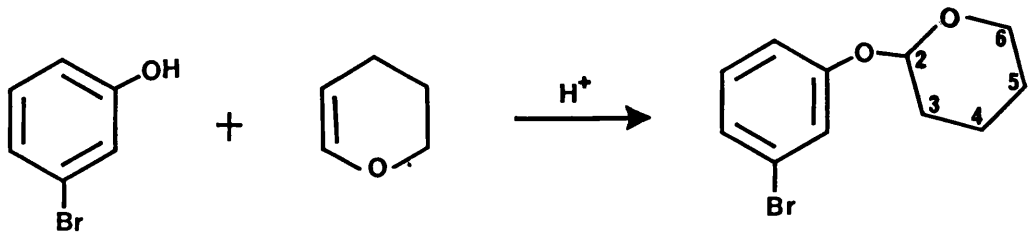
Scheme 22

the formation of isomeric products, particularly the O-

metal derivative (Kharasch&Reinmuth,1954), hence the need to protect the phenolic group prior to formation of the organometallic reagent.

One commonly employed technique is to use the phenolic ether, especially the methyl ethers, but this suffers from the disadvantage that most conditions required for the cleavage of the ether (O-demethylation) in the final product are so vigorous that considerable loss by decomposition may result. It should be noted however, that while the present work was in progress, Portoghese and co-workers (1981) described a method of effecting O-demethylation under mild conditions. One other way of protecting the phenolic group is by cyclic acetal formation with dihydropyran. Such cyclic acetals, while being stable to alkali, are readily hydrolysed by dilute acids to regenerate the hydroxyl group (Parham & Anderson, 1948). The acetal protecting group has been used successfully in the synthesis of some phenolic analogues of the reversed esters of pethidine (Zimmerman, 1981, private communication). It was therefore considered best to use the cyclic acetal protecting group in the present work.

m-Bromophenol reacted quite rapidly with dihydropyran in the presence of a few drops of conc. HCl as catalyst (Scheme 23) with the liberation of heat necessitating the cooling of the reaction mixture. The unreacted bromophenol was removed by washing the reaction mixture with 10 % sodium hydroxide solution. Extraction



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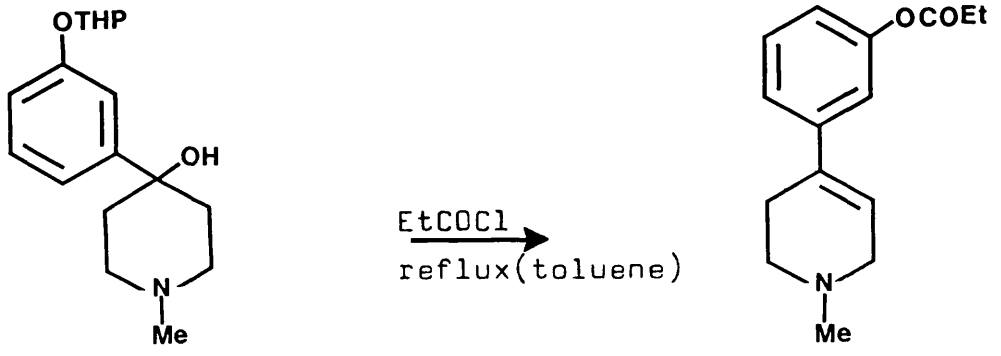
Scheme 23

into ether, drying and evaporation of the solvent yielded an oily product which on dilution with n-hexane gave colourless crystals (m.p 39-40°C) on storage at refrigerator temperature. The ^{1}H-n.m.r spectrum of the pure cyclic acetal(151) displayed groups of multiplets at δ 1.75 ppm (6H, due to the pyranyl C-3, C-4 and C-5 protons), δ 3.65 ppm (2H, due to the C-6 proton), δ 5.4 ppm (1H, due to the C-2 proton), and the aromatic protons resonating from δ6.75 to 7.5 ppm(4H). The ^{13}C-n.m.r spectrum displayed carbon resonances consistent with the structure (details in the experimental section).

The acetal reacted with magnesium turnings in THF to form the Grignard reagent (152) in the normal way. Nevertheless, in most of the cases, the reaction had to be initiated by warming the reaction mixture with a few crystals of iodine, avoiding stirring of the mixture until the reaction commenced in order to ensure a local concentration of iodine to initiate the reaction. In an initial trial, the Grignard complex (154, R_1=Me, R_2= H)

made by reacting the 152 (page 117) with 1-methyl-4-piperidone, was decomposed with aqueous ammonium chloride in order to isolate the corresponding alcohol. ^{1}H-n.m.r analysis of the resulting product (157) showed that the tetrahydropyranyl (THP) protecting group was still intact judging from the characteristic proton resonances of the cyclic acetal. However, attempted esterification of the product by refluxing it with propionyl chloride in toluene, as was the case with the non-phenolic analogues discussed in section one, was unsuccessful. The IR spectrum of the

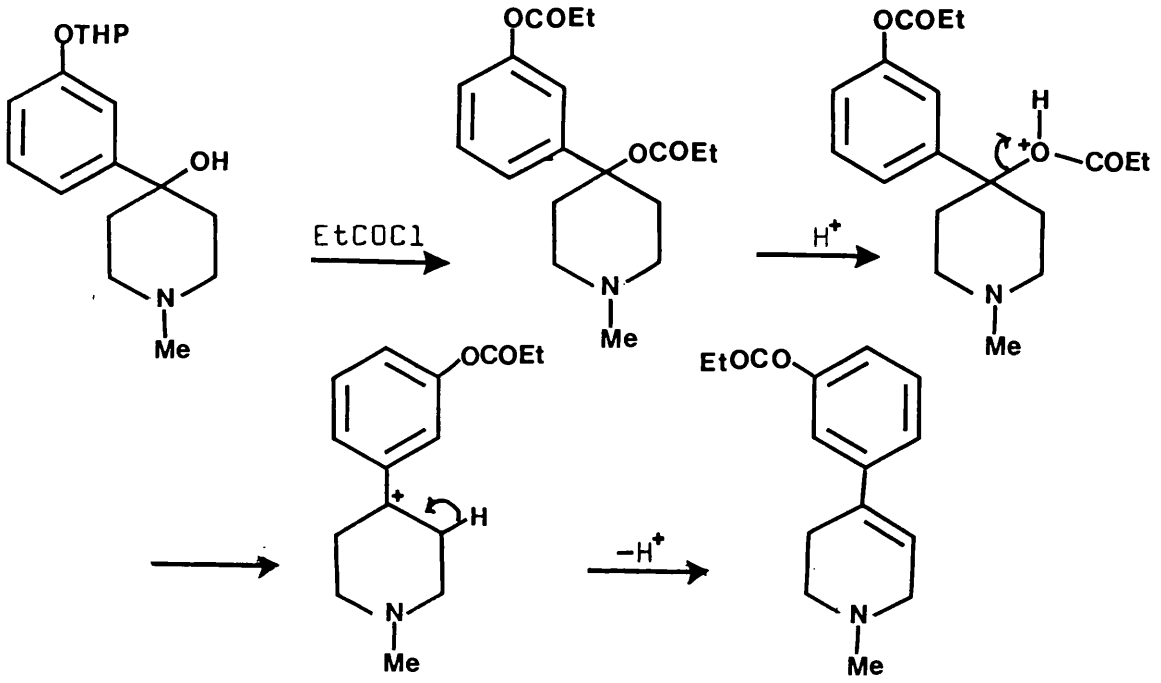


157 158

product showed a strong carbonyl absorption at 1765 cm^{-1}. The ^{1}H-n.m.r spectrum (vinylic proton signal at δ 6.2 ppm), and the ^{13}C-n.m.r chemical shift data (Table IX, entry 5) are consistent with the structure (158) in which the dehydrated product is esterified at the phenolic hydroxyl group.

Such a transformation may be accounted for by alkyl-oxygen heterolysis of the ester, analogous to those reported by Casy, Beckett and Armstrong (1961), conceived in

terms of the hydrochloric acid generated from a reaction of the propionyl chloride and the hydroxyl group catalysing the cleavage, as well as that of the protecting group as illustrated in Scheme 24. The method was therefore



Scheme 24.

considered unsuitable, and esterification of the different analogues effected by decomposing the corresponding Grignard complex directly with propionic anhydride. The protecting group was still retained in the corresponding products (155, page 117), as evident from the ^{1}H-n.m.r spectrum. However, on conversion to the hydrochloride salt by treating the base with ethanolic hydrochloric acid (a condition under which the ester group is unaffected),

the free phenolic group was regenerated. The IR spectrum of the product (156) showed a strong carbonyl absorption at 1725 cm^{-1}, and the phenolic O-H absorption at 3200 cm^{-1} (in nujol mull). The ^{1}H-n.m.r spectrum (60 MHz) of the hydrochloride salts of 156 derivatives (page 117) in DMSO-d_6 showed the phenolic hydroxyl resonance at δ 9.38 ppm. The melting point of the 3-desmethyl compound (156, R_1=Me, R_2= H) was 205-206^{o}C compared to the melting point of 196-198^{o}C reported for the same compound prepared via another route (Portoghese et al, 1981). It should be noted, however, that the reported compound co-crystallised with one-half mole of water from acetone-ethylacetate mixture, while that described here was anhydrous.

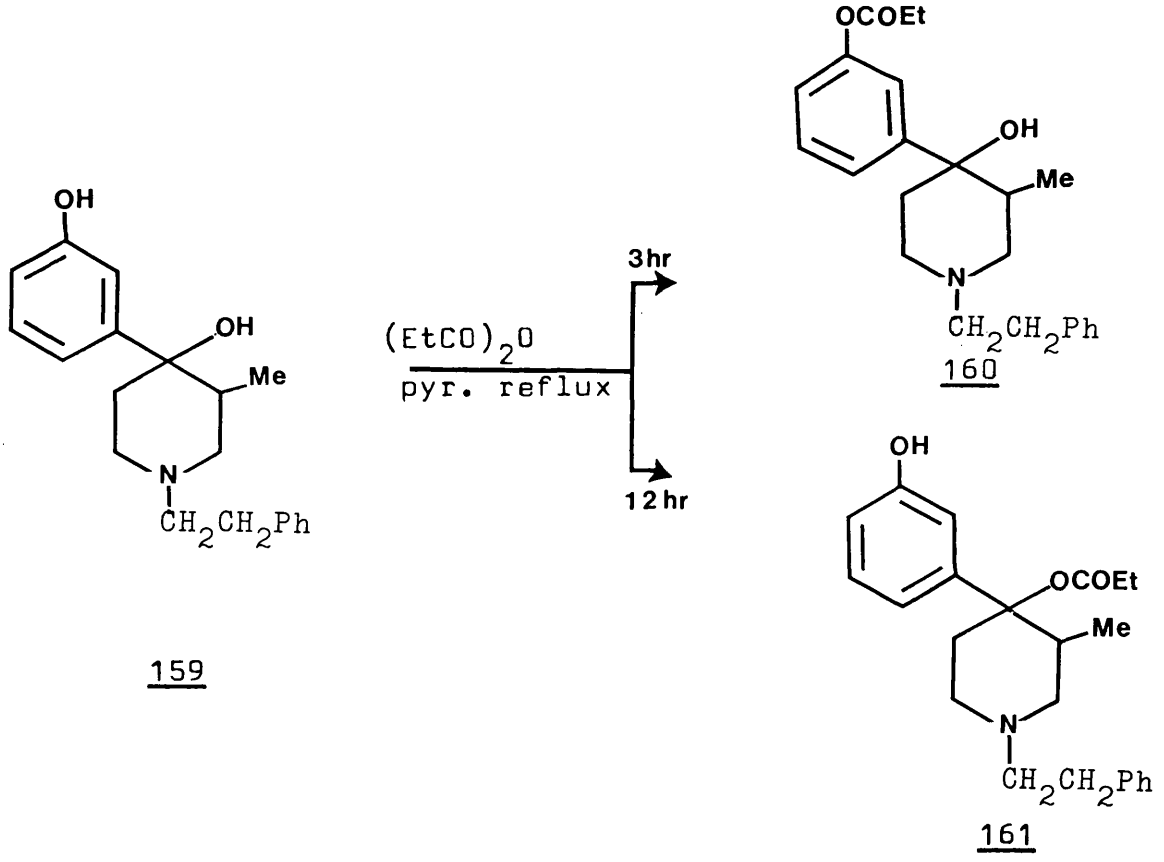
The Grignard reagent reacted with the 3-methyl-4-piperidones to produce cis-trans isomeric mixtures in a ratio of about 18:1, as judged from the relative intensities of the corresponding 3-methyl proton resonances. In the case of the 1,3-dimethyl derivative, the major isomer was readily isolated by fractional crystallisation of the hydrochloride salt. The minor isomer, on the other hand, was separated from the residual major isomer by converting the residue from the mother liquor into the malate salt. The resulting mother liquor, after collecting the major isomer malate salt, was basified, and the minor isomer isolated by fractional crystallisation of the oxalate salt. The progress of the isolation procedure was monitored by the disappearance of the 3-methyl doublet of the major isomer from the ^{1}H-n.m.r spectrum, and by the melting point

of the hydrochloride salt. There was no correlation in the data on the same compound by Zimmerman and co-workers (1981) and those obtained in the present work. In the first place, the α-isomer (trans 3-Me/4-Ph) was the major product contrary to the reported β-isomer (cis 3-Me/4-Ph); in addition to this, the reported melting point of 144°C was much too low for the value (206-207°C) we obtained for the β-isomer, and the α-isomer melting point (168-170°C). Similar treatment of the N-phenethyl-3-methyl derivative afforded the major isomer. Attempts to isolate the minor isomer from the resulting mother liquor were unsuccessful.

Another feature of the reaction worth mentioning is the observation that when 3-methyl substituted derivatives of the Grignard complex (154, page 117) were decomposed with propionic anhydride, a mixture of the corresponding esters and the free alcohol were isolated in all cases, but never in the unsubstituted derivative where decomposition of the Grignard complex with propionic anhydride gave only the corresponding ester in quantitative yields. This phenomenon must have been caused by the additional steric influence of the 3-methyl substituent, since the free alcohol was never isolated from the corresponding 3-desmethyl analogues.

Isolation of the free alcohols as the hydrochloride salts led to cleavage of the protecting group which rendered a selective esterification of the 4-hydroxyl group difficult. However, an attempt to esterify both the phenolic and the C-4 hydroxyl groups (159) by refluxing the

N-phenethyl analogue with propionic anhydride in pyridine for three hours led to a selective esterification of the phenolic group. The IR spectrum of the product (160) showed a strong carbonyl absorption at 1760 cm^{-1} and an O-H absorption at 3550 cm^{-1}. The ^{1}H-n.m.r spectrum of the salt in DMSO-d_6 failed to display the phenolic O-H resonance at about δ9.6 ppm. On the other hand, a longer reflux time (12 hr.) under the same conditions gave the prouct esterified at the C-4 hydroxyl group (161).



159 160 161

The IR and the ^{1}H-n.mr spectra of the product were consistent with the structure (161). Elucidation of the structures of the two products was facilitated by the ^{13}C-n.m.r chemical shift of the C-4 carbon. Evidence from ^{13}C-n.m.r

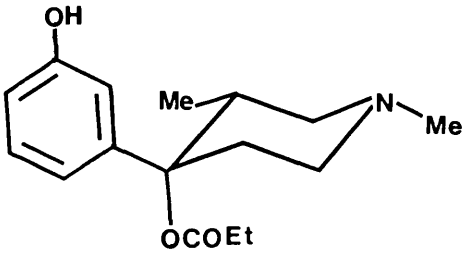
studies on similar 4-piperidinols and their corresponding esters show that esterification of the 4-hydroxyl group generally deshields the C-4 carbon by up to 9 ppm(Jones, Casy & McErlane, 1973). The C-4 chemical shift of 160 is similar to that of the starting piperidinol (159), both of which are at higher field (upfield by about 9.8 ppm) of the C-4 shift for 161 (Table IX, entries 6, 7 & 8).

Stereochemical Assignments

The stereochemical assignments of the phenolic analogues of the reversed esters of pethidine prepared in this work were based on ^{13}C-n.m.r data following similar assignments of the non-phenolic derivatives (Jones, Casy & McErlane, 1973). For reasons of solubility, the spectra were run in $CDCl_3$-DMSO-d_6 mixture and the resonances recorded relative to tetramethylsilane (TMS).

Data on the α- and β-prodines, compounds of established stereochemistry, showed that equatorial 3-methyl substituents in such systems have chemical shifts near δ 12.0 ppm, while axial 3-methyl substituents resonate near δ 15.0 ppm with a corresponding upfield shift of the C-5 resonance by about 5-6 ppm in both $CDCl_3$ and DMSO-d_6 (Jones, Casy & McErlane, 1973; Casy, Iorio & Podo, 1981). The 3-Me chemical shift of the α-isomer of the phenolic analogue (156, R_1=Me, R_2=Me) is δ 12.62 ppm, evidence for an equatorial orientation, while the 3-Me chemical shift

(δ 15.06 ppm) of the β-isomer is evidence for an axial 3-methyl orientation (Table IX, enties 2 & 3). This view is supported by the upfield shift for C-5 of the β-isomer (δ 25.89 ppm), compared to those of the α-isomer (δ 32.34 ppm) and the 3-desmethyl analogue (δ 35.64 ppm). Since it has been shown that the piperidine ring adopts a chair conformation with equatorial 4-phenyl group in the α- and β-prodines (Jones, Casy & McErlane, 1973), the data on the phenolic analogues are in accord with a preferred eq-3-Me/eq-4-Ph chair conformation (162) for the α-isomer, and ax-3-Me/eq-4-Ph chair conformation (163) for the β-isomer.



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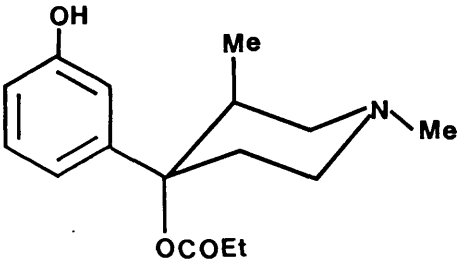

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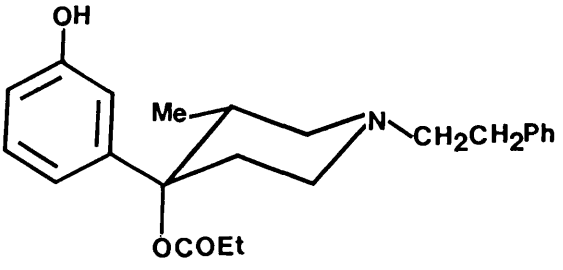
The ^{13}C-n.m.r data on the α-isomer of the N-phenethyl analogue (Table IX, entry 4) are also in accord with an eq-3-Me/eq-4-Ph chair conformation (164). The C-q chemical shifts of the α-isomers (162 and 164) are to



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TableIX: ^{13}C Chemical shifts (δ, ppm) of some 4-(m-hydroxyphenyl)-4-piperidinol esters in $CDCl_3$-DMSO-d_6 (TMS standard).

Entry	Compound	Substituents R_1	Substituents R_2	Isomer	C-2	C-3	C-4	C-5	C-6	1-CH_3 (1-CH_2-)	3-CH_3	C-q
1.	156	Me-	H	-	51.57	35.64	79.74	35.64	51.57	45.93	-	146.o5
2.	162	Me-	Me-	α	58.88	42.14	83.32	32.34	51.19	45.72	12.62	143.18
3.	163	Me-	Me-	β	58.02	40.63	82.67	25.89	51.57	46.37	15.06	145.07
4.	164	$PhCH_2CH_2$-	Me-	α	57.09	42.52	83.91	32.93	49.19	60.02	12.40	143.83
5.	158			-	51.62	116.47	134.19	24.24	50.16	42.31	-	139.93
6.	159			α	56.55	40.25	73.02	39.49	49.19	62.95	12.51	150.11
7.	160			α	57.09	40.90	74.00	39.70	49.56	60.51	12.40	149.86
8.	161			α	57.18	42.42	83.80	32.55	49.10	60.45	12.73	143.15

higher field of that of the β-isomer (163, Table IX, entries 2, 3, 4, and 8) in line with a γ-gauche influence of equatorial 3-Me on the C-q carbon of the phenyl group in the α-isomers.

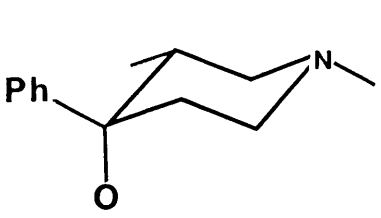
C H A P T E R T H R E E

PHARMACOLOGY AND STEREOCHEMICAL STRUCTURE-ACTIVITY CORRELATIONS

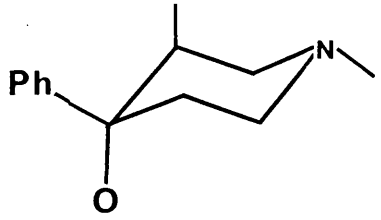
SECTION ONE

The Reversed Esters Of Pethidine

The prodines provided the first examples demonstrating the dramatic influence of configuration on the analgesic potency of the reversed esters of pethidine. In α-prodine (165) where the 3-methyl group is oriented trans to the phenyl group, the activity is similar to that of the parent desmethyl compound, whereas a cis orientation giving β-prodine (166) increases the analgesic potency several folds (Casy, 1970). These observed potency differences



165



166

ED_{50} mg/kg mice hot plate test	0.95	0.18

(desmethyl analogue 0.85)

(Note: In order to simplify these and subsequent formulae, the methyl groups are represented by straight lines depicting their orientations, and the acyloxy group, mainly OCOEt, represented by oxygen).

could possibly be explained in terms of pharmacokinetic factors such as metabolism and distribution, which determine the availability of the drug at the active site. On the other hand, these results may well represent events at receptor sites. The potency difference has been interpreted in terms of the latter, since in a series of metabolic and binding studies on pethidine and homologues, in no case were pharmacokinetic factors able to account for the observed pharmacological differences (Abdel-Monem et al, 1972). Support for this view also comes from a detailed study of prodine isomers labelled at the aromatic part of the molecule by tritium (Abdel-Monem, Harris & Portoghese, 1972). In no case were differences in analgesic potency fully accounted for by metabolism and distribution.

The potency ratio between the diastereoisomeric pair observed for the prodines is also true for the N-phenethyl derivative, and 3-methyl substituted pethidine (Table X, page 131). The observed trend is however unique to the 3-methyl substituted congeners. Substitution with higher 3-alkyl homologues such as ethyl, allyl and propyl groups, have consistently produced isomeric pairs in which the α-isomers (trans 3-alkyl/4-Ph) are more potent than the β-isomers (for examples see Table I, page 29). Assuming a close correspondence of binding and preferred conformations, one interpretation of these findings is that the influence of the β-methyl may be achieved through a direct interaction with a binding site on the receptor specific for methyl. Since larger hydrocarbon groups are assumed

Table X Analgesic activity of some des-3-methyl, α- and β-3-methyl-4-phenylpiperidine Triads.

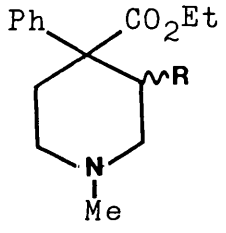
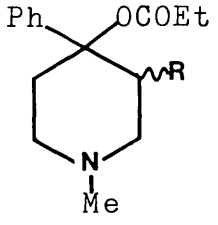
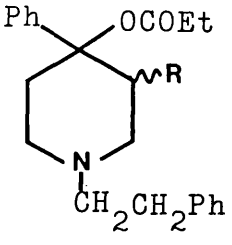
Type	Activity in mice by hot-plate test		
	R = H	R = -Me (trans 3Me/4Ph)	R = -Me (cis 3Me/4Ph)
 (pethidine)	1.0 (pethidine=1.0)	1.3	11.0[a]
 (prodine)	9.2 (pethidine = 1)	7.1	34.0[b]
	3.5 (morphine = 1)	4.5	22.0[c]

Table X contd.

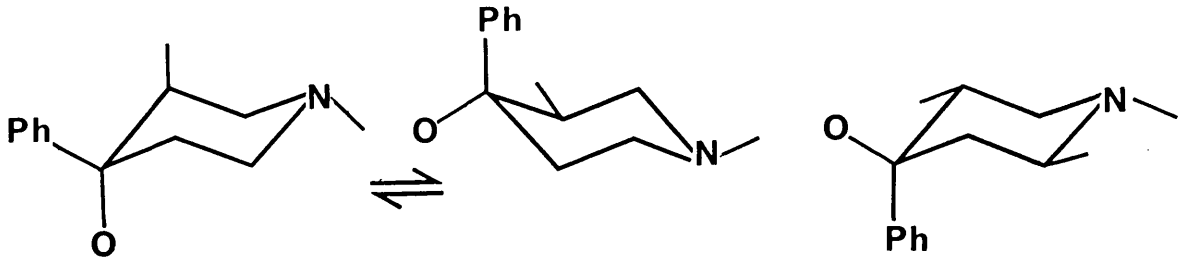
Note: a Ref. Casy, Chatten and Khullar,(1969).

b Ref. Portoghese and Larson (1968).

c Ref. Beckett, Casy and Kirk (1959).

---

to be not accommodated at the said site, they may therefore act against drug-receptor association (Casy, 1978). An alternative explanation on the other hand, is that a β-Me may exert an indirect influence on ligand-receptor association by inducing a rise in the population of axial 4-phenyl reversed ester conformations (167) that may bind more effectively than equatorial 4-phenyl chairs favoured in the unsubstituted and the α-3-alkyl substituted derivatives. This proposal is supported by the fact that the most potent isomer of the promedols (α-isomer, 168) has an axially oriented phenyl group in the preferred conformation.

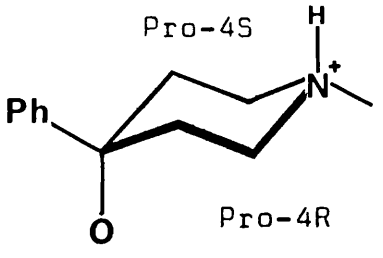


167 168

However, when the 3-substituent exceeds one carbon atom in chain length, it is assumed that the axial 4-phenyl chair conformation loses its superiority over equatorial 4-phenyl

geometry, as found in the cases of α-3-ethyl, α-3-propyl, α-3-allyl and α-3-butyl derivatives.

Attempts to build up a consistent stereochemical structure-activity pattern in the various C-alkyl substituted reversed esters of pethidine have been greatly facilitated by Larson and Portogheses' (1973) treatment of the reversed ester of pethidine in its preferred equatorial 4-phenyl chair conformation based on the absolute stereochemistry of the derivatives. By employing biochemical nomenclature, the two sides of the achiral reversed ester of pethidine (169) can be differentiated as pro-chiral 4R (Pro-4R) and pro-chiral 4S (Pro-4S). If an alkyl group is inserted in the Pro-4S edge, the formerly symmetric C-4 carbon is turned into an asymmetric centre acquiring the S configuration according to the Cahn-Ingold-Prelog convention (IUPAC, 1970), while a similar insertion in the Pro-4R edge gives C-4 an R configuration. The question then

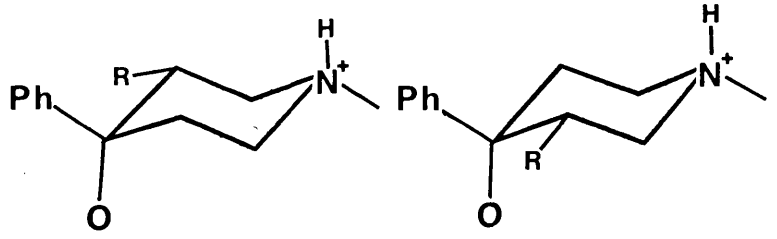


169

arises as to whether the opiate receptor discriminates between the enantiotopic edges of the molecule in the same

sense enzymes differentiate chemically alike paired groups of substrates of the Caabc type such as citrate, the so-called Ogston effect (Ogston, 1958). Data on the antipodal forms of 3-alkyl derivatives of the prodine type strongly suggest that the opiate receptor does infact discriminate between the enantiotopic edges. Thus it was found that the more potent antipodal forms of α-3-alkyl derivatives of the reversed esters of pethidine (Table XI) all have the same configuration (3R, 4S).

Table XI. Analgesic activity of the antipodal forms of some 3-alkyl substituted reversed esters of pethidine(ED_{50}mg/kg, s.c mice hot-plate test).

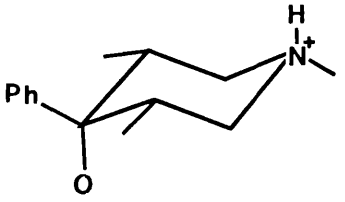


R	3R, 4S	3S, 4R	Ref.
methyl	0.91	22.4 (cf R=H 1.3)	a
ethyl	0.9	25.0 (cf R=H 0.85)	b
n-propyl	1.0	25.2	b
allyl	0.03	7.8	b

Note: a Larson and Portoghese (1973).

b Bell and Portoghese (1973).

One interpretation of these findings is that the reversed esters present the Pro-4R edge rather than the Pro-4S side of the molecule to the receptor; substituents positioned in the Pro-4S side are remote from the receptor surface and therefore do not hinder the approach of the ligand to the receptor binding site. The lack of any significant difference between the potency of the 3R,4S antipodes and the parent compound (the allyl derivative being an exception) shows that the substituents on this side of the molecule play a passive role in the drug-receptor interaction. On the other hand, equatorially-placed 3-alkyl substituents on the Pro-4R edge prevent effective drug-receptor association because they are now immediately adjacent to the receptor surface, hence an α-3-alkyl substituent situated on the Pro-4R edge is disadvantageous to analgesic potency. This probably explains the inactivity of the cis-(meso) 3,5-dimethyl analogue (170) in which one of the methyl groups is always disadvantageously placed, while the other plays no active role in the drug-receptor interaction.

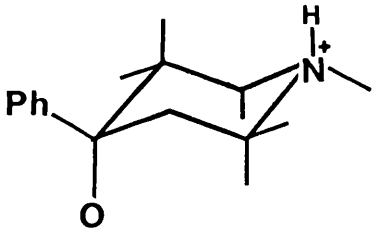


inactive

170

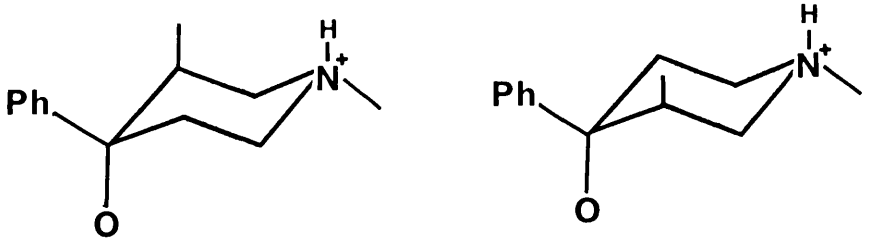
Following this approach, it has been possible to correlate the absolute orientations of methyl substitution

in both the mono- and dimethyl substituted derivatives with analgesic potency thereby establishing with a fair approximation, the specific contributions of methyl in its various locations (Casy, 1982). The absolute methyl orientations that enhance activity, or those that are not detrimental but just play passive roles , can be summarised by 171.



171

Thus while equatorial 3-methyl substitution on the Pro-4S edge is passive and not detrimental to activity (see Table XII, page 134), axial 3-methyl on the same edge has a potency raising influence. However, a similar substitution on the Pro-4R side is unfavourable, as shown by the data on the antipodal forms of β-prodine (172).



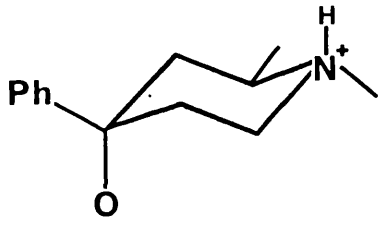
(+)-3S,4S (-)-3R,4R

172

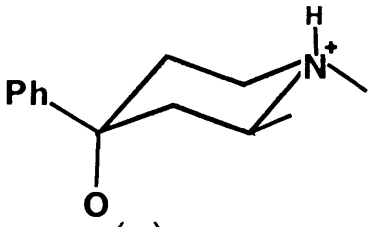
ED_{50} mg/kg	0.25	3.3

When the methyl substitution is adjacent to the

nitrogen centre (i.e 2-methyl substitution), the effects of the absolute orientation are opposite to those of 3-methyl substitution. Insertion of an equatorial 2-methyl group on the Pro-4S edge is unfavourable for optimum ligand-receptor association, whereas such substitution on the Pro-4R edge has no detrimental influence on analgesic activity, and can therefore be accommodated by the receptor, as shown from the data on the antipodal forms of the β-2-methyl analogue of the reversed ester of pethidine (173, Fries et al, 1982). On the other hand, axial 2-methyl substitution



(+)-2R,4S



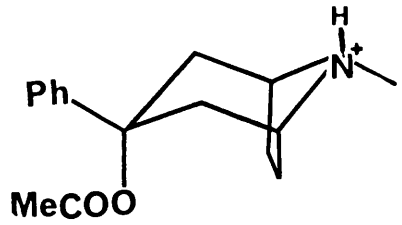
(-)-2S,4R

ED_{50} mg/kg	5.5	0.53

173

on the Pro-4R edge appears to enhance potency, whereas a similar substitution on the Pro-4S side has little or no influence, and is not severely detrimental to activity. This view is supported by the retention of activity in the tropane analogue of the acetoxy reversed ester of pethidine (174), and stands in contrast to the receptor sensitivity towards equatorial 2-methyl substituents as described above.

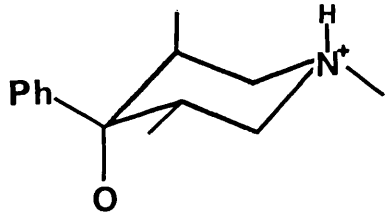
The data on the various C-dimethyl substituted esters have been shown to be consistent with the stereochemical structure-



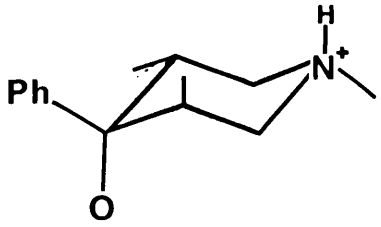
ED_{50} mg/kg 3.4 (cf 4.7 for acetoxy reversed ester of pethidine; Casy, 1978).

174

activity correlations discussed above (cf 175-177). It is therefore of interest to see if the 2,3-dimethyl analogues fit into this general pattern of correlations.



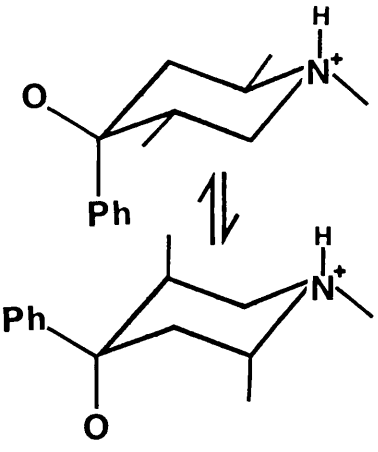
(+)-3S,5S



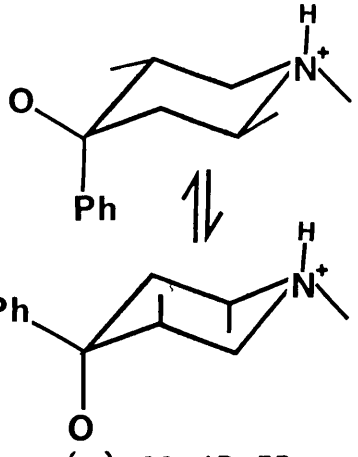
(-)-3R,5R

ED_{50} mg/kg	4.91	25.01

175



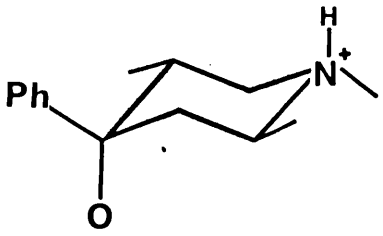
(+)-2R,4S,5S



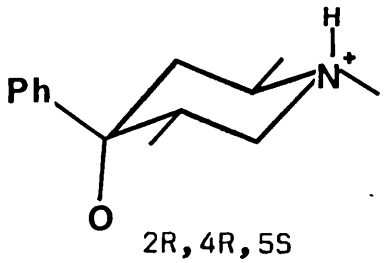
(-)-2S,4R,5R

ED_{50} mg/kg	0.06	inactive to 50.0

176



2S,4S,5R



2R,4R,5S

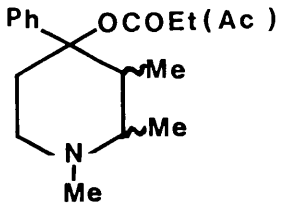
0.94 8.8

(ED_{50} mg/kg, s.c mice hot plate test; Fries & Portoghese,1976).

177

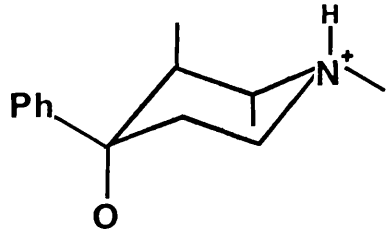
The pharmacological results on the 2,3-dimethyl substituted analogues of the reversed ester of pethidine as antinociceptive agents in mice by the hot plate method, and in rats by the tail withdrawal test are given in Table XII .

Table XII . Analgesic potency in the isomeric 1,2,3-trimethyl-4-phenyl-4-propionoxypiperidine hydrochloride, and the desmethyl analogue (acetate ester values in brackets).

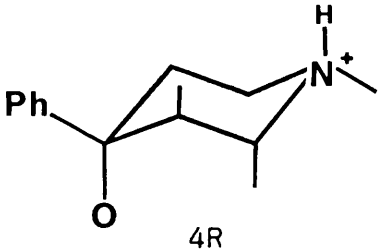


Entry	Isomer	ED_{50} mg/kg mice(hpm)	rats(twt)
1.	Desmethyl analogue	0.6(4.7)	
2.	α	1.6(6.5)	1.25
3.	β	30.7(toxic)	10.0
4.	γ	0.28(0.26)	0.04

The antipodal forms of the 2,3-dimethyl analogues have not been examined yet. Nevertheless, the racemic mixture of the most potent isomer (γ-isomer) is about 4 times as active as the reversed ester of pethidine, and 100 times as active as the racemic β-isomer. This result is in accord with the stereochemical structure-activity correlations enumerated above. In the 4S antipode, both



4S



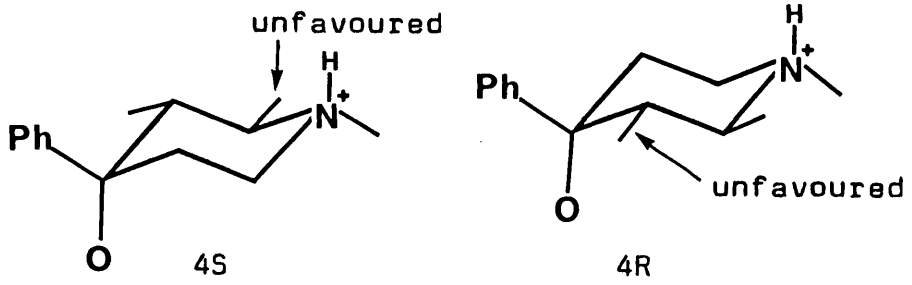
4R

ED_{50} mg/kg (mice hpm)	racemic mixture	0.28
	desmethyl analogue	0.6

178

methyl groups are placed in favourable orientations, the axial 3-methyl group on the Pro-4S edge having a potency raising influence. It is therefore expected that the 4S antipode will be much more potent than the 4R form in which, although the 2-methyl is favourably placed, the axial 3-methyl on the Pro-4R edge is disadvantageous to activity (cf β-prodine,172, page 136; and the α-2,5-dimethyl analogue of similar configuration,176, page 138).

The very weak analgesic potency of the racemic β-isomer (179) is readily explained from the absolute orientations of the methyl substituents. In both antipodal forms, while none of the methyl groups are placed in potency enhancing orientations, at least one methyl is disad-



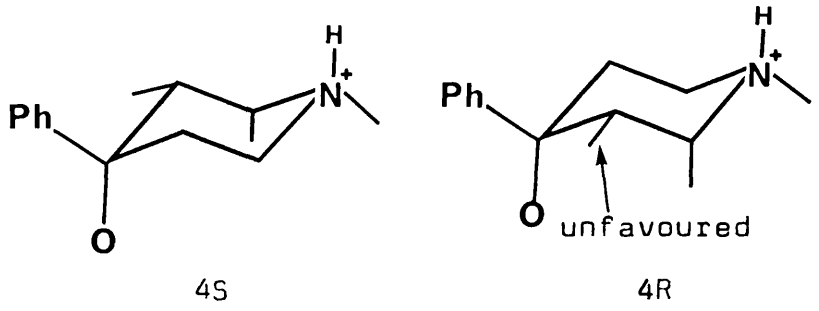
(ED_{50} mg/kg, mice hot plate test;

racemic mixture	30.7
desmethyl analogue	0.6

179

vantageously placed (cf Table XII, R = Me, page 134; and the β-2-methyl analogue, 173, page 137).

The α-isomer is represented by equatorial 4-phenyl chair conformations with equatorial 3-methyl, and axial 2-methyl substituents (180). Of the two antipodal forms,



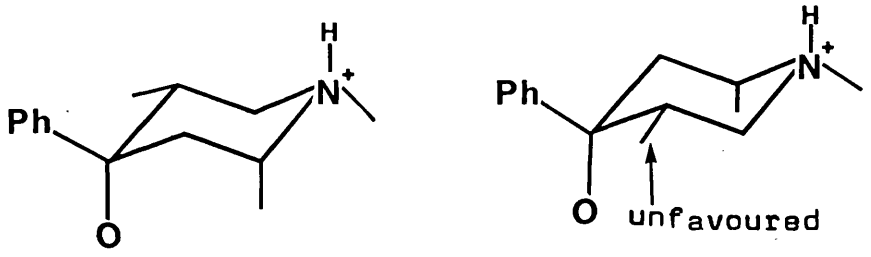
ED_{50} mg/kg;

racemic mixture	1.6
desmethyl analogue	0.6

180

the 4S form is expected to be active with a potency close to that of the desmethyl analogue, since the orientations of both methyls, while not being detrimental to activity, are not expected to enhance the analgesic potency. On the

other hand, the 3-methyl is unfavourably placed in the 4R isomer. The 4R antipode may therefore be inactive or weakly so. This analysis is in accord with the finding that the desmethyl analogue is about twice as active as the racemic mixture of the α-isomer. This view is also supported by the data on the racemic mixture of the β-2,5-dimethyl analogue of similar configuration (181) with the 2-methyl advantageously placed in the 4S isomer giving a higher analgesic activity, compared to the desmethyl analogue.

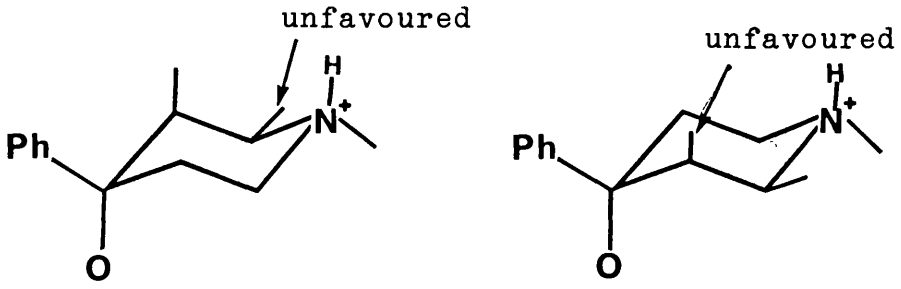


4S 4R

ED_{50} mg/kg; racemic mixture 0.6 (2.6 acetate)
desmethyl analogue 0.85 (4.7 acetate)

181

The δ-isomer, by elimination, has the configuration in which at least one methyl is unfavourably placed in each of the antipodal forms (182) in accord with the finding that the δ-isomer is inactive (Mastryukov & Shvetsov, 1961). Thus, on the basis of the presently available evidence, the stereochemical structure-activity relationships in the 1,2,3-trimethyl-4-phenyl-4-propionoxypiperidine analgesics correlate well with similar relationships in other substituted reversed esters of pethidine.



4S 4R

(Racemic mixture; inactive)

182

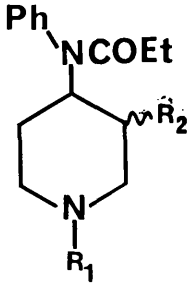
SECTION TWO

Analogues Of Fentanyl.

The similarities in the stereochemical structure-activity relationships of the 3-methyl substituted analogue of fentanyl and those of the analogous substitution in the prodines prompted the proposal that fentanyl might represent a variant of the 4-phenylpiperidine analgesics of the pethidine and its reversed ester type (Casy, 1978). In the 3-methyl substituted analogue of fentanyl, a cis-methyl configuration next to the phenylpropionamido group causes a substantial rise in the analgesic potency of the parent compound, while a trans-configuration has little or no influence on activity (Casy, 1973; van Bever et al, 1974), the effects of which are same in the 4-phenylpiperidine analgesics of the pethidine type (Casy, 1973). The same proposal was also supported by the finding that the phenolic congeners in both classes are inferior in opiate affinity and/or antinociceptive potency to respective parent compounds (Lobbezoo et al, 1980; Portoghese et al, 1981). An examination of higher 3-alkyl analogues of fentanyl was carried out to investigate further comparative structure-activity relationships in the two groups of analgesics, the result of which are presented in Table XIII.

In the 3-allyl analogues of the prodines, the potency of the parent compound is raised several fold by trans-substitution, but depressed by cis (Bell & Portoghese, 1973). The cis 3-allyl analogue of fentanyl proved to be

Table XIII. Analgesic Potency Of Some Analogues Of Fentanyl.



Entry	R_1	R_2	Isomer designation	ED_{50} mg/kg (i.v rat twt)
1.	Me-	H	-	inactive (Casy, et al, 1969)
2.	Me-	Allyl	cis	10.0
3.	$PhCH_2CH_2$-	H	-	0.011(Casy, et al, 1968)
4.	$PhCH_2CH_2$-	Allyl	cis	0.08
5.	$PhCH_2CH_2$-	n-Propyl	cis	0.02
6.	$PhCH_2CH_2$-	n-Propyl	trans	0.04

0.13 to 0.14 times as active as the parent compound (Table XIV, entries 3&4), a result apparently in close correspondence with the influence of a cis-3-allyl on the potency of the reversed esters of pethidine. However, a result from an independent source quoted a similar order of analgesic potency (ED_{50} mg/kg 0.04) for both the cis- and trans-3-allyl fentanyl derivatives (Janssen Pharmaceutica,

1982), in contradiction of the expected order of potency in the two diastereoisomers. The data on the 3-propyl analogues (Table XIV, entries 5 & 6) are also contrary to the order of potency observed for the 3-propyl analogues of the reversed ester of pethidine (Iorio et al, 1972). While the cis-3-propyl fentanyl derivative proved to be more potent than the trans-isomer (ED_{50} mg/kg 0.02, and 0.04 respectively), the analogous cis-3-propyl derivative of the reversed ester of pethidine is less potent than the trans-isomer (ED_{50} mg/kg, trans 2.0, cis 14.7).

The fact that these results are clearly not in close correspondence with the observed trend in the reversed esters of pethidine makes the question of a similarity in the relative modes of uptake of both types of analgesic look doubtful. This view is further reinforced by the markedly weak activity of the N-methyl derivative of the 3-allyl analogue of fentanyl, a further illustration of the importance of the N-phenethyl feature of fentanyl to activity in contradistinction to the pethidine-type analgesics (Casy, et al, 1969). Further more, it should be noted that the 3-propyl and the 3-allyl derivatives of fentanyl have the same order of potency, whereas the 3-allyl derivative is much more potent than the 3-propyl analogue in the pethidine-type of analgesic . It will therefore be of great value to examine more of the antipodal forms of the methyl substituted derivatives of fentanyl to establish any links with the opiate receptor differentiation between enantiotopic edges in 4-phenylpiperidine analgesics as a means of furth-

er structure-activity correlations in both types of analgesics.

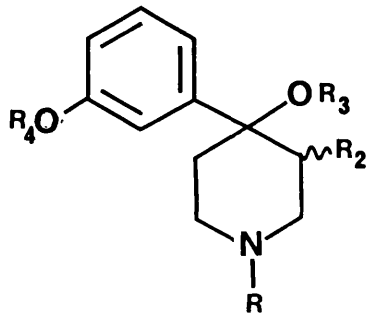
SECTION THREE.

Phenolic Analogues Of The Prodines And The 1-Phenethyl Analogue.

The report that the phenolic analogue of the reversed ester of pethidine is devoid of any significant analgesic activity (Portoghese et al, 1981) further highlights the differences between the pethidine type of analgesics and the rigid analgesics of the morphine, morphinan, and the 6,7-benzomorphan derivatives in which the presence of a meta-placed phenolic group is essential if high potency is to be achieved. Unlike the rigid analgesics however, the phenolic analogue of β-prodine was reported to possess antagonist activity (AD_{50} mg/kg, s.c rats, 6.2; mice, 9.9), and be devoid of any agonist activity in rats (Zimmerman et al, 1978). These findings are of particular interest from a stereochemical view point since it would clearly demonstrate the delicate inter-relationships between the ligand-receptor association in the agonist mode on one hand, and the antagonist mode on the other. However, the report quoted above did not include data on α-prodine analogues, and provided no chemical characterisations.

The phenolic analogues of α- and β-prodine together with those of the N-phenethyl derivatives, and the desmethyl parent compound were therefore synthesised and biologically evaluated in order to investigate this phenomenon further. The results of the biological evaluations are presented in Table XIV.

Table XIV Analgesic agonist and antagonist activities of some phenolic analogues of the reversed ester of pethidine.



Entry	R_1	R_2	R_3	R_4	Isomer	Agonist activity[a]	Antagonist activity[b]
1.	Me	H	COEt	H	-	inactive	inactive
2.	Me	Me	COEt	H	α	inactive at 10 mg/kg.	inactive
3.	Me	Me	COEt	H	β	weak activity in 1 out of 3.	inactive
4.	$PhCH_2CH_2$-	Me	COEt	H	α	inactive	active at 2.5, inactive at 0.65 mg/kg
5.	$PhCH_2CH_2$-	Me	H	COEt	α	completely inactive	

Note: a Agonist activity at 2.5 mg/kg, i.v, tail withdrawal test in rats.

b Fentanyl antagonism in rats at 2.5 mg/kg dose level.

With regard to activity, the phenolic analogue of the reversed ester of pethidine (Table XV, entry 1) is inactive either as an agonist or an antagonist in accord with the earlier report (Portoghese et al, 1981). On the other hand, of all the compounds evaluated, only the N-phenethyl derivative of α-prodine has any measurable antagonist activity (Table XV, entry 4), but it is completely devoid of any activity as an agonist. This coupled with the very weak level of agonist activity of the β-prodine analogue, with no measurable antagonist activity (Table XV, entry 3) is contrary to the earlier report by Zimmerman and co-workers. The results are, however, consistent with the observed abolition of activity in the 3-allyl phenolic congeners, a result interpreted as evidence for a divergent modes of interaction between the rigid analgesics of the morphine and the pethidine types (Portoghese et al, 1981).

These results on the other hand, are contrary to the structure-activity patterns found in the bemidone and ketobemidone series, which are narcotic analgesics classified with the reversed ester of pethidine. It was found that the analgesic potency of the non-phenolic compound (53, page 30) was enhanced when a meta-phenolic function was present (Braenden et al, 1955). Since such phenolic derivatives have little or no activity in the reversed esters of pethidine, the assumption of similarities in the relative modes of uptake of these, the bemidones, and the ketobemidones at the receptor site is open to some doubt. It

could be argued, however, that a difference in the relative stabilities of the phenolic and non-phenolic esters may be responsible for the inactivity of the phenolic reversed ester analogues, since some hydroxy or alkoxy phenyl derivatives of the reversed ester of pethidine have been found to undergo ester-oxygen heterolysis quite readily (Casy, Beckett & Armstrong, 1961). Nevertheless, a stability experiment on the phenolic analogue of the reversed ester of pethidine as solute in D_2O, monitored by the ester carbonyl resonance and the C-4 signal in the ^{13}C-n.m.r spectra over 72 hours, showed no evidence of hydrolysis. Thus the stability of the ester group does not therefore appear to be a factor responsible for the observed divergency in the structure-activity pattern of both groups. More data on specific receptor interactions are therefore needed to elucidate the structure-activity correlations in these derivatives.

C O N C L U S I O N S

The relative stereochemistry of the isomeric 1,2,3-trimethyl-4-phenyl-4-piperidinols and their preferred solute and solid conformations, together with those of the propionate and acetate esters have been unambiguously established. The β-alcohol exists as the equatorial 4-phenyl chair conformation with both the 2- and 3-methyl substituents equatorially oriented, while the α-alcohol exists mainly in the equatorial 4-phenyl chair conformation with axial 2-methyl and equatorial 3-methyl groups. The solute and solid conformations are similar for both isomers as established by X-ray crystallographic studies. The γ-alcohol provided an example of the strength of hydrogen bonding in the preferred conformation of 4-phenylpiperidinols, since it exists largely in the boat conformation stabilised by hydrogen bonding in non-polar solvents. The hydrochloride salt exists as the equatorial 4-phenyl chair, with both the 2- and 3-methyl substituents axially oriented, a rare occurence. The diaxial methyl 4-phenyl chair was shown to be the solid state conformation of the hydrochloride salt by X-ray analysis. The pharmacological results obtained for the racemic mixtures of the propionate esters of the various isomers correlate well with established structure-activity patterns in the substituted derivatives of the reversed ester of pethidine. Potency data on the antipodal forms of the α- and the γ-esters, together with the establishment of their absolute stereochemistry are needed to

confirm the proposed stereochemical structure-activity relationships.

The data obtained on the potency evaluation of the 3-alkyl derivatives of fentanyl are not in accord with the general trend in the analogous 3-alkyl derivatives of the reversed esters of pethidine. The results do not support the proposed similarity in the modes of uptake of both analgesic classes at the receptor site, and therefore still leaves the question of classification of the fentanyls open. It would therefore be worthwhile to investigate further mono- and disubstituted fentanyl derivatives to see if there be any similarities in the correlation of their absolute stereochemistry with activity, and such correlations in the reversed esters of pethidine.

The results of the biological evaluation on the phenolic analogues of the reversed ester of pethidine failed to confirm the reported antagonist activity of the β-prodine analogue. A comparative structure-activity pattern in pethidine and the bemidone and ketobemidone analgesics appears to highlight the dissimilarities between the two groups.

This work amply demonstrates the versatility of ^{13}C-n.m.r coupled with ^{1}H-n.m.r in stereochemical analyses, and in studies of piperidine chemistry.

C H A P T E R F O U R

DETAILS OF EXPERIMENTAL PROCEDURES

All melting points were determined on a Townson and Mercer capillary melting point apparatus, and are uncorrected. The Infrared spectra for the hydrogen bonding dilution studies were recorded on a Perkin-Elmer 577 Grating Infrared Spectrophotometer, while all routine IR spectra were recorded on a Pye-Unicam SP 100 Spectrophotometer. Routine 60 MHz ^{1}H-n.m.r spectra were recorded on a Perkin-Elmer R12B spectrometer, 100 MHz spectra on a JEOL PS100, and the 220-MHz spectra were recorded by the Physico-Chemical Measurement Unit (PCMU), Harwell. Proton noise off-resonance decoupled ^{13}C spectra were measured on a JEOL FX90Q NMR Spectrometer operating at 22.5 MHz; samples were prepared in 5mm o.d. tubes as approximately 10 % solutions, and the deuterium of the solvents provided the lock signal. Spectra were recorded with 8K data points, the probe temperature was 23^{o}C, and for an average spectra width of 5000Hz, a 4μs pulse corresponding to a tilt angle of 30^{o} was employed with a 1.8192s interval (acquisition time plus 1s pulse delay) between pulses.

Elemental analyses were carried out by the microanalytical laboratories of Janssen Pharmaceutica, Belgium.

Dried solvents were distilled from lime or P_2O_5 and stored over type 4A molecular sieves, or were dehydrated with freshly pressed sodium wire. Commercial chemicals were not further purified unless otherwise specified. Distillation under reduced pressure was carried out with an oil pump and conventional glass apparatus, or in some cases with Büchi GKR-50 Glass tube oven.

3-Methyl-3-penten-2-one (60).

A mixture of freshly distilled butanone (100g, 15.24 mol.) and 10 % sodium hydroxide solution (7.0 ml) was charged into a three-necked 2-litre flask equipped with a stirrer. The mixture was vigorously mixed while being cooled to 8-9°C. A solution of freshly distilled acetaldehyde (103g, 2.34 mol.) in butanone (200g) was added slowly to the mixture over a period of 5 hr. and then stirred for an additional 1 hr. Excess base was neutralised with tartaric acid (2.0g) and the mixture stirred for another 30 min. Excess butanone was distilled off over a short column and the last trace removed under reduced pressure (water pump). The aldol product was dehydrated by warming (60-80°C) with 47 % aqueous HBr (1.0 ml) for 30 min. Careful fractional distillation of the mixture gave the titled compound as a pale yellow liquid (154g, 67 % yield).
b.p 138-140°C (Kyrides, 1933; reported b.p 138-141°C).
IR spectrum (film):
γ_{max} 1660 (C=O str.) cm^{-1}.
m.p (2,4-dinitrophenylhydrazone) 181-182°C
(House & Ro, 1958; reported m.p trans 200-202°C,
cis 140-142°C)

1-(N,N-Dimethylamino)-4-methyl-4-hexen-3-one Hydrochloride(61).

A mixture of 3-methyl-3-penten-2-one (98g, 1.0 mol.), paraformaldehyde (33g, 1.1 mol.), dimethylammonium chloride

(89g, 1.1 mol), and 5 drops of conc. HCl was refluxed in absolute ethanol (200 ml) for 5 hr. The mixture was diluted with hot acetone (150 ml) and left overnight at room temperature to give a white crystalline solid. A further crop of crystals was collected by chilling the mother liquor in the refrigerator. The combined yield was 118g (60 %). Recrystallisation was from ethanol-acetone mixture.

m.p 165.5-166°C (with decomposition).

IR spectrum (nujol):

ν_{max} 1650 (C=O str.), 2500 ($\overset{+}{N}$-H str.) cm^{-1}.

^{13}C-nmr spectrum: 8 carbon resonances (3 quartets, 2 triplets, 1 doublet, and 2 singlets in the off-resonance spect.).

^{1}H-nmr spectrum characteristics: δ 6.8 ppm (quartet) due to the vinylic proton.

1,2,3-Trimethyl-4-piperidone (58)

A mixture of the Mannich base (100g, 0.52 mol), 33 % solution of methylamine in ethanol (160 ml, 1.7 mol), water (60 ml, 3.3 mol), and absolute ethanol (200 ml) was stirred overnight (18 hr) at room temperature. Excess methylamine and ethanol were distilled off, and the residual mixture extracted with ether (2 x 100, 4 x 25 ml). The ethereal extract was dried ($MgSO_4$) and the solvent removed in vacuo. Careful fractional distillation of the residue at a reduced pressure gave the titled compound as a colour-

less oil (44.8g, 60 %) which was a cis-trans mixture.

b.p 66-68°C/6mm Hg (Nazarov et al, 1961; reported b.p 63-64°C/2.5 mmHg.)

IR spectrum (film):

υ_{max} 1702 cm^{-1} (C=O str.)

Anal. calcd. for $C_9H_{18}NOI$ (methiodide salt), C 38.17, H 6.40, N 4.94 %. Found C 38.02, H 6.54, N 4.89 %.

Methyl 1-ethylvinyl Ketone (71).

2-Pentanone (430g, 5 mol) and paraformaldehyde (30g, 1 mol) were mixed in a three-necked flask equipped with stirrer, reflux condenser, and thermometer. The cloudy reaction mixture was heated to 45°C and 3.5 ml of 0.5N alcoholic KOH was added. The mixture was stirred at 45-50°C for 1.5 hr, during which time the reaction was complete (negative test for formaldehyde with Tollens reagent). The slight excess of alkali was neutralised with 1.0 ml of 2N acetic acid in 2-pentanone. Excess pentanone was removed by distillation, and the residue (crude aldol product) was heated to 80°C with 1.0 ml of 47 % aqueous HBr and 0.5g of hydroquinone to prevent polymerisation. Careful fractional distillation of the product gave the ketone as a pale yellow liquid (42g).

b.p 122-124°C/atmospheric pressure.

IR spectrum (film):

υ_{max} 1665 cm^{-1} (C=O str.)

Methyl-isopropenyl Ketone (74)

The ketone was synthesised from butanone (350g, 5 mol) and paraformaldehyde (30g, 1 mol) following the same procedure as described for methyl 1-ethylvinyl ketone above. The yield of product was 38g.

b.p 97-98°C (Landau et al,1947; reported b.p 96-97°C)

IR spectrum (film):

ν_{max} 1665 cm^{-1} (C=O str.).

1-Methyl-3-ethyl-4-piperidone (73)

Method A.

A mixture of methyl 1-ethylvinyl ketone (49g,0.5 mol), paraformaldehyde (18g, 0.6 mol), and dimethylamine hydrochloride (40.5g, 0.5 mol) was refluxed in absolute ethanol (150 ml) containing 5 drops of conc. HCl for 6 hr. The homogenous mixture was cooled and mixed with 33 % methylamine solution in ethanol (100 ml) and water (50 ml). The mixture was stirred at room temperature for 24 hr, concentrated, and extracted with ether. Evaporation of the ethereal extract gave the crude product which was distilled at a reduced pressure (14.2g).

b.p 95-98°C/ water pump pressure.(Ziering et al, 1957; reported b.p 102°C/33 mmHg).

IR spectrum (film):

ν_{max} 1705 cm^{-1} (C=O str.).

Method B.

A mixture of methyl 1-ethylvinyl ketone (57.5g, 0.58 mol), paraformaldehyde (18g, 0.6 mol), and methylammonium chloride (40.5g, 0.6 mol) in absolute ethanol (100 ml) was refluxed for 4 hr with stirring. The mixture was then stirred for a further 24 hr at room temperature, concentrated, basified with 10 % sodium hydroxide solution, and extracted with chloroform. The chloroform extract was dried ($MgSO_4$), and evaporated to give an oil which was distilled under reduced pressure to give a colourless oil (22.5g).

b.p 45-47°C /1.5 mmHg.

IR spectrum (film):

ν_{max} 1705 cm^{-1} (C=O str.).

The ^{13}C-n.m.r spectrum of the ketone obtained from both methods were identical; δ 45.71(N-Me), 61.9(C-2), 51.43(C-3), 212.05(C-4), 41.27(C-5), 56.8(C-6), 20.63(3-CH_2-), and 11.75(3-CH_2-$\underline{CH_3}$) ppm.

1-(N,N-Dimethylamino)-4-methyl-4-penten-3-one Hydrochloride (75).

A mixture of methyl isopropenyl ketone (63g, 0.74 mol), paraformaldehyde (25g, 0.83 mol), and dimethylammonium chloride (62.5g, 0.8 mol) was refluxed in ethanol(100 ml) with a few drops of conc. HCl for 4 hr. The mixture was diluted with hot acetone (120 ml) and left to crystallise

at the refridgerator temperature. Needle-like crystals separated (21.0g), and was recrystallised from acetone.

m.p 120-121°C

IR spectrum (nujol):

ν_{max} 1655 (C=O str.), 2400-2600 ($\overset{+}{N}$-H str) cm^{-1}.

1,3-Dimethyl-4-piperidone (76).

A mixture of 1-(N,N-dimethylamino)-4-methyl-4-penten-3-one hydrochloride (19.76g, 0.11 mol), 33 % solution of methylamine in ethanol (24 ml, 0.25 mol), water (10.4g, 0.6 mol), and ethanol (35 ml) was stirred at room temperature for 24 hr. The mixture was concentrated and extracted with ether. Evaporation of solvent and distillation of the residue gave a colourless oil (6.2g).

b.p 64-65°C/10 mmHg. (Howton, 1945; reported b.p 43-43.4°C/5.5 mmHg).

m.p (hydrochloride salt) 195-196°C (reported m.p 194-195°C).

IR spectrum (film):

ν_{max} 1703 cm^{-1} (C=O str.).

1-Phenethyl-2,3-dimethyl-4-piperidone (70).

A mixture of 1-(N,N-dimethylamino)-4-methyl-4-hexen-3-one (49.0g), 2-phenethylamine (40.5g), and water (20g) was refluxed in ethanol (150 ml) for 3 hr. The mixture was then stirred for 24 hr at room temperature, concentrated, and extracted into ether. The ethereal extract was washed with water, dried, and evaporated to give the crude product as an oil. The oil was distilled under a reduced pressure to give 26g of the pure product, which was a cis-trans isomeric mixture.

b.p $150^{o}C/0.5$ mmHg (Buchi GKR-50).

IR spectrum (nujol):

ν_{max} 1703.cm^{-1} (C=O str).

^{13}C-n.m.r chemical shift data: Table II, page 46, entries 6 and 7.

Methiodide salts of some 1-methyl-4-phenyl-4-piperidinols.

The sample of the pure piperidinol (0.5g) was dissolved in minimum amount of ethanol. Excess iodomethane was added, and the solution thoroughly mixed. Ether was then added until the mixture was just about to be cloudy, and the mixture left to crystallise at room temperature. Recrystallisation was from methanol, ethanol, or a mixture of ethanol and ether.

1,2,5-Trimethyl-4-phenyl-4-piperidinol Methiodides.

Anal. calcd. for $C_{15}H_{24}NOI$, C 49.87, H 6.69, N 3.87 %;

α-isomer.

m.p 232-233°C (from methanol-ether).

Anal. found C 50.16, H 6.65, N 3.9 %.

β-isomer.

m.p 273.5-274°C (from ethanol).

Anal. found C 49.64, H 6.80, N 3.83 %.

γ-isomer.

m.p 218-218.5°C (from ethanol-ether).

Anal. found C 49.68, H 6.78, N 3.87 %.

1,2-Dimethyl-4-phenyl-4-piperidinol Methiodide.

α-isomer.

m.p 198-199°C (from ethanol-ether).

Anal. calcd. for $C_{14}H_{22}NOI$, C 48.4, H 6.38, N 4.03 %;

Found C 47.89, H 6.34, N 4.03 %.

1,2,3-Trimethyl-4-phenyl-4-piperidinol (78).

A solution of 1,2,3-trimethyl-4-piperidone (65g, 0.46 mol) in dry ether (50 ml) was carefully added with stirring to a cooled ethereal solution of phenyllithium made from Lithium (9.18g, 1.3 gr.at.), bromobenzene (103.7g, 0.66 mol), and dry ether (200 ml). The mixture was stirred for 1 hr at room temperature. The product complex was decomposed with 5N hydrochloric acid (300 ml) with cooling. The ethereal portion was washed with water (2 × 50 ml), and the combined aqueous portions basified with sodium hydroxide pellets (60g). The aqueous mixture was extracted with ether (2 × 100, 4 × 50 ml). While extracting with ether, a solid (13g), corresponding to the α-isomer, separated at the water-ether interphase and was collected. The ethereal extract was dried ($MgSO_4$) and evaporated to give a brownish oil (53g) which solidified in the fridge. Fractional crystallisation of the isomeric mixture from toluene and iso-octane afforded the pure α-isomer (10g), the pure β-isomer (15g), and a mixture of the two isomers (16g). The combined mother liquors was converted to the hydrochloride salt from which the γ-isomer was isolated. It was recrystallised from ethanol-ether mixture.

α-isomer.

m.p (base) 144-145.5°C (Nazarov et al, 1961; reported m.p 143-145°C).

(methiodide salt) 221.5-222.5°C

Anal. calcd. for $C_{15}H_{24}NOI$, C 49.87, H 6.69, N 3.87 %;

Found C 49.65, H 6.62, N 3.80 %.

β-isomer.

m.p (base) 117.5-119°C (reported m.p 118-119°C).

(methiodide salt) 234°C.

Anal. calcd. for $C_{15}H_{24}NOI$, C 49.87, H 6.69, N 3.87.%.

Found C 49.72, H 6.75, N 3.89.%.

γ-isomer.

m.p (hydrochloride salt) 240-242°C (reported m.p 248°C).

(methiodide salt) 234°C.

Anal. calcd. for $C_{15}H_{24}NOI$, C 49.87, N 3.87, H 6.69 %.

Found C 49.94, H 6.55, N 3.67 %.

1,2,3-Trimethyl-4-phenyl-4-acetoxypiperidine Hydrochloride (79b).

A mixture of the pure isomers of 1,2,3-trimethyl-4-phenyl-4-piperidinol (1.0g, 0.0043 mol), and freshly distilled acetyl chloride (1.0g, 0.014 mol) was refluxed in dry toluene (8 ml) for 12 hr. The mixture was kept in the refridgerator overnight, and the solid hydrochloride salt which separated was collected. Recrystallisation from ethanol-ether mixture gave the pure acetate ester hydrochloride salt of the corresponding isomers in up to 90 % yield in each case.

α-isomer.

m.p 182°C

IR spectrum (nujol):

ν_{max} 1720 (C=O str.), 3485 (H_2O) cm^{-1}.

Anal. calcd. for $C_{16}H_{24}NO_2Cl.\frac{1}{2}H_2O$, C 62.70, H 8.16, N 4.57 %.

Found C 63.05, H 8.13, N 4.58 %.

β-isomer.

m.p 244°C.

IR spectrum (nujol):

ν_{max} 1720 cm^{-1}(C=O str).

Anal. calcd. for $C_{16}H_{24}NO_2Cl$, C 64.70, H 8.12, N 4.70 %.

Found C 64.70, H 8.36, N 4.97 %.

γ-isomer.

m.p 195-196°C.

IR spectrum (nujol):

ν_{max} 1720 cm^{-1}(C=O str).

Anal. calcd. for $C_{16}H_{24}NO_2Cl$, C 64.70, H 8.12, N 4.70 %.

Found C 64.88, H 8.32, N 4.74 %.

1,2,3-Trimethyl-4-phenyl-4-propionoxypiperidine Hydrochloride (79a).

A mixture of the pure isomers of 1,2,3-trimethyl-4-phenyl-4-piperidinol (1.0g, 0.0043 mol), freshly distilled propionyl chloride (1.0g, 0.012 mol), and dry toluene (8 ml) was refluxed for 12 hr. The mixture was left overnight in

the fridge, and the solid hydrochloride salt which separated was collected, and recrystallised from ethanol-ether mixture to give the propionate ester of the corresponding alcohols.

α-isomer.

m.p 154-155°C.

IR spectrum (nujol):

ν_{max} 1735 cm^{-1}(C=O str).

Anal. calcd. for $C_{17}H_{26}NO_2Cl.\frac{1}{2}H_2O$, C 63.54, H 8.41, N 4.36 %.

Found C 63.46, H 8.49, N 4.22 %.

β-isomer.

m.p 236°C.

IR spectrum (nujol):

ν_{max} 1736 cm^{-1}(C=O str).

Anal. calcd. for $C_{17}H_{26}NO_2Cl$, C 65.4, H 8.4, N 4.4 %;

Found C 65.2, H 8.4, N 4.3 %.

γ-isomer.

m.p 189-190°C.

IR spectrum (nujol):

ν_{max} 1735 cm^{-1}(C=O str).

Anal. calcd. for $C_{17}H_{26}NO_2Cl$, C 65.4, H 8.4, N 4.4 %;

Found C 65.5, H 8.4, N 4.5 %.

1-Methyl-4,4-diallyloxypiperidinium Tosylate (120).

p-Toluene sulphonic acid monohydrate (50.5g, 0.255 mol) was refluxed in a mixture of cyclohexane (300 ml) and toluene (300 ml) until 5.2 ml. of water was collected in a Dean Stark apparatus, and an additional 100 ml. of solvent was distilled off to remove any traces of water. The mixture was cooled, and 1-methyl-4-piperidone (28.25g, 0.25 mol), 2,2-dimethoxypropane (28.6g, 0.25 mol), and allyl alcohol (37.75g, 0.6 mol) were added to the mixture. The mixture was refluxed under a column fitted with a "variable" take-off head (achieved by connecting taps and adaptors to the column such that the flow of distillate can be regulated). The head temperature was maintained at 52-64°C until 45 ml. of distillate was collected, then allowed to rise gradually to about 70°C until another 10 ml. of distillate was collected (6 hr). The mixture was allowed to cool slowly at room temperature and the first crop of crystals collected. An additional crop of crystals was collected by chilling the mother liquor in the fridge. The combined yield was 71.4g (72 %). Recrystallisation from toluene afforded the pure compound.

m.p 124.5-126°C (Bell & Portoghese, 1973; reported m.p 125.5-126°C from benzene).

1-Methyl-3-allyl-4-piperidone (122).

A mixture of 1-methyl-4,4-diallyloxypiperidinium tosylate (113g, 0.306 mol), p-TsOH.H_2O (0.2g), and toluene (400 ml) was refluxed under a column fitted with a "variable" take-off head. The head temperature was maintained at 91-94°C while collecting the distillate (35 ml). The head temperature was then allowed to rise gradually until an additional 20 ml. was collected. The mixture was thereafter refluxed for 1.5 hr., cooled, and the lower layer run into water (100 ml). The upper layer was washed with water (2× 50 ml), and the combined aqueous portions basified (20 % NaOH) and extracted with ether. The ethereal extract was dried ($MgSO_4$), evaporated, and the residual oil distilled to give a colourless oil (27.5g).

b.p 72-74°C / 2.5 mmHg. (Bell & Portoghese, 1973; reported b.p 93-94°C / 10 mmHg).

IR Spectrum (film):

ν_{max} 1705 cm^{-1} (C=O str).

^{1}H-n.m.r Spectrum: δ 5.05(doublet, 1H), 5.2(br. singlet, 1H), and 5.7 ppm(multiplet, 1H) due to the allylic protons.

1-Methyl-3-allyl-4-anilidopiperidine (Schiff base 123).

A mixture of 1-methyl-3-allyl-4-piperidone (30g, 0.195 mol), freshly distilled aniline (20.4g, 0.21 mol),

p-TsOH (0.1g), and toluene (250 ml) was refluxed under a Dean Stark apparatus until approximately the theoretical equivalent of water was collected (3.5 ml, approx. 18 hr). The mixture was evaporated and the residue distilled under reduced pressure to give a pale yellow oil (19.5g, 64 %).

b.p 139-141^{o}C/3.0 mmHg.

IR spectrum (film):

ν_{max} 1660 cm^{-1} (C=N str).

^{13}C-n.m.r spectrum; C-4 resonance δ 172.6 ppm (characteristic of C=N-Ph group).

1-Methyl-3-allyl-4-anilinopiperidine (124).

Method A.

Sodium borohydride (2.6g, 0.072 mol) was added in small portions to a solution of the schiff base (18g, 0.072 mol) in methanol (70 ml). The mixture was refluxed on a water bath for 1 hr., and then diluted with water (50 ml). The mixture was concentrated and extracted with ether. The ethereal extract was washed with water, dried ($MgSO_4$), and evaporated to give a faintly yellow oil (15.2g), which was distilled under reduced pressure.

b.p 156^{o}C/o.7 mmHg (Buchi GKR-50).

IR spectrum (film): Absence of the absorption at 1660 cm^{-1}.

^{13}C-n.m.r spectrum: Absence of δ 172.6 ppm signal, displayed 14 pairs of carbon resonances in the alicyclic region (18:1 ratio of isomers).

Method B.

A solution of the Schiff base (8g, 0.044 mol) in dry ether (20 ml) was added dropwise to a suspension of $LiAlH_4$ (1.92g, 0.048 mol) in dry ether (50 ml). The mixture was refluxed for 1 hr. Water (1.92 ml) was cautiously added to the stirred mixture, followed by 5N NaOH solution (1.0 ml), and finally 7.0 ml. of water was added. The white precipitate which formed was filtered off, and the ethereal fraction evaporated. Distillation of the residue gave the titled compound (6.2g) as an isomeric mixture in similar proportions to the product obtained by the $NaBH_4$ method.

cis-1-Methyl-3allyl-4-(N-phenylpropionamido)piperidine (125).

A mixture of the isomeric 1-methyl-3-allyl-4-anilinopiperidine (15.0g, 0.055 mol), propionic anhydride (12g, 0.092 mol), and dry toluene (75 ml) was refluxed for 12 hr. The mixture was cooled, and basified (10 % NaOH). The organic layer was separated, washed with water, dried, and evaporated to give an oily residue (14.5g) which was an isomeric mixture of the titled compound as judged from the ^{13}C-n.m.r spectrum. A TLC analysis of the crude product showed four spots.

The oil was chromatographed on a column of silica gel (200g) and eluted with chloroform. Fractions were

collected in 15-ml portions. Fractions 1-13 (1.3g) were mixtures of aniline and the amide, 14-18 (6.8g) contained the major isomer, while 19-30 (3.4g) was a mixture of the major and minor isomers which could not be separated by further columns or fractioal crystallisation of the salt. The pure fraction was converted to the hydrochloride salt. Recrystallisation was from ethanol-ether mixture.

m.p 136-137°C.

IR spectrum (nujol):

ν_{max} 1660 cm^{-1} (C=O amide str.).

Anal. calcd. for $C_{18}H_{27}N_2OCl$, C 66.9, H 8.4, N 8.6 %;

Found C 66.7, H 8.6, N 8.6 %.

Methiodide salt; m.p 195-196°C.

Anal. calcd. for $C_{19}H_{29}N_2OI$, C 53.21, H 6.82, N 6.54 %;

Found C 52.97, H 6.99, N 6.16 %.

1-Methyl-4-anilinopiperidine (116).

A mixture of 1-methyl-4-piperidone (34g, 0.30 mol), freshly distilled aniline (35g, 0.38 mol), zinc chloride (0.1g), and dry xylene (500 ml) was refluxed under a Dean Stark apparatus until 5.7 ml. of water was collected (12 hr). The solvent was evaporated and the residue distilled to give the Schiff base (115) as a light yellow oil (33.8g).

IR spectrum (film):

ν_{max} 1660 cm^{-1} (C=N- str).

^{13}C-n.m.r spectrum: C-4 resonance at δ 172.5 ppm, displayed 5 carbon resonances in the alicyclic region due to the non-symmetry of the molecule as a result of the geometry of the anil.

Sodium borohydride (6.0g) was added in small portions to a solution of the Schiff base (30g) in methanol (75 ml), and the mixture refluxed for 1 hr. on a water bath. The mixture was diluted with water until it was slightly turbid, and then set aside to yield colourless crystals (27.5g). The sample was recrystallised from aqueous methanol.

m.p 80-81°C (Casy et al, 1969; reported m.p 81-82°C from aqueous ethanol).

1-Methyl-4-(N-phenylpropionamido)piperidine (117).

A mixture of 1-methyl-4-anilinopiperidine (10g, 0.053 mol), propionic anhydride (9.1g, 0.07 mol), and dry toluene (50 ml) was refluxed for 12 hr. The mixture was basified (10 % NaOH), the organic layer separated, washed with water, and dried ($MgSO_4$). Removal of the solvent gave the titled compound (9.2g). It was converted to the hydrochloride salt and recrystallised from ethanol-ether mixture.

m.p 263-264°C (Casy et al, 1969; reported m.p 265-266°C).

IR spectrum (nujol): ν_{max} 1660 cm^{-1} (C=O amide str).

Methiodide salt; m.p 214-215°C.

1-Carbethoxy-4-(1-pyrollidino)piperid-4-ene (127).

A mixture of 1-carbethoxy-4-piperidone (35g, 0.204 mol), pyrollidine (17.8g, 0.25 mol), p-TsOH (0.1g), and dry toluene (150 ml) was refluxed in a Dean Stark apparatus for 3 hr. The mixture was cooled, the solvent removed, and the residue distilled under reduced pressure to give the enamine as a pale yellow oil (39.8g, 87 %).
b.p 130°C/0.8 mmHg (Buchi GKR-50).

1-Carbethoxy-3-allyl-4-piperidone (129).

A solution of allylbromide (39.7g, 0.32 mol) in dry acetonitrile was added dropwise to a stirred solution of the enamine (39.7g, 0.17 mol) in acetonitrile (150 ml) under nitrogen gas. The mixture was refluxed for 72 hr. under nitrogen, cooled, and then boiled with water (100 ml) for 1 hr. to hydrolyse the iminium salt. Extraction of the mixture with chloroform (2 × 100, 4 × 25 ml) and removal of the solvent gave a residue which was distilled under reduced pressure to give a colourless oil (25g, 70 % yield).
b.p 110°C/0.3 mmHg (Buchi GKR-50).

TLC analysis of the oil (silica, chloroform) gave four spots corresponding to the starting ketone for the enamine, the titled compound, and an isomeric mixture of the 3,5-diallyl substituted ketone.

Purification of the sample: A sample of the total product (40g) was adsorbed onto a column of silica gel (800g),

and eluted with a mixture of chloroform-ethylacetate (80:20). Fractions were collected in 25-ml portions. Fractions 1-4 (6.5g), showing two spots on tlc, corresponded to the isomeric 1-carbethoxy-3,5-diallyl-4-piperidone. Fractions 8-13 (25.2g), one spot on tlc, corresponded to the titled compound, while the remaining fractions (7.0g) contained a mixture of the titled compound and 1-carbethoxy-4-piperidone. A similar experiment with iodoethane gave a yield of less than 15 % of total neutral ketone after hydrolysis.

1-Carbethoxy-3-allyl-4-anilidopiperidine (Schiff base).

The above-named Schiff base was prepared from 1-carbethoxy-3-allyl-4-piperidone (21.4g, 0.1 mol), freshly distilled aniline (14.0g, 0.15 mol), and a few crystals of p-TsOH in toluene (150 ml) following the procedure described for Shiff base 123,(page 169). The yield of product was 26.5g (92 %) as a yellow oil.

b.p 155^{o}C/0.3 mmHg (Buchi GKR-50).

IR spectrum (film):

ν_{max} 1660 cm^{-1} (C=N- str)

^{13}C-n.m.r spectrum: C-4 resonance δ172.5 ppm (C=N-Ph).

cis-1-Carbethoxy-3-allyl-4-(N-phenylpropionamido)piperidine (137).

1-carbethoxy-3-allyl-4-anilidopiperidine (26.5g,

0.092 mol) was reduced with $NaBH_4$ (3.5g) in methanol (100 ml). The distilled product from the reduction procedure (22.2g, b.p 180°C/0.2 mmHg, Buchi GKR-50) was refluxed with propionic anhydride (13.0g) for 12 hr. The mixture was cooled and basified with 10 % NaOH solution. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated. Distillation of the residue gave a semi-solid oil (20.5g) which when diluted with n-hexane yielded white crystalline solid on standing at room temperature. The crystals were isomerically pure and corresponded to the titled compound. Recrystallisation was from n-hexane-acetone mixture.

m.p 76-78°C

Anal. calcd. for $C_{20}H_{28}N_2O_3$, C 69.73, H 8.26, N 8.11 %;
Found C 69.73, H 8.19, N 8.13 %.

cis-1-Phenethyl-3-allyl-4-(N-phenylpropionamido)piperidine (140).

A sample of cis-1-carbethoxy-3-allyl-4-(N-phenylpropionamido)piperidine (6.0g) was refluxed with KOH (7.1g) in isopropanol (70 ml) for 48 hr. The mixture was cooled, evaporated, and the residue dissolved in water. Extraction of the aqueous mixture with chloroform, and removal of the solvent gave an oil (3.4g) which was distilled under a reduced pressure (b.p 130°C/0.2 mmHg, Buchi GKR-50). Both the IR and ^{13}C-n.m.r spectra lacked the signals due

to the 1-carbethoxy, and the amide groups.

The oil (3.4g, 0.0158 mol) was refluxed with a mixture of 2-phenethylbromide (3.1g, 0.0168 mol), sodium carbonate (6.4g, 0.0607 mol), dry acetonitrile (60 ml), and a few crystals of potassium iodide for 12 hr. The mixture was cooled, filtered, and the filtérate evaporated to give an oily residue. The base was isolated as the hydrobromide salt (7.3g, m.p 225-226^{o}C). The salt was reconverted to the base and acylated with propionic anhydride (8.0g) in the usual manner to give the titled compound (4.05g), which was converted to the hydrochloride salt. Recrystallisation was from ethanol-ether mixture.

m.p 113.5-116^{o}C.

IR spectrum (nujol):

ν_{max} 1660 (C=O amide str), 3490 (H_2O) cm^{-1}.

Anal. calcd. for $C_{25}H_{33}N_2OCl.\frac{1}{2}H_2O$, C 71.15, H 7.88, N 6.63 %; Found C 71.39, H 8.28, N 6.40 %;

calcd. for $C_{25}H_{33}N_2OCl.H_2O$, C 69.60, H 8.12, N 6.50 %;

Found C 70.07, H 7.69, N 6.34 %.

cis-1-Carbethoxy-3-propyl-4-anilinopiperidine (141 & 142).

Method A.

A sample of 1-carbethoxy-3-allyl-4-anilidopiperidine (6.0g) in ethanol was hydrogenated under pressure (3 atm) at room temperature over active Raney Nickel catalyst for 6 hr. The mixture was filtered, and the solvent evaporated to give an oily residue which later solidified.

Recrystallisation from n-heptane gave the titled compound (4.5g)

m.p 75.5-77°C.

Anal. calcd. for $C_{17}H_{26}N_2O_2$, C 70.30, H 9.02, N 9.64 %;
Found C 70.39, H 9.28, N 9.63 %.

Hydrogenation of the Schiff base over Adam's catalyst (PtO_2) gave the same product in similar isomeric proportions.

Method B.

A sample of the Schiff base (9.0g) was reduced with sodium borohydride (2.0g) in the usual way. The resulting product (8.0g) was catalytically hydrogenated over active Raney Nickel catalyst (3 atm., room temp.) in ethanol. The product (5.0g) corresponded to the titled compound, and was recrystallised from n-heptane.

m.p 75-76°C.

Both the ^1H- and ^{13}C-n.m.r spectra of the compound were identical with those of the product obtained by Method A.

trans-1-Carbethoxy-3-propyl-4-anilinopiperidine (141 & 142).

The combined mother liquors from the catalytic hydrogenation reactions was evaporated. The resulting isomeric mixture (2.5g) was chromatographed on a silica

gel column (30g), and eluted with chloroform. Fractions were collected in 10-ml portions. Fraction 1-6 (1.8g) was about an 80:20 mixture of the trans- and cis-isomers, while the remaining fractions contained mainly the cis-isomer. The 80:20 isomeric mixture was rechromatographed twice on silica column (20g) and eluted with chloroform, and the fractions were monitored by tlc. Fractions made up of mainly the trans-isomer (with just traces of the cis-) were bulked (1.2g), and converted to the oxalate salt. The first crop of cystals (1.1g) was made up of the trans-isomer, and it was isomerically pure, as judged from the tlc characteristics. The salt was recrystallised from a methanol-ether mixture.

m.p 186-188°C.

cis-1-Phenethyl-3-propyl-4-(N-phenylpropionamido)piperidine (144).

A sample of cis-1-carbethoxy-3-propyl-4-anilinopiperidine (6.2g) was decarbethoxylated with KOH (7.1g) in isopropanol (50 ml). The product (4.3g) was refluxed with a mixture of 2-phenethylbromide (3.9g), sodium carbonate (8.1g), a few crystals of KI, and acetonitrile (80 ml) for 12 hr. The reaction mixture was worked up as usual, and the product isolated as the hydrochloride salt

(7.4g). Recrystallisation was from methanol-ether mixture (m.p 199-201°C). The sample was reconverted to the base (5.2g) and acylated with propionic anhydride (3.2g) in toluene (50 ml) to give the titled compound (5.9g). The sample was converted to the hydrochloride salt, and recrystallised from an ethanol-ether mixture.

m.p (hydrochloride salt) 163.5-166°C.

(oxalate salt) 134-136°C.

IR spectrum (nujol):

ν_{max} 1660 cm^{-1} (C=O amide str).

Anal. calcd. for $C_{25}H_{35}N_2OCl$, C 72.34, H 8.50, N 6.75 %;

Found C 71.76, H 8.48, N 6.77 %.

trans-1-Phenethyl-3-propyl-4-(N-phenylpropionamido)piperidine (144).

The titled compound was prepared from trans-1-carbethoxy-3-propyl-4-anilinopiperidine (0.8g) with proportionate amount of reactants following the procedure describe for the cis-isomer. The product was isolated as the oxalate salt, part of which was basified and converted to the hydrochloride salt for pharmacological evaluation.

m.p (hydrochloride salt) 124-126°C, from ethanol-ether.

(oxalate salt) 190-191°C, from ethanol.

Anal. calcd. for $C_{27}H_{36}N_2O_5$, C 69.20, H 7.74, N 5.97 %;

Found C 69.49, H 7.82, N 6.07 %.

1,3-Dimethyl-4-phenyl-4-propionoxypiperidine (Prodines).

A solution of 1,3-dimethyl-4-piperidone (30g, 0.236 mol) in dry ether was added to a stirred, cooled solution of phenyllithium, made from lithium (3.92g, 0.58 gr. at.), bromobenzene (43.96g, 0.280 mol), and dry ether (250 ml). The mixture was stirred for 1.5 hr. at room temperature. A solution of propionic anhydride (42.94g, 0.33 mol) in dry ether was added to the stirred, ice-cooled mixture, and the mixture stirred for a further 1 hr. at room temperature. The mixture was then poured onto a mixture of 5N HCl (200 ml) and crushed ice. The ethereal layer was washed with water, and the combined aqueous portions basified with 10 % NaOH solution. Extraction with ether, and removal of the solvent gave a brownish oil (49.5g), which was an isomeric mixture of the titled compound. The oil was distilled under a reduced pressure (b.p 150°C/0.4 mm, Buchi GKR-50).

The α-isomer (major) was isolated as the hydrochloride salt (40.16g). Recrystallisation from an ethanol-ether mixture afforded the pure white crystalline salt. m.p 219-220.5°C (Ziering & Lee, 1947; reported m.p 220-221°C).

After collecting as much of the α-salt as possible, the combined mother liquor was reconverted to the base (7.5g). A solution of the free base in acetone (8 ml) was mixed with a solution of dl-malic acid (3.8g) in acetone (10 ml), and the mixture allowed to crystallise at room temperature.

The crude malate salt of the α-isomer was collected. The resulting mother liquor was evaporated, and the residue converted to the free base. On conversion of the crude base to the hydrochloride salt, the β-isomer (minor) salt (2.6g) separated. Fractional crystallisation from ethanol-ether mixture got rid of the traces of the α-isomer, and the pure β-salt was obtained.

m.p 198-200°C (Ziering & Lee, 1947; reported m.p 199-200°C).

1,3-Dimethyl-4-phenyl-4-piperidinol (Prodinols).

A solution of the α-prodine base (10g, 0.038 mol) in ether was added dropwise to a stirred suspension of $LiAlH_4$ (1.45g, 0.038 mol) in dry ether (50 ml). The mixture was stirred for an additional 30 minutes, and worked up as described in the procedure for $LiAlH_4$ reduction (see page 171). The product was a solid which on recrystallisation from petroleum ether (60/80) afforded the pure α-prodinol.

m.p 100-100.5°C (Ziering *et al*, 1957; reported m.p 100-101°C).

Methiodide salt: m.p 153-154°C.

Anal. calcd. for $C_{14}H_{22}NOI$, C 48.42, H 6.38, N 4.03 %;

Found C 47.75, H 6.34, N 3.94 %.

β-Prodinol. The β-isomer was prepared following the same

procedure.

m.p 118-118.5°C (reported m.p 116-118°C).

Methiodide salt: m.p 230-231°C.

Anal. calcd. for $C_{14}H_{22}NOI$, C 48.42, H 6.38, N 4.03 %;

Found C 48.13, H 6.43, N 3.90 %.

m-(2-Tetrahydropyranyloxy)bromobenzene (151).

m-Bromophenol (50g) was added dropwise to a mixture of dihydropyran (100g) with a few drops of hydrochloric acid with stirring, while the mixture was being cooled in ice. The mixture was stirred for an additional 1.5 hr. at room temperature, after which it was diluted with ether (100 ml). The ethereal mixture was washed with 10 % NaOH solution (2 x 25 ml), water, and then dried (anhy. K_2CO_3). Evaporation of the solvent left a residue which solidified at the refrigerator temperature. Recrystallisation from n-hexane afforded the pure, colourless crystals of the titled compound (32.2g, 87 % yield).

m.p 39-40°C (Zimmerman, 1981; reported an oil).

Anal. calcd. for $C_{11}H_{13}O_2Br$, C 51.38, H 5.06 %;

Found C 51.51, H 5.26 %.

1-Methyl-4-(m-hydroxyphenyl)-4-propionoxypiperidine (156).

Dried magnesium turnings (2.1g) were suspended in dry THF (50 ml). About a third of a solution of m-(2-tetrahydropyranyloxy)bromobenzene (THP, 20g, 0.0778 mol) in dry THF (20 ml) was added to the suspension, and the mixture warmed to about 45°C with stirring under a reflux condenser. A few crystals of Iodine were added if there was any difficulty in the initiation of the reaction (taking care not to stir the mixture on addition of Iodine until the reaction has started). Once the reaction had started, the remainder of the solution was added to the mixture at such a rate that a gentle reflux was maintained. The mixture was stirred for a further 3 hr., and a solution of 1-methyl-4-piperidone (8.8g, 0.0778 mol) in dry THF was added from a dropping funnel, and the mixture stirred for another 3 hr. and cooled. A solution of propionic anhydride (11.9g) in dry THF was added, and the mixture stirred for 2 hr, after which it was poured onto a mixture of ice and saturated ammonium chloride solution. Extraction with ether, drying, and removal of the solvent gave the titled compound as the THP ether (19.1g). On conversion of the crude base to the hydrochloride salt, the THP protecting group was cleaved to yield 12.5g of the titled compound as the hydrochloride salt. Recrystallisation was from methanol.

m.p 205-206°C (Portoghese *et al*, 1981; reported m.p of 196-198°C, sample co-crystallised with $\frac{1}{2}H_2O$).

Anal. calcd. for $C_{15}H_{22}NO_3Cl$, C 60.09, H 7.39, N 4.67 %;
Found C 60.45, H 7.40, N 4.64 %.

1,3-Dimethyl-4-(m-hydroxyphenyl)-4-propionoxypiperidine (156).

Method A.

A solution of 1,3-dimethyl-4-piperidone (12.3g, 0.0972 mol) in dry THF (20 ml) was added from a dropping funnel to a solution of the Grignard reagent made from dry magnesium turnings (2.9g, 0.12 gr.at.), and m-bromophenol-THP ether (28.27g, 0.11 mol) in dry THF (100 ml). The mixture was stirred at 40°C for 3 hr., cooled, and decomposed with saturated ammonium chloride solution. The mixture was poured onto crushed ice, and extracted with ether. The ethereal fraction was washed with water, dried, and evaporated to yield an oil (25g) on which the protecting group was still retained (^{1}H-n.m.r evidence). The oil was esterified by refluxing it in a mixture of propionic anhydride (11.2g), and pyridine (100 ml) for 5 hr. The mixture was concentrated, poured into water (50 ml), made basic with 5 % NaOH solution, and extracted with ether. Removal of the solvent yielded the crude isomeric mixture of the titled compound as an oil (24.5g). The α-isomer (major component) was isolated as the hydrochloride salt (9.0g). The mother liquor contained a mixture of the

free alcohol, the α-, and the β-isomers, which was very difficult to separate.

Method B.

The Grignard reaction mixture from magnesium turnings (2.9g), bromophenol THP ether (29.2g), 1,3-dimethyl-4-piperidone (12.5g), and dry THF (150 ml), was decomposed with a solution of propionic anhydride (18.8g) in dry THF (25 ml), and the mixture stirred for 2 hr. The reaction mixture was poured into a mixture of saturated ammonium chloride solution and ice. Extraction with ether, drying and evaporation of the solvent yielded an oil (24.8g) which was the free base of the titled compound with the protecting group still intact. When the aqueous portion was basified (NH_3 solution) and extracted with ether, removal of the solvent gave an oil (5.2g) from which the free alcohol (4.2g) was isolated as the hydrochloride salt. Conversion of the total base (24.8g) to the hydrochloride salt gave 8.6g of the crude α-salt (m.p 156-189°C) with some traces of the β-salt. Fractional crystallisation from ethanol-ether mixture afforded the pure α-isomer as the hydrochloride salt.

m.p 168-170°C.

Anal. calcd. for $C_{16}H_{24}NO_3Cl$, C 61.2, H 7.7, N 4.4 %;

Found C 60.8, H 7.55, N 4.4 %.

The combined mother liquors was reconverted to the free base (6.8g) and dissolved in 10 ml. of acetone. A

solution of dl-malic acid (3.0g) in acetone (10 ml) was mixed with the solution of the base in acetone, and the mixture left at room temperature to crystallise. The first crops of the malate salt were mainly those of the α-isomer. The combined mother liquors from the malate salts was basified (NH_3 solution), extracted with ether, and the ether evaporated to give an oil from which the β-isomer was isolated as the hydrochloride salt (0.95g). Recrystallisation was from methanol-ether mixture.

m.p 206-207°C

Anal. calcd. for $C_{16}H_{24}NO_3Cl$, C 61.23, H 7.70, N 4.46 %;
Found C 61.33, H 7.78, N 4.31 %.

1-Phenethyl-3-methyl-4-(m-hydroxyphenyl)-4-propionoxypiperidine (156).

A solution of propionic anhydride (39.0g, 0.3 mol) in dry THF (50 ml) was added from a dropping funnel to the Grignard complex from bromophenol-THP ether (30.0g, 0.116 mol), magnesium turnings (3.0g, 0.126 gr. at.), and 1-phenethyl-3-methyl-4-piperidone (18.0g, 0.08 mol) in dry THF, and the mixture stirred for 3 hr. The reaction mixture was worked up as usual to give the crude product as an oil (29.0g). Conversion of the base to the hydrochloride salt yielded 10.2g of the α-isomer. Recrystallisation

from ethanol-ether mixture afforded the pure α-salt.

m.p 204.5-205°C.

IR spectrum (nujol):

ν_{max} 1725 cm^{-1} (C=O str).

Anal. calcd. for $C_{23}H_{30}NO_3Cl$, C 68.38, H 7.48, N 3.46 %;

Found C 68.65, H 7.3, N 3.43 %.

Attempts to isolate the β-isomer from the mother liquors following the procedure described for the N-methyl analogue (see page 186) were unsuccessful. However, work up of the aqueous portion from the reaction mixture gave 5.3g of the free alcohol. Isolation of the product by forming the hydrochloride salt gave the α-alcohol without the protecting group.

Esterification of 1-phenethyl-3-methyl-4-(m-hydroxyphenyl)-4-piperidinol (159).

Method A.

The piperidinol named above (2.0g) was refluxed in a mixture of propionic anhydride (3.0g) and pyridine (15 ml) for 3 hr. The product was worked up as usual, and converted to the hydrochloride salt. Recrystallisation was from ethanol-ether mixture.

m.p 254-255°C (compound 160, page 124).

IR spectrum (nujol):

ν_{max} 1760 cm^{-1} (C=O ester str), 3550 cm^{-1} (O-H str).

Anal. calcd. for $C_{23}H_{30}NO_3Cl$, C 68.38, H 7.48, N 3.4 %;

Found C 68.51, H 7.33, N 3.49 %.

Method B.

The procedure described for Method A above was followed with the exception that the mixture was refluxed for 12 hr. The product was converted to the hydrochloride salt, and recrystallised from ethanol-ether mixture.

m.p 204-205°C.

IR spectrum (nujol):

ν_{max} 1725 cm^{-1} (C=O ester str).

The compound was identical with the main product of the reaction desribed above (compound 161, page 124).

Attempted esterification of 1-methyl-4-(m-OTHPphenyl)-4-piperidinol with propionyl chloride.

An attempt to esterify a sample of 1-methyl-4-(m-OTHP phenyl)-4-piperidinol (2.9g, 0.001 mol.) by refluxing it with propionyl chloride (2g, 0.002 mol.) in toluene as described for the 1,2,3-trimethyl-4-phenyl-4-piperidinols (page 166), resulted in a product which on characterisation turned out to be the dehydrated compound esterified on the phenolic hydroxyl group (158, page 120). Recrystallisation was from ethanol-ether mixture.

m.p 130-131°C.

IR Spectrum (nujol):

ν_{max} 1765 cm^{-1}(C=O ester str.), 3400 cm^{-1} (H_2O).

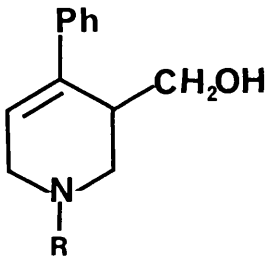
Anal. calcd. for $C_{15}H_{20}NO_2Cl.H_2O$, C 60.39, H 7.38, N 4.67 %; Found C 60.85, H 7.29, N 4.72 %.

A P P E N D I X

The Prins Reaction Of 1-Benzyl-3,4-dimethyltetrahydropyridine.

As a result of our general interest in the piperidine chemistry, we decided to investigate further an unconcluded work on the Prins reaction product of 1-benzyl-3,4-dimethyltetrahydropyridine (Staniforth, 1974).

The Prins reaction (Prins, 1919) is an acid catalysed addition of formaldehyde and water to a double bond to give a vicinal hydroxyl and hydroxymethyl derivative in which the addition is stereospecifically trans (Smissman & Witiak, 1960; Lebel *et al*, 1963; Dolby, 1962; Portoghese *et al*, 1962). Previous studies of 4-substituted 1,2,3,6-tetrahydropyridines in the Prins reaction have led to the isolation of 3-hydroxymethyl analogues (182), and with a large excess of formaldehyde, the cis-bicyclic 1,3-dioxane analogue (183; Schmidle & Mansfield, 1957; Casy *et al*, 1972). However, when a mixture of 1-benzyl-dimethyl



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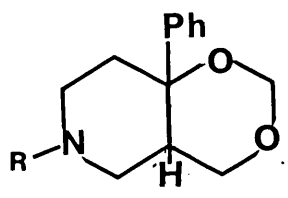

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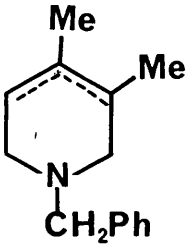
tetrahydropyridine (184) was used as the alkene substrate, neither type of product was isolated. Instead, a product which on the basis of the elemental analysis, the ^{1}H-n.m.r, IR, and the Mass spectra evidence corresponded to 185, was isolated (Staniforth, 1974). However, when attempts to reduce the double bond in the proposed struc-



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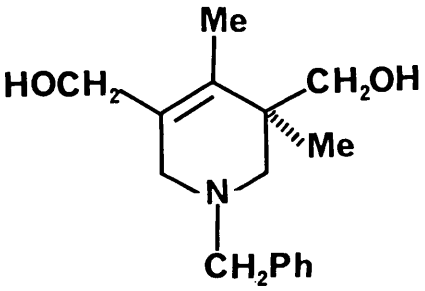

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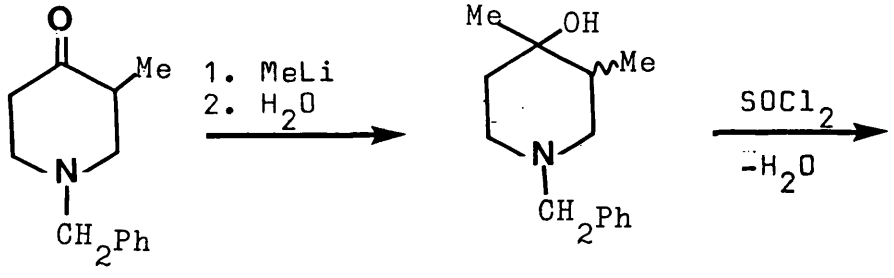
ture failed, it was considered worthwhile to re-investigate the reaction.

The synthetic procedure employed is as illustrated in Scheme 24. Reaction of methyllithium with 1-benzyl-3-methyl-4-piperidone gave a diastereoisomeric mixture of the corresponding alcohol (186) on decomposition with water.



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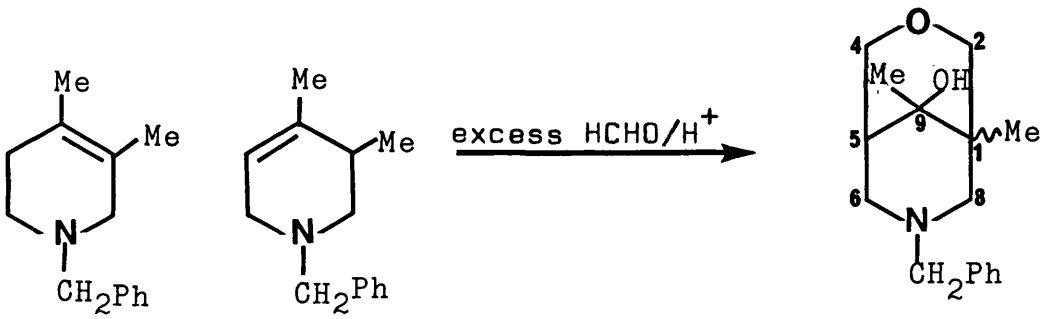
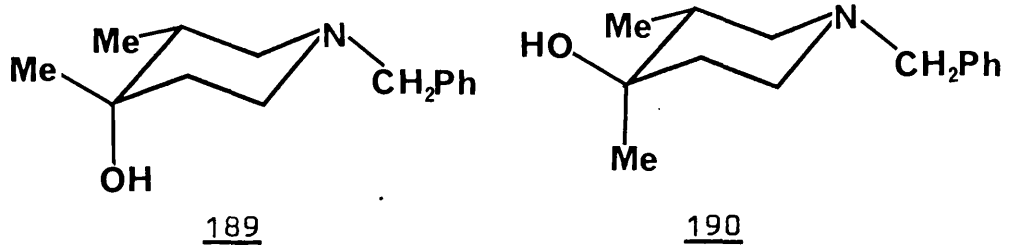


Scheme 24

The mixture was separated into its pure isomers by chromatographic techniques (details in the experimental section), and the major and minor isomers assigned trans-(189) and cis-(190) stereochemistry respectively on the basis of the relative C-4 methyl chemical shifts as explained in Table XVI. Dehydration of the isomeric alcohols (186)



with thionyl chloride afforded a mixture of alkenes (187) in which 187a was the major isomer as judged by the ^{1}H-n.m.r spectral evidence (the 3-methyl protons resonance was a singlet in the major isomer, while it was a doublet in the minor isomer).

The Prins reaction product of the tetrahydropyrid-

Table XVI. ^{13}C Chemical shifts of some 1-benzyl-4-methyl-4-piperidinols in $CDCl_3$ (δ, ppm from TMS)[a]

Entry	Compound	Isomer designation	C-2	C-3	C-4	C-5	C-6	3-Me	4-Me	N-CH_2-
1.	1-benzyl-4-methyl-4-piperidinol.	-	49.79	38.84	67.72	58.84	47.79	-	29.74	63.11
2.	186 (3-Me)	major	56.72	39.27	69.07	39.49	49.41	12.13	28.00	63.11
3.	186 (3-Me)	minor	57.64	41.06	71.13	39.76	51.08	13.11	21.42[b]	62.42

Notes:

a Assignments based on off-resonance spectra and chemical shift data of related compounds (Stothers, 1972; Casy, Iorio & Podo 1981; Jones, Casy & McErlane, 1973), and application of well-known principles; the phenyl group carbon resonances were near 138.6, 129.1 and 126.9 ppm in all cases.

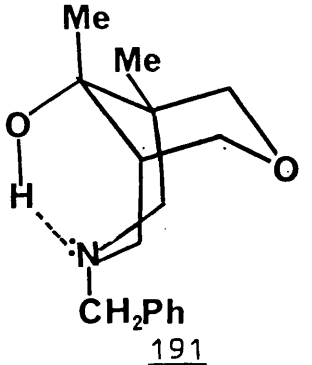
b The higher field resonance of this carbon compared with corresponding shifts of the des-3-methyl analogue and the major isomer is evidence that 4-Me of the minor isomer has a preferred axial orientation (Vierhapper & Willer, 1977).

ines (188) was a solid base, which melted at 98.5°C after recrystallisation from n-hexane.

Structural and stereochemical assignments.

The ^{1}H-n.m.r spectrum of the product lacked a low field resonance near δ5.0 ppm, characteristic of methylene protons flanked by oxygen atoms as in a 1,3-dioxane (Casy et al, 1972), which ruled out the possibility of the product being an analogue of 183 (page 190). The ^{13}C-n.m.r spectrum of the product, on the other hand, lacked resonances due to olefinic carbon atoms such as would be expected if the structure were 185; instead, the off-resonance spectrum showed a doublet at δ 41.82 ppm which could not be accounted for by the stucture (185) originally proposed. In addition to this, on esterification of the product with acetyl chloride, only a mono-acetate was formed.

Both the ^{1}H- and ^{13}C-n.m.r data were, however, consistent with its formulation as a 3-oxa-7-azabicyclo-[3.3.1] nonane (188, Table VII). Evidence for the stereochemistry (191), cis-N/9-OH piperidine boat-chair



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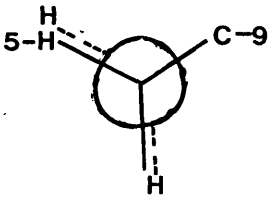
conformation, was largely based on a demonstration of ext-

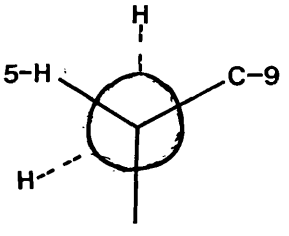
ensive intramolecular hydrogen bonding for a 0.003 molar solution in CCl_4 (cf. see page 65), and the magnitude of the couplings of the C-5 proton to those of C-6. ^3J coupling constant values were obtained from the 220 MHz spectrum which was fully resolved; models revealed that a large value is only to be expected when the piperidine ring is in a boat conformation with the C-5 eclipsing one of the C-6 protons.

view down C-5/C-6 bond,



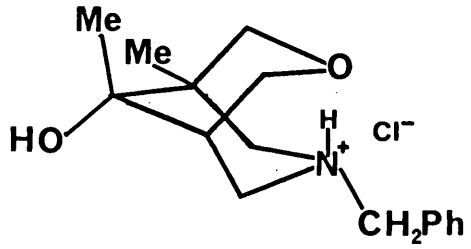
if piperidine chair conformation, one would expect;

view down C-5/C-6 bond



The C-5 proton resonance was reduced to a broad singlet ($W_{\frac{1}{2}}$ = 6.5 Hz, base width = 16.5 Hz) in the spectrum of the hydrochloride salt of (188) in DMSO-d_6, hence the salt (in which N--H-O intramolecular bonding is not possible) has an all-chair conformation where the C-5 proton

is subject only to small couplings (192).



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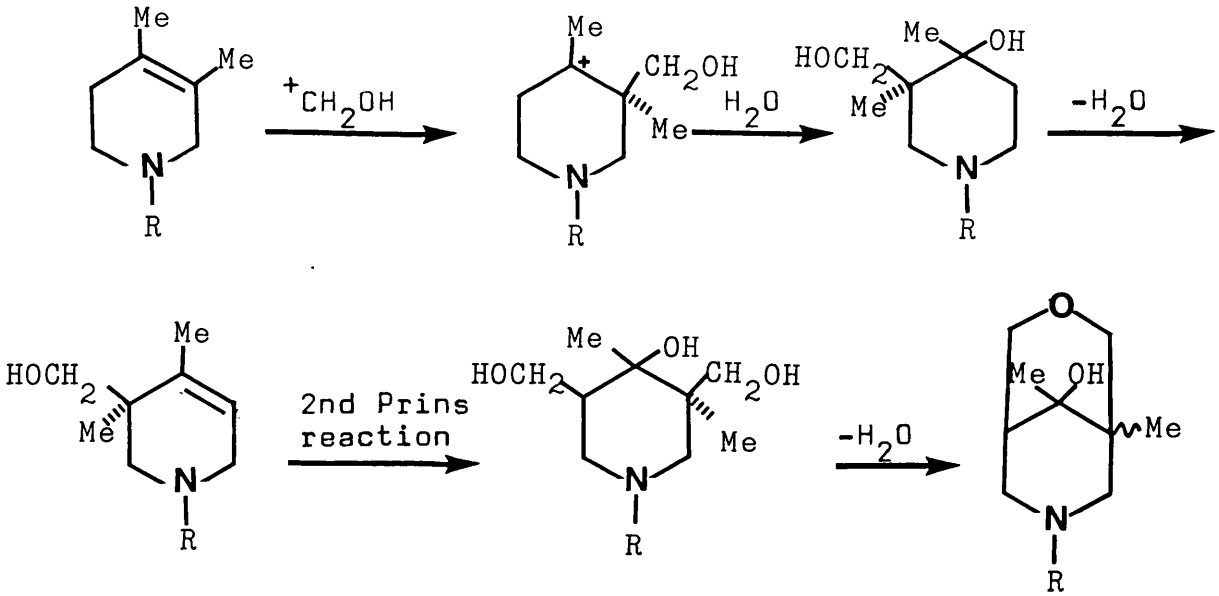
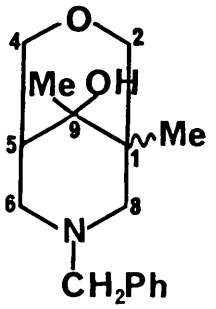
The conversion of the tetrahydropyridines (187) to a 3-oxa-7-azabicyclo [3.3.1] nonane rather than a bicyclodioxane derivative is probably a result of excessive steric interactions in a compound of the latter type when it contains a pair of bridge-head substituents. The production of 188 represents a double Prins reaction concluded by formation of the tetrahydropyran ring through loss of water (Scheme 25).



Scheme 25

The n.m.r data (Table XVII) presents several points of interest. Observation of the N-benzylic methylene proton resonance as an AB quartet ($\Delta\delta$ = 0.06 ppm) rather than a singlet illustrates the influence of axial substituents beta to a nitrogen on the magnetic non-equivalence of methylene protons of this type (Iorio & Casy, 1975), while the large downfield shift of the C-9 resonance on acylation (+ 11.1 ppm) provides a further example of contrasting acylation shifts in secondary (about 3 ppm) and tertiary cycloalkanols (Stothers, 1972; cf the C-4 shift of 159 and 161, TableIX, page 127). Finally, a comparison of C-1 and C-5 chemical shifts of 188 (δ 39.2 and 41.8 ppm respectively) shows that the usual α-shielding effect of equatorial methyl (5-6 ppm; Dalling & Grant, 1967) is absent. Chemical shift comparisons of C-3 and C-5 of the isomeric 4-piperidinols (186) likewise show that the methylated carbon (C-3) has an unusually high-field resonance (Table XVI). The relief of gauche interactions between vicinal pairs of methyl substituents, a common feature of all these compounds, may induce ring deformations responsible for such chemical shift anomalies.

Table XVII. N.m.r characteristics of the Prins product in $CDCl_3$.



C, H positions	Chemical shifts (δ, ppm from TMS) ^{13}C (22.5MHz)[a,b]	^1H (220MHz)
C-1	39.22 (39.0)	-
CH_2-2	75.08 (74.65)	3.33d, 3.42d, J_{gem} 11 Hz
CH_2-4	70.21 (69.23)	3.63dd, 3.76dd[e], J_{gem} 11 and 2 Hz.
CH-5	41.82 (38.57)	1.88 mult., ^3J 9.5 Hz plus 3 other small couplings(base width 23 Hz).
CH_2-6	53.85 (53.14)	2.54dd[c], ^3J 11&3 Hz, 3.18dd[c,d], ^3J 11 and 9.5 Hz.
CH_2-8	61.32 (59.37)	2.67d(broad), 2.70 (broad), ^3J 11 Hz.
C-9	71.24 (82.34)	-
C_1-Me	17.72 (17.68)	0.84 s
C_9-Me	20.15 (21.60)	1.2 s
N-CH_2- (benzyl)	61.59 (62.46)	3.51d, 3.57d, ^3J 13Hz[f]
C_9 (OCO<u>Me</u>)	- (16.09)	2.32 s
C_9 (O<u>C</u>OMe)	- (169.8)	-

Table XVII contd.

Note:

a Footnote a of Table XVI applies.

b Chemical shift of corresponding acetate ester in parentheses.

c Collapsed to broad doublet when C-5 proton was irradiated.

d Each line showed additional small coupling.

e Collapsed to doublets (^3J = 11 Hz) when C-5 proton was irradiated.

f Assigned on the basis of chemical shift and ^2J value (Iorio & Casy, 1975).

Details Of Experimental Procedure.

1-Benzyl-3,4-dimethyl-4-piperidone (186).

Methyllithium in ether (300 ml, 0.5 M) was added to an ice-cooled solution of 1-benzyl-3-methyl-4-piperidone (30g, 0.142 mol) in dry ether (100 ml), the mixture stirred for 1 hr, and then poured on ice-water. The ethereal fraction was separated, dried, and the solvent evaporated to yield an oil (25.6g) which solidified after distillation. The oil was an isomeric mixture, and was therefore chromatographed on silica gel (300g). Elution

with ethyl acetate/chloroform (3:1) gave the trans isomer as a solid.

m.p (base) 48-49°C

(hydrobromide salt) 154.5-155°C, from ethanol-ether.

Anal. calcd. for $C_{14}H_{21}NO.HBr$, C 56.00, H 7.38, N 4.66 %;

Found C 56.05, H 7.44, N 4.55 %.

The column was then eluted with methanol from which the cis-isomer (minor) was isolated. Evidence for the stereochemistry was obtained from the ^{13}C-n.m.r data of the alcohol as explained in Table XVI.

1-Benzy-4-methyl-4-piperidinol was similarly synthesised from the corresponding 4-piperidone. It gave a hydrochloride salt which was recrystallised from ethanol-ether mixture.

m.p 130-133°C.

Anal. calcd. for $C_{13}H_{19}NO.HCl.\frac{1}{2}H_2O$, C 62.24, H 8.37, N 5.58 %;

Found C 62.48, H 8.54, N 5.51 %.

Dehydration products of 1-benzyl-3,4-dimethyl-4-piperidinol (187).

A mixture of the alcohols (18.6g) and chloroform was heated under reflux for 4 hr. with freshly distilled thionyl chloride (18.6g). Excess thionyl chloride was removed by repeated distillation with chloroform. The residue was made basic with 10 % NaOH. The free base was recovered as usual and distilled to give a mixture of 3,4-

and 4,5-dimethyl-1-benzyl-1,2,3,6-tetrahydropyridines (187) in which the latter isomer preponderated as judged from the relative integrals of the 3-H (multiplet, δ 5.3 ppm), 3-Me (doublet, δ 1.0 ppm) for the minor isomer, and 4,5-diMe (broad singlets, δ1.56, 1.62 ppm) proton resonances for the major isomer in $CDCl_3$.

7-Benzyl-1,9-dimethyl-9-hydroxy-3-oxa-7-azabicyclo[3.3.1]-nonane (188) and derivatives.

A mixture of the tetrahydropyridines (187; 10g), aqueous formaldehyde (84 ml of 37 % solution), conc. H_2SO_4 (41.6 ml), and water (42 ml) was refluxed for 5 hr. The cooled mixture was made alkaline with sodium hydroxide solution, extracted with ether, the ethereal extract washed with water, dried, and the solvent evaporated. The residue was distilled under reduced pressure to give the titled compound (8.75g) which was isolated as the hydrobromide salt.

m.p 255-256°C (from isopropanol).

Anal. calcd. for $C_{16}H_{23}NO_2.HBr$, C 56.14, H 7.10, N 4.10 %;
Found C 56.22, H 7.10, N 4.02 %.

The base derived from the hydrobromide salt was a solid, and it was recrystallised from petroleum ether-acetone mixture.

m.p 98.5-99°C.

IR spectrum (3×10^{-3}M in CCl_4, 5 mm cell);

υ_{max} 3600 (free OH), 3240 (intramolecular hydrogen bonding) cm^{-1}.

Mass spectrum: m/e 261 (M^+).

Anal. calcd. for $C_{16}H_{23}NO_2$, C 73.52, H 8.87, N 5.36 %;
Found C 73.62, H 8.98, N 5.39 %.

Acetate ester.

The base (1g) was refluxed with acetic anhydride (1g) in toluene (10 ml) for 12 hr, and worked up as usual. The product was isolated as the hydrochloride salt.

m.p 205.5-206°C (from ethanol-ether mixture).

IR spectrum (nujol):

υ_{max} 1730 cm^{-1} (C=O ester str).

Anal. calcd. for $C_{18}H_{25}NO_3.HCl$ (mono-acetate ester), C 63.61, H 7.71, N 4.12 %; Found C 63.33, H 7.78, N 3.82 %.

R E F E R E N C E S

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