NATIONAL LIBRARY
OTTAWA

CANADA

BIBLIOTHÈQUE NATIONALE
OTTAWA

8100

NAME OF AUTHOR....E.T.H. MICHAEL JOSEPH MCERLANE

TITLE OF THESIS..STEREOCHEMICAL STUDIES
...OF 4-PHENYLPIPERIDINE
.....ANALGESICS.....

UNIVERSITY.....ALBERTA.....

DEGREE FOR WHICH THESIS WAS PRESENTED.....Ph. D.....

YEAR THIS DEGREE GRANTED.....1971.....

Permission is hereby granted to THE NATIONAL LIBRARY OF CANADA to microfilm this thesis and to lend or sell copies of the film.

The author reserves other publication rights, and neither the thesis nor extensive extracts from it may be printed or otherwise reproduced without the author's written permission.

(Signed).....E.T.H. McErlane.....

PERMANENT ADDRESS:

15634-80 Ave....
Edmonton 52, Alberta
.....

DATED Jan. 27.....19 71

NL-91 (10-68)

THE UNIVERSITY OF ALBERTA

STEREOCHEMICAL STUDIES OF 4-PHENYLPIPERIDINE ANALGESICS

by

© KEITH MICHAEL JOSEPH McERLANE

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF DOCTOR OF PHILOSOPHY

FACULTY OF PHARMACY

AND PHARMACEUTICAL SCIENCES

EDMONTON, ALBERTA

SPRING, 1971

UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Stereochemical Studies of 4-Phenylpiperidine Analgesics", submitted by Keith Michael Joseph McErlane, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

A.W. Casy
Supervisor

L.T. Coutts

D.F. Brien

R.A. Lovick

[illegible]

William F. Trager
External Examiner

ACKNOWLEDGEMENTS

The author wishes to extend his grateful appreciation to Dr. A.F. Casy for his supervision, guidance and friendship throughout the course of this investigation. And also to Dr. R.T. Coutts for his helpful suggestions in the latter part of this work.

Thanks are extended to Dr. E.L. May, Chief of the Medicinal Chemistry section of the National Institute of Health, Bethesda, Maryland, who arranged the determination of the analgesic activities of compounds synthesized during the course of these investigations. Special thanks are also due to Dr. G. Kotowycz of the Department of Chemistry, University of Alberta, who graciously performed the 220 MHz spectral analysis on some of the compounds isolated in this work.

The cooperation of Mrs. S. Li and Mr. W. Dylke for determining the PMR and infrared spectra, and the microanalyses needed for this project, and as well, the capable typing of this manuscript by Miss J. Dorsey, is gratefully acknowledged.

Finally, the financial assistance of the Medical Research Council of Canada, in the form of a Studentship, is most gratefully acknowledged.

To my wife, Barbara,
whose unfailing support and unselfish
assistance made the completion of this
work possible.

ABSTRACT

The more common analgesics introduced over the years either of natural or synthetic origin are selectively reviewed with an attempt to show the importance of configuration and conformation in the mediation of an analgesic response.

The synthesis of the precursor 4-piperidones via an acrylate condensation or pyridine reduction, or by an exchange of the basic centre functional group was investigated.

The subsequent reaction of these ketones with phenyllithium to produce the alcohols, esters or 4-H analogues of 3-methyl, 2,5-dimethyl or 2-methyl piperidines was carried out and the isomers, where possible, were separated and examined for stereochemical relationships.

PMR characteristics of many of the compounds synthesized in this work were reported and these provided evidence for both the configuration and preferred conformation in a variety of solvents.

Conformational free energy considerations were examined with the finding that they are in general agreement with the data supplied by PMR analysis.

Finally, pharmacological results, using the hot plate method in mice, demonstrated the superiority of a cis 3-Me/4-Ph geometry in these 4-phenylpiperidine analgesics.

TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

INTRODUCTION

INTRODUCTION

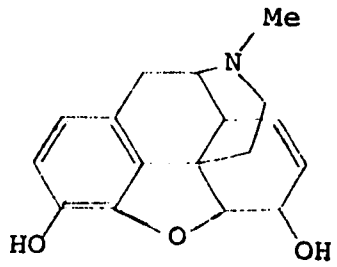
The perception of pain involves many receptors, conductors and cerebral integrative mechanisms. Reflex response to pain occurs in the spinal cord; for example, the reflex jerk when the hand is placed on a very hot object occurs before the brain is conscious of any noxious stimulus, yet the higher centers are necessary for an evaluation of the type and severity of pain. The actual site of this awareness of pain in the brain has not been traced to a single source, for lesions of the brain do not affect the sense of pain, or if they do, it is only temporary.

To purposefully prevent the awareness of pain several techniques have been introduced. Nerve block, a method which employs the use of a local anaesthetic injected in the area of a nerve fibre, is effective for both local pain, or if spinal anaesthesia is used, pain from a large section of the body. Alcohol can also be used if injected directly onto the nerve fibre. Nerve sectioning can be employed for relief from local pain symptoms which appear to be more or less permanent, but for which the underlying cause cannot be remedied. Finally, and perhaps most important, from the convenience standpoint, are the systemic analgesics. The broad spectrum of these compounds produced both naturally and synthetically allows the ready choice of any degree of analgesia desired.

The first drug used in this capacity was the dried exudate from the poppy fruit (Papaver somniferum). The

Sumerians are thought to have used crude opium as early as 4000 B.C. for its ability to relieve pain and instil a feeling of euphoria in the user, hence they called it "hul gil", or joy plant. In the third century B.C. Theophrastus is credited with the first undisputed reference to its medicinal values. The term, opium, comes from the Greek name for juice, since the drug is the juice from the capsule of the poppy.

A German pharmacist, Sertürner, in 1803 isolated the chief alkaloid from opium and called it morphine, after the Greek god of dreams, Morpheus. It was synthesized in 1952 by Gates and Tschudi who confirmed the structure (1) proposed by Gulland and Robinson (1923).



1

Such drugs, whose predominant site of action is the central nervous system where they act as C.N.S. depressants that alleviate or abolish pain without the loss of consciousness, are called analgesics. These analgesics are effective against all types of pain but are arbitrarily classed as drugs which are effective against severe or chronic pain, while antalgics encompass the salicylate group of drugs, which

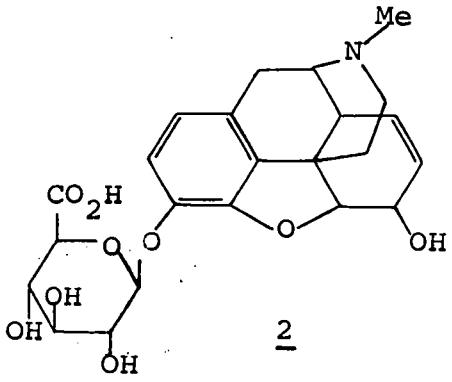
are effective against moderate or mild pain. The latter's action may be due to an anti-inflammatory response elicited from the body (Goodman and Gilman, 1965). Since analgesics do not cause the loss of consciousness in the dose required to relieve pain they are also separated from the anaesthetics and barbiturates, which have a general central nervous system depressant effect.

Morphine, a drug that has become somewhat of a classic in the field of analgesics, possesses a specific site of action. This is noted from the high activity associated with one isomer, (-) morphine compared to the other inactive (+) morphine enantiomer. A subcortical site of action of analgesics has been suggested (Wikler, 1952) from the observation that the lip twitch following electrical stimulation of a tooth in decorticated dogs was inhibited, this response being integrated subcortically. If the cortex was involved in the site of action of analgesics and not the subcortex then this response would not be inhibited. Also the same animals, when addicted to morphine or methadone and suddenly removed from the drug regimen, exhibited the typical abstinence syndrome. Therefore, the author concluded that the subcortex at least must be involved or be a major site of action.

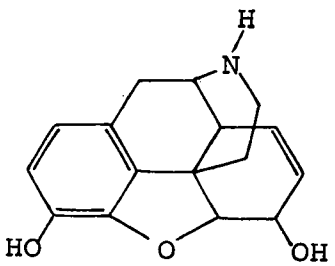
Unfortunately morphine affects many of the vital centres in the brain; the respiration slows, the emetic centre is stimulated resulting in nausea and vomiting, the pupils of the eye become constricted and vision is affected, the

intestinal smooth muscle is stimulated but at the same time constipation results due to the loss of peristaltic waves. The genito-urinary tract is adversely affected producing contraction of the bladder and hence urinary urgency, but at the same time causing the vesical sphincter to constrict (Schaumann, 1956).

Morphine is metabolised almost completely but quite slowly. The effects of a single dose last only 4 - 6 hours but the half-life of the drug in the body is 24 hours. Ninety percent of a single dose is excreted in the urine as the glucuronide (2) and a small amount is demethylated and excreted as the nor compound (3) (Beckett and Casy, 1965, and refs therein).

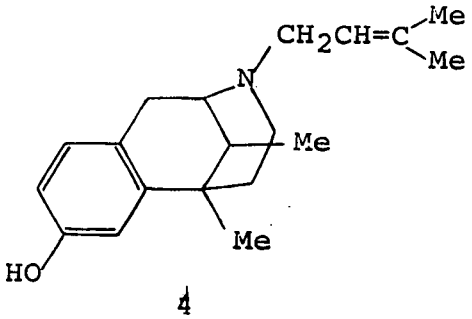


2



3

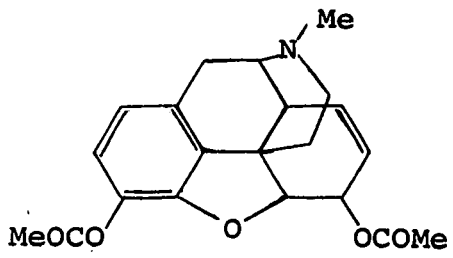
As with almost all narcotic analgesics (pentazocine (4) may be an exception), tolerance develops in time after repeated



4

doses. The normal dose of morphine required for analgesia is 10 - 15 mg. from which the side effects mentioned are minimal; however, with the development of tolerance the dose required to produce analgesia must be increased. Unfortunately the need for ever increasing doses to maintain the euphoria and prevent withdrawal symptoms also increases the degree of side effects such as nausea and constipation, and the addict suffers from these to greater and greater extents. Addicts have been known to take up to 4 g. of morphine daily in order to maintain their habit. The multiple side effects of morphine prompted the search for an analgesic lacking such properties and to this end many synthetic analgesics have been introduced, some of which are very potent but in most cases they are accompanied by side effects similar to those of morphine. Schaumann (1956) has suggested that the side effects are inseparable from the analgesia produced; however, the search will continue until a more perfect analgesic is developed or until proof of the inter-relationship between the euphoria experienced and the pain relief obtained is definitely established as being physiologically related.

Heroin, or diacetylmorphine (5) was introduced as a non-addicting cough sedative (Eddy, 1953), but it soon became evident that due to the euphoria produced and the rapid tolerance developed, this drug was to become one of the most addicting of all the narcotics.



5

This search for new and better analgesics lacking the undesirable side effects of morphine while maintaining the degree of pain relief desired has created volumes of literature on the development and testing of analogues related in some way to morphine.

TESTING ANALGESIC DRUGS

Quantitative evaluation of analgesics is difficult in man since the painful experience depends not only on the actual stimuli but also on the psychological state of mind. In this respect, "placebos" have been known to relieve pain successfully even though they contain an inert substance (Keats and Beecher, 1952). Clinical studies of analgesics are therefore difficult and conflicting reports arise frequently in the literature (Harris and Blockus, 1952; and Kuhn and Bromiley, 1951).

Several types of animal tests have been introduced in an effort to initially test the effective dose (ED_{50}); that is, the dose required in mg./Kg. to cause an effect in 50% of the animals, and also the lethal dose (LD_{50}), or the dose that results in death of 50% of the animals. Naturally any

analgesic developed must go through exhaustive animal studies before it is released for clinical evaluation in man.

Radiant heat has been used as the pain stimulus by Ercoli and Lewis (1945) who exposed a shaved area on a rat's back to a constant heat source. The response, a twitching of the skin and finally an attempt to escape, is timed and the length of time it takes for the skin to twitch is related to the degree of analgesia.

Green and Young (1951) developed a method where a rat's tail is subjected to variable pressure which is measured by a manometer. The endpoint is taken as a squeak or struggle as the rat attempts to escape. Thus the pressure required can be related to the degree of analgesia or, as also suggested, the drug being investigated should not be deemed effective unless the pain threshold has been raised to at least twice that of morphine.

Electric shocks have been used on mice by Grewal (1952). With this technique a current is applied to the animal's tail and the endpoint taken as a squeak and the effective dose to cause 50% of the mice to respond is then determined.

Perhaps the most popular method introduced has been the hot plate procedure originally developed by Woolfe and MacDonald (1944) and later modified by Eddy and Leimbach (1953). This apparatus consists of a copper cylinder on top of a boiling mixture of equal quantities of ethyl formate and acetone which maintains the bottom of the cylinder at 55°. The endpoint is taken at one of several responses, for the

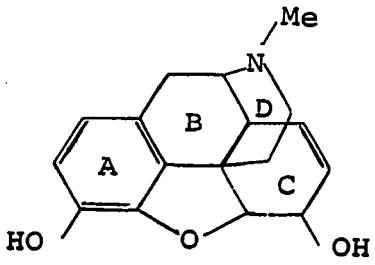
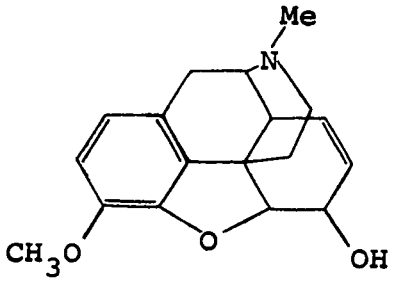
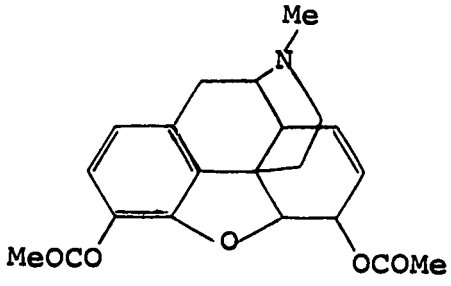
mouse first sits on its haunches and licks the front paws, then as the rear limbs can no longer bear the heat it will jump about trying to escape from the container. The latter effect is generally used as the endpoint. This particular test was the one used in the present work and will be discussed in an appropriate section.

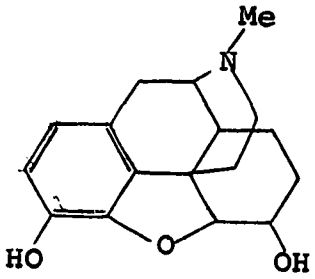
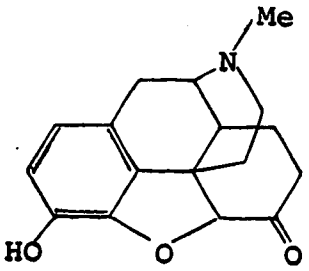
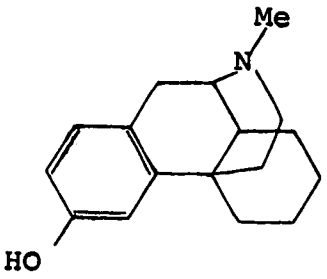
The tests that have been used in man generally suffer from one or more disadvantages. Artificially induced pain is thought by some not to represent the actual physiological picture in the body as when "true pain" is the cause. Beecher (1957) in his extensive review has presented an evaluation of pain and analgesia and concludes that natural pain should be a prime prerequisite for testing analgesic effectiveness. Clinical evaluation of an analgesic using postoperative or cancer patients would appear to be ideal; however, another drawback is the patient's evaluation of his own condition. Sometimes patients, in an effort to please the interviewer, will exaggerate the amount of pain relief obtained and thereby produce misleading results.

Many modifications of the morphine molecule have been introduced over the years in an attempt to produce the ideal analgesic. The properties of such a compound are simple: it should be rapid in onset and the duration of relief relatively long. Respiratory depression, which is a severe disadvantage in childbirth where the respiration of the foetus is depressed, should be absent. Gastro-intestinal side effects should be minimal. Finally, and most important, the drug

should not produce euphoria or tolerance so that addiction will not occur. These modifications fall into four main categories and a few representative examples from hundreds available are shown below.

COMPOUNDS RETAINING MOST OF THE MORPHINE SKELETON (Eddy et al., 1956)

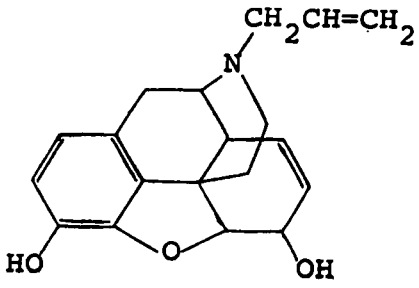
Name	Structure	Relative Activity in mice
Morphine		1.0
Codeine		0.15
Diacetyl Morphine		2.3

Name	Structure	Relative Activity in mice
Dihydro-morphine		1.2
Hydromorphone		7.0
Desomorphine		12.0

Most of the modifications occur on ring C because this ring is chemically easier to modify and the results show more dramatic differences in analgesic potency.

The character of the nitrogen substituent has been

investigated by Winter et al. (1957) and Weijlord et al. (1956) with the rather curious finding that as the length of the N-alkyl chain is increased to 3 carbons an antagonist is suddenly produced. For example nalorphine (6) is a potent morphine antagonist lacking analgesic properties in animals.



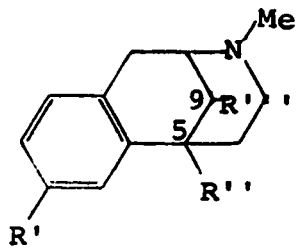
6

It is, however, an analgesic in man roughly equal in potency to morphine. The drug appears to be nonaddicting since it cannot be substituted for morphine in addicts. Unfortunately, nalorphine produces an undesirable side effect described as a feeling of "unrealness" in humans and hence is not used as an analgesic.

Extending the chain length or branching, reverse the series again to that of an analgesic. N-phenethyl substitution results in a very potent compound which, as will be shown later, foreshadowed the potent piperidine analgesics.

BENZOMORPHANS

The benzomorphans form another group of morphine-like analgesics, but in this case ring C has been opened giving the general structure (7).



7

Diastereo isomers exist in the benzomorphan series at carbons 5 and 9. The two alkyl groups R'' and R''' can be oriented trans or cis to each other. The trans isomer is arbitrarily called the β-form and the cis isomer is given the α- designation. The difference, in a series of benzomorphan isomers, is shown in Table I using the hot plate test data with mice (Eddy and May, 1966).

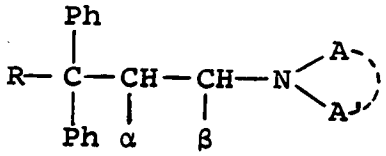
TABLE I. ANALGESIC POTENCY OF DIASTEREOISOMERIC BENZOMORPHANS (HOT PLATE TEST, SUBCUTANEOUS INJECTION)

R'	R''	R'''	Isomer	ED_{50} mg./kg.
OH	Me	Me	α	3.0
OH	Me	Me	β	0.4
OH	Et	Me	α	4.9
OH	Et	Me	β	0.1
OH	Et	Et	α	4.2
OH	Et	Et	β	0.3
OH	Me	Et	α	1.5
OH	Me	Et	β	0.5
OH	n-Pr	n-Pr	α	71.2
OH	n-Pr	n-Pr	β	0.9

The β-isomeric form is shown to be the more active thus giving substance to the stereospecificity of the analgesic receptor site.

ACYCLIC DERIVATIVES OF THE METHADONE CLASS

In 1946 methadone was introduced into clinical use (Janssen, 1960; and Denton, 1949).



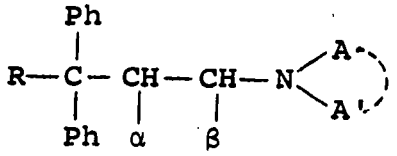
Methadone Skeleton

This drug was similar in potency and duration of action to morphine, but produced less constipation and less sensual dulling. It does cause respiratory depression, however, and is thus not used in childbirth. Drug induced dependence develops but when withdrawn the symptoms are less severe than with other narcotics. It has come into use as a narcotic substitute for addicts, whereby a person addicted to another narcotic is switched to a dose of methadone sufficient to prevent withdrawal (Isbell et al., 1947). When successful substitution has been accomplished, the user is psychologically and physically rehabilitated, then the methadone is discontinued. Symptoms of withdrawal are still present but to a lesser degree and the addict is generally in better health to withstand the ordeal (Isbell and Fraser, 1953). Whether or not

the addict remains abstinent from narcotic drugs depends largely upon the environment and social structure he returns to. In some reports continuous treatment with methadone is maintained at a controlled level so that the addict, although still on narcotics, can lead a more normal existence in society (Garb et al., 1964).

Some of the methadone analogues as well as their analgesic potency are shown in Table II (Eddy et al., 1956).

TABLE II. METHADONE ANALOGUES AND THEIR POTENCY IN MICE (HOT PLATE METHOD) (SUBCUTANEOUS INJECTION)



Compound	R	α	β	N-AA'	ED_{50} mg./kg.
dl methadone	COEt	H	Me	$N\text{-}Me_2$	1.6
dl isomethadone	COEt	Me	H	$N\text{-}Me_2$	2.5
dl Phenadoxone	COEt	H	Me	$N\text{-}(CH_2)_4O$	2.0
dl Dipipanone	COEt	H	Me	$N\text{-}C_5H_{10}$	2.5
dl Normethadone	COEt	H	H	N-Me	2.5

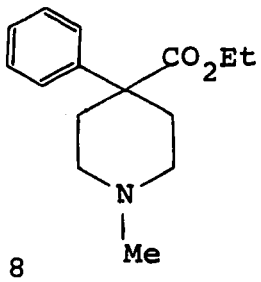
As a group the methadone series offers little advantage over the morphine analogues as analgesics; however, the less pronounced side effects and lower addictive liability do show some promise as clinically useful narcotics.

DERIVATIVES OF 4-ARYLPIPERIDINES

The present thesis is concerned with this group of compounds and hence considerable detail will be provided concerning

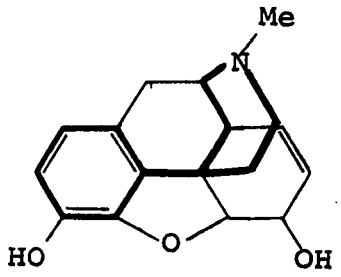
the pharmacology and chemistry.

N-methyl-4-phenyl-4-carbethoxypiperidine (pethidine) (8) was the first in this series introduced in 1939 by Eisleb and Schaumann. Originally the compound was synthesized as an antispasmodic; however, during screening it was observed to produce the Straub tail reflex in mice (which is indicative of an analgesic).



8

Pethidine, after its analgesic properties were investigated, was recognized as bearing a resemblance to part of the morphine molecule, as illustrated in structure (9).



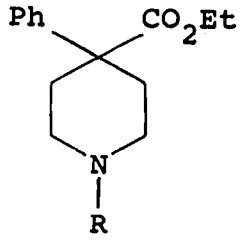
9

At the present time it remains the most widely used synthetic analgesic with an effective dose in man of 50 - 100 mg. as compared to 10 mg. of morphine. Employed for moderate pain, pethidine produces less respiratory depression

and in general possesses less severe side effects than those of morphine (Lasagna and Beecher, 1954).

Due to its effectiveness many modifications to the basic 4-phenylpiperidine molecule have been investigated with an eye to determining more about the structure - activity relationship of analgesics in general.

Elpern et al. (1957) altered the character of the nitrogen substituent and related the length of the alkyl chain to activity. They found activity is increased two-fold when a phenethyl moiety is linked to the ring nitrogen atom (10a) and further increases in activity occur until 3 carbons separate the basic and aromatic centres (10b), then the activity

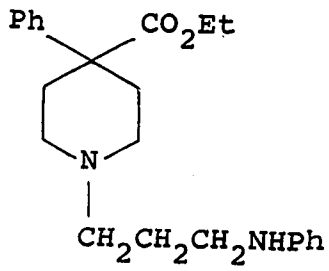


10a R = CH_2CH_2Ph

10b R = $CH_2CH_2CH_2Ph$

10

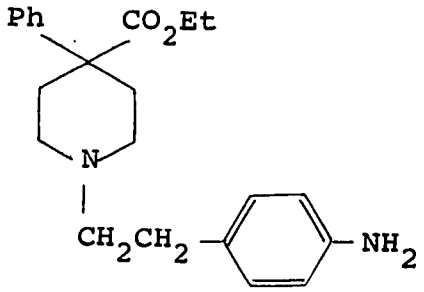
drops. When heteroatoms are in the aryl ring the most active analogue occurs when two carbons separate the aryl ring from the nitrogen. Other alterations of the nitrogen substituent met with varying degrees of success (Elpern et al., 1957); however, one noteworthy example occurs when an imino group is placed between the piperidine and the phenyl ring (11).



11

This particular compound is 30 times as active as pethidine in rats but slightly less active than morphine in man and is used clinically under the name piminodine (Alvodine). It offers no real advantage in man, although the incidence of side effects appears to be lower (De Kornfield and Lasagna, 1960).

Another of these norpethidine derivatives used clinically is N-p-aminophenethyl norpethidine (12) (anileridine, Leritine) (Weijlard et al., 1956) which is 10 - 12 times more active than pethidine (Orahovats et al., 1957) in dogs and 2 - 3 times as potent in man (Eddy et al., 1957). It is

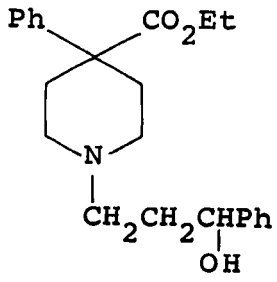


12

used to supplement N_2O anaesthesia and can be used in obstetrics since the duration of respiratory depression is short

(Chang et al., 1958).

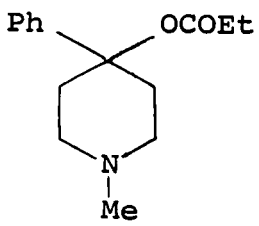
Janssen and Eddy (1960) have investigated the findings of several authors in respect to the effect on analgesic potency in mice that the N-alkyl substituent causes. Their ultimate conclusion was that a secondary alcohol between the aryl group and the nitrogen produced the most potent derivative (13) having about 300 times the activity of pethidine. Side effects in the series were not discussed.



13

A second possible modification to the basic structure of pethidine is to alter the ester function (Braenden et al., 1955). When the carboethoxy function was changed to a carbomethoxy, the activity dropped four-fold in mice.

By changing the ethoxy carbonyl group to a propionyloxy group, the so called reversed esters of pethidine (14) are produced (Jensen et al., 1943).

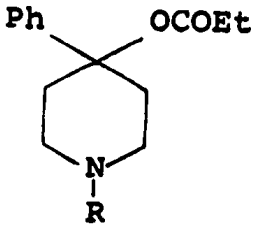


14

This alteration is accompanied by a twenty-fold increase in activity in rats over pethidine itself (Janssen and Eddy, 1960). Beckett and coworkers (1959) showed that the activity increases three-fold in mice when an acetyloxy ester is changed to a propionyloxy group. However, in the N-phenethyl series the acetoxy ester was found have higher activity than the propionoxy (Foster, 1947).

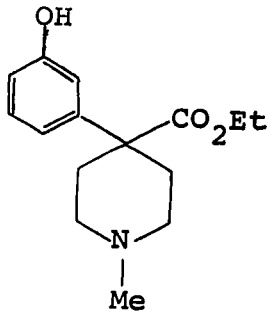
In the propionoxy series the nitrogen substituent was found to influence the activity drastically as shown in Table III (Janssen and Eddy, 1960).

TABLE III. INFLUENCE OF THE NITROGEN SUBSTITUENT ON ANALGESIC EFFECTIVENESS (HOT PLATE TEST, SUBCUTANEOUS INJECTION)



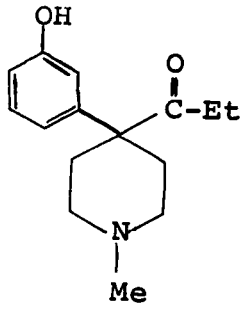
R	Relative Activity
$Ph-CH_2CH_2CH_2CH_2-$	54
$Ph-CH_2CH_2CH_2-$	160
$Ph-CH_2CH_2-$	255
$Ph-CH_2-$	1
$Ph-\underset{\underset{OCOET}{|}}{CH}-CH_2CH_2$	1500

Few changes to the aromatic ring have been attempted; however, one noteworthy analogue is bemidone (15), whose activity is 1.5 times that of pethidine in mice, and its



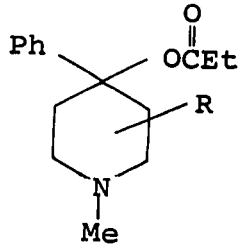
15

keto-analogue ketobemidone (16) which is ten times as active as pethidine in the same test (Braeden et al., 1955).



16

The effect on activity of introducing an alkyl substituent into the piperidine ring is of particular interest because it results in the production of isomers (17) which



17

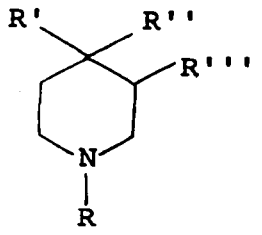
differ significantly in potency.

The isomeric nature (two diastereo isomers composed of four enantiomeres) of these reversed esters was studied by Ziering and Lee (1947). When the alkyl group is methyl, the α-isomer (alphaprodine) is about one half as active as morphine in mice and is isomeric at the 3 position (the actual configuration of which will be discussed later). The β-form (beta prodine) has the opposite configuration and is twice as potent as morphine in the same test (Beckett et al., 1959). In virtually all cases substitution in the piperidine ring results in increased activity. Activity remains high when the nitrogen substituent is methyl and increases substantially when changed to an β-phenethyl group. The nature of the aromatic substituent in position 4 does not greatly alter activity; however, an o-tolyl does appear to be optimal for activity (McElvain, 1958). It is interesting to note that again in the N-methyl series, changing the acetyloxy esters to a propionyloxy increases the potency; however, in the N-phenethyl series the reverse is found. See Table IV (Beckett et al., 1959).

The same authors studied the effects of substituting various alkyl groups into the piperidine ring at the 3-position (see Table V).

It will be noted that the 3-methyl substitution in most cases results in a compound with enhanced activity. In 1957 Ziering and coworkers prepared 1-methyl-3-allyl-4-phenyl-4-propionyloxy piperidine (18). The activity of this compound

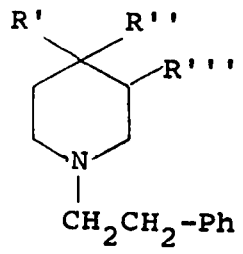
TABLE IV. EFFECT OF REPLACING N-METHYL BY N-PHENETHYL IN A SERIES OF REVERSED ESTERS OF PETHIDINE ON ANALGESIC ACTIVITY (HOT PLATE TEST - SUBCUTANEOUS INJECTION)



R'	R''	R'''	Config Me/Ar	Relative Analgesic Potency * R=CH_3	R=$(CH_2)_2Ph$
C_6H_5	$OCOCH_3$	H	-	9	633
C_6H_5	$OCOC_2H_5$	H	-	260	346
C_6H_5	$OCO\underline{n}\text{-}C_3H_7$	H	-	44	107
C_6H_5	$OCOC_2H_5$	CH_3	cis	870	2195
C_6H_5	$OCOC_2H_5$	CH_3	trans	200	450
$\underline{o}\text{-}CH_3C_6H_4$	OH	CH_3	trans	20	77
$\underline{o}\text{-}CH_3C_6H_4$	$OCOCH_3$	CH_3	trans	75	1325
$\underline{o}\text{-}CH_3C_6H_4$	$OCOC_2H_5$	CH_3	trans	85	259
$\underline{m}\text{-}CH_3C_6H_4$	OH	CH_3	trans	20	80
$\underline{m}\text{-}CH_3C_6H_4$	$OCOCH_3$	CH_3	trans	20	179
$\underline{m}\text{-}CH_3C_6H_4$	$OCOC_2H_5$	CH_3	trans	50	39
$\underline{p}\text{-}CH_3C_6H_4$	OH	CH_3	trans	15	97
$\underline{p}\text{-}CH_3C_6H_4$	$OCOCH_3$	CH_3	trans	30	88
$\underline{p}\text{-}CH_3C_6H_4$	$OCOC_2H_5$	CH_3	trans	15	17

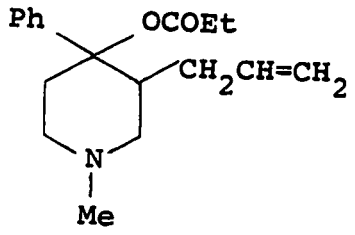
*Morphine 100

TABLE V. EFFECT OF 3-ALKYL SUBSTITUENT INTO THE PIPERIDINE RING OF N-PHENETHYL ANALOGUES ON ANALGESIC POTENCY (HOT PLATE TEST - SUBCUTANEOUS INJECTION)



R'	R''	Relative Analgesic Potency *(R'''=) H	CH_3	C_2H_5	n-C_3H_7
C_6H_5	OH	35	70	-	33
C_6H_5	$OCOCH_3$	633	385	-	450
C_6H_5	$OCOC_2H_5$	346	430	-	-
o-$CH_3C_6H_5$	OH	-	77	41	-
o-$CH_3C_6H_5$	$OCOCH_3$	-	1325	760	-
o-$CH_3C_6H_5$	$OCOC_2H_5$	-	259	142	-
m-$CH_3C_6H_5$	OH	62	80	-	-
m-$CH_3C_6H_5$	$OCOCH_3$	117	179	-	-

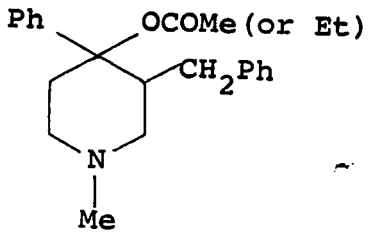
*Morphine 100



18

was found to be eight to ten times that of alpha prodine and the toxicity was not increased (as was often the case) (Benson and Cunningham, 1957).

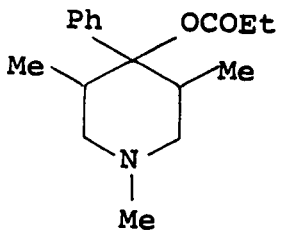
When the 3-alkyl substituent is further increased in size to 3-benzyl (19), the compound becomes completely



19

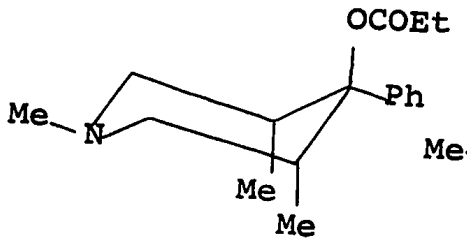
inactive (McElvain and Barnett, 1956).

Sorokin (1961) synthesized a series of 1,3,5-trimethyl-4-phenyl-4-propionyloxy piperidine isomers (20).

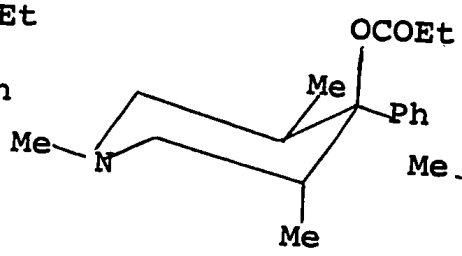


20

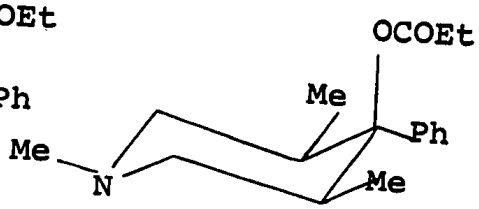
In this case three diastereo isomers are possible (21 - 23), depicted here in the chair conformation with the 4-phenyl equatorial.



21



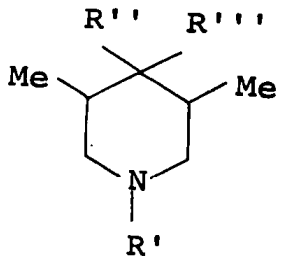
22



23

Isomers (21) and (23) have a plane of symmetry, therefore no optical isomers exist; however, compound (22) has two enantiomorphic forms, but these have not been separated. The γ-isomer (22) was found to be several times as active as pethidine while the α- (23) and β- (21) forms were inactive.

Harper et al. (1964) synthesized a series of N-alkyl-3,5-dimethyl derivatives of the general type:

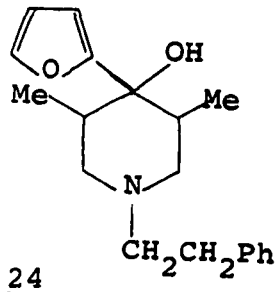


where R' = $Ph-CH_2CH_2-$
$Ph-CH_2-$
Me

R'' = C_6H_5
$\underline{o}-CH_3-C_6H_4-$
H
2-furyl

R''' = OH
OCOMe
OCOEt

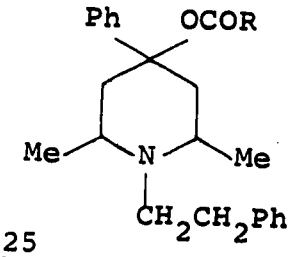
Interestingly enough only one compound, 4-(2-furyl)-3, 5-dimethyl-N-phenethyl-4-piperidinol (24) showed any activity at all. When assayed by the hot plate method it showed one fifth the activity of pethidine in mice.



24

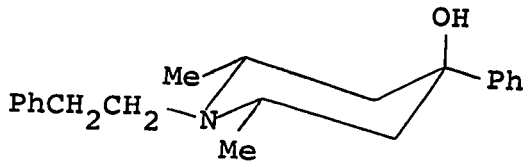
It would appear that an anomaly exists here, in that Sorokin found the 1,3,5-trimethyl series to have one isomer with significant activity. It is likely that the compound synthesized by Harper, that is identical to those of Sorokin, was one of the α- or β- (inactive) forms, since configurational data was not proposed by Harper.

Another series of isomeric piperidinol derivatives was prepared by Harper et al. (1960) with the piperidine alkyl substitution on the 2- and 6- position (25).



25

The pharmacology of the acetyloxy and propionyloxy forms of the trans 2-Me/6-Me (26) was determined and the results showed

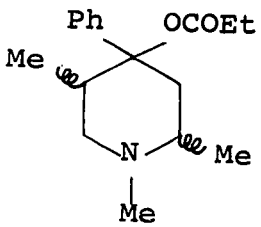


26

the two esters to have four times the activity of morphine when assessed by the hot plate method.

When the alkyl substitution on the piperidine ring is moved from the 3- position to the 2- position, the activity drops. To this date only one compound in this class has been tested, i.e., N-phenethyl-2-methyl-4-phenyl-4-propionyloxy-piperidine (Harper et al., 1960). This analogue was found to have only one-fifth the activity of the unsubstituted form or about 5 times the activity of pethidine in mice.

From Russia in 1948 emerged a very potent and clinically valuable analgesic, due to the work of Nazarov and Rudenko (1948); namely one of the isomeric forms of 1,2,5-trimethyl-4-phenyl-4-propionyloxypiperidine (27) (promedol, trimeperidine).



27

The pharmacological aspects of this piperidine analogue together with two other isomeric forms were later investigated by Nazarov et al. (1956) with the finding that the γ-isomer, which is formed in the greatest amount during the synthesis, has twice the activity of morphine. The α-isomer has 8 times and the β-isomer 4 times the activity of morphine. The fourth isomer (δ-) has been reported by Shvetsov and Kucherov (1959) as having four to six times the activity of morphine. The test animals used were rats, but the actual test was not specified.

Promedol, the γ-isomer, is used clinically in Russia as an analgesic. The more potent isopromedol (β-) and alpha promedol (α) isomers are not in clinical use, probably because they are minor products (approximately 8% and 4% respectively) as compared to 88% of the γ- form isolated from the synthesis. Side effects found with the isomers do not vary to any significant amount, but actual detail concerning these was not available.

RELATIONSHIP BETWEEN STEREOCHEMISTRY AND ACTIVITY IN ISOMERIC 4-PHENYLPIPERIDINES

Up to this point little has been mentioned concerning the stereochemistry of these analgesics. Stereoisomeric forms of many pharmacologically active molecules are known and in many cases one member of a series has a greatly enhanced activity over that of the others (Beckett and Casy, 1954). This effect was shown previously in the benzomorphan series (Table I) where the (±)-β- diastereoisomer is frequently the more potent analgesic.

While clear activity differences exist between two diastereoisomers, enantiomeres of each member of a diastereoisomeric pair may also exhibit significant potency differences. In Table VI data are given upon racemates of isomeric pairs which have been separated and the analgesic effectiveness of the enantiomorphs tested.

TABLE VI. ACTIVITY DIFFERENCES BETWEEN ENANTIOMERS OF MORPHINE-LIKE ANALGESICS

(Subcutaneous in Mice) (Mellett and Woods, 1963)

Class	Compound	Enantiomer	ED mg./Kg.
Morphine	see page 1	+	2.1
Morphinan	3-hydroxy-N-methyl morphinan	-	inactive
		-	1.7
Benzomorphan	α-2-hydroxy-2,5,9 trimethyl-6,7-benzomorphan	+	25.0
		-	6.5
Methadone	$Me_2NCH(CH_3)CH_2CPh_2COEt$	+	58.2
		-	0.8
		+	25.7

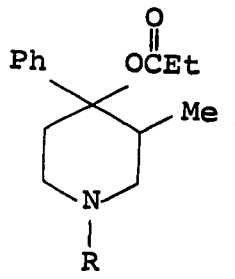
It should be emphasized here that the Greek letter notations used to designate isomers are merely a convenience for the initial investigator and bear no definite inter-relationship; also the sign of optical rotation is not related to analgesic potency but is a result of total stereochemical arrangements within the molecule.

The striking differences in activity seen amongst stereoisomeric forms of analgesics suggest that a stereoselective receptor site or transport and/or metabolism route is involved in the mediation of analgesia. Hence it is of some interest to determine the stereo-structure-activity relationships of asymmetric analgesics in order to obtain more information about their site of action.

In the 3-methyl piperidine series, distinct activity differences exist between isomers. Since 3-alkyl-4-phenyl-4-piperidinol possesses two asymmetric centres there are 2^2 or 4 isomers (2 racemic diastereoisomers composed of 4 optical isomers).

The stereochemistry of the α- and β-prodine isomers has been the subject of much investigation over the past two decades and some detail found in the literature will now be presented.

Beckett and Walker (1952 and 1955) measured the hydrolysis rate of the propionate esters of α- and β-prodinol type compounds (28) and found that the β-isomer of both the N-methyl and N-phenethyl analogues hydrolyzed faster than the corresponding α-isomers. They concluded that the β- form must



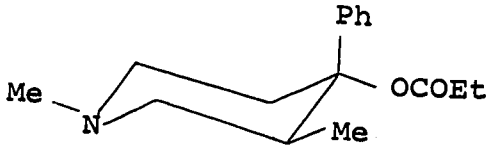
28

Where

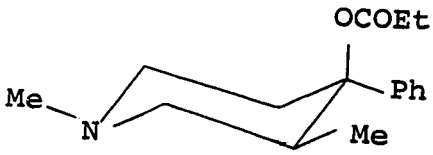
R = Me

CH_2CH_2Ph

have a more accessible ester function (29), hence it must be equatorial while the α-isomer (30) has an axial ester group.



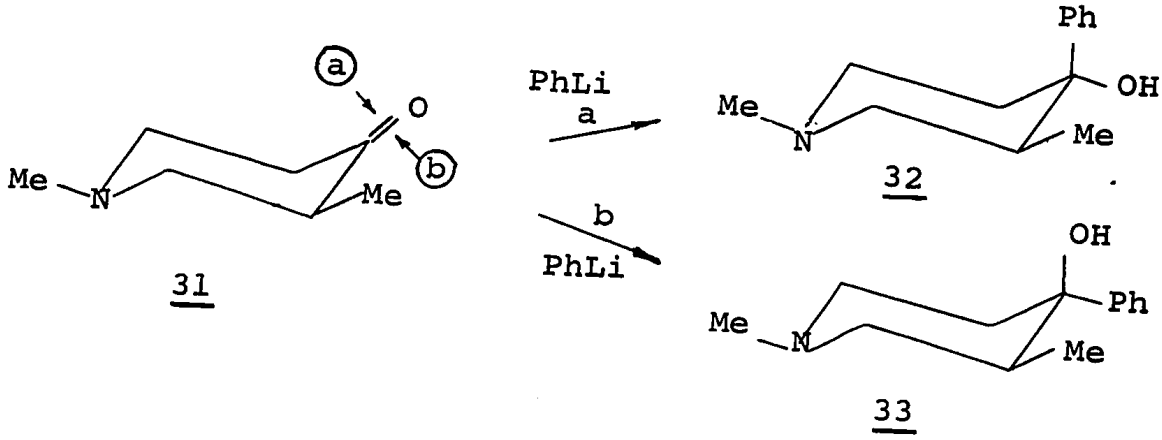
29



30

If the 3-methyl is taken to be equatorial then the β-isomer has a cis 3-Me/4-Ph configuration and the α- form is then trans 3-Me/4-Ph.

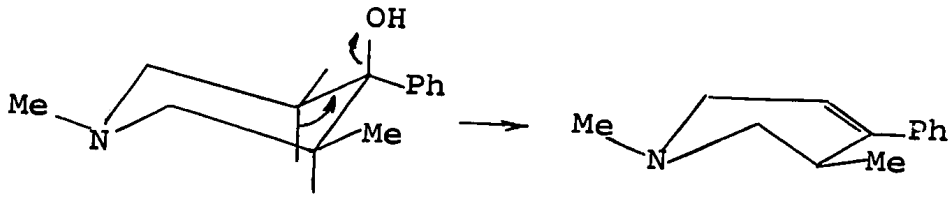
In 1959, Beckett and others considered the stereochemistry of aryl lithium additions as a means of determining the configuration of 1,3-dimethyl-4-aryl-4-piperidinols, in which the 3-methyl substituent is again considered to be equatorial in the most favoured conformation. Since attack from the least hindered side (b) of the 1,3-dimethyl-4-piperidone (31) should be favoured then (33) should be the major product while (32) should constitute the minor isomer. The reason this is so is that the 2,6-diaxial hydrogens offer steric



31 32 33

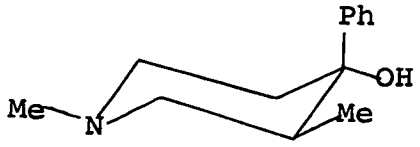
interference from attack in the (a) direction. The 3-methyl group is actually pointed away from the carbonyl function although this does not appear so in the figure. Subsequent treatment with aryl lithium compounds of increasing bulk showed an increasing predominance of the α-isomer with a trans 3-Me/4-Ph configuration. When o-tolyl or o-methoxyphenyl were the adducts only one isomer (trans 3-Me/4-Ph) was isolated.

Casy (1961) investigated the effect thionyl chloride produced when reacted with α- and β-prodinol. He found that α-prodine alcohol (33) eliminated water while the β-isomer (32) gave the corresponding 4-chloro compound almost exclusively

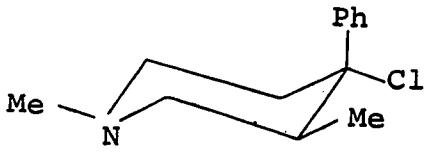


33

(32a). These results were interpreted to mean that the α-isomer had an axial hydroxyl function, since elimination should



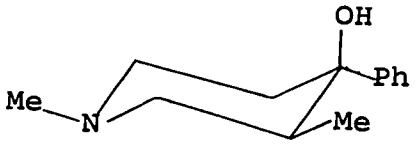
32



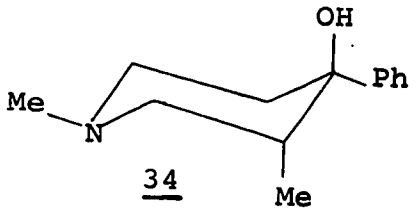
32a

occur readily with two trans diaxial pathways available, while the β- form possessed an equatorially oriented hydroxy group which would not readily eliminate water with the single trans hydrogen available. The chloro compound should also result due to a more favourable steric environment (see later).

Archer (1958), after reviewing the literature to that time, proposed structure (33) for α-prodine alcohol, which was in accord with the previous assignments; but suggested the β- form had the other chair conformation with the phenyl moiety in the more favourable equatorial position and the 3-methyl group axial (34) (β- still maintains the cis configuration).



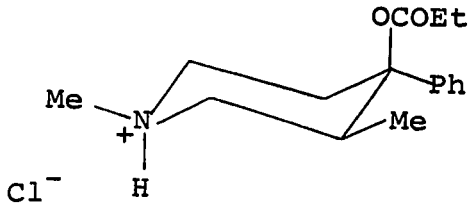
33



34

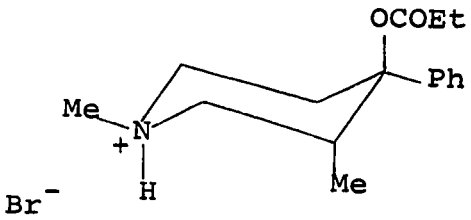
The question of configuration (and conformation in the solid state) was finally resolved in 1959 by Ahmed et al., who studied α-prodine hydrobromide in the crystalline state

by X-ray crystallography (see also Kartha et al., 1960). These studies showed the piperidine ring existed in the chair form with the 4-phenyl and 3-methyl groups equatorially oriented (35).



35

Then in 1962, Ahmed and his coworkers subjected the β-prodine isomer to X-ray crystallography also (see also Ahmed et al., 1963). The analysis indicated that the piperidine ring was again in the chair conformation but with the 4-phenyl ring in an equatorial orientation (as Archer suggested) and the 3-methyl and 4-propionyloxy groups in axial positions (36).

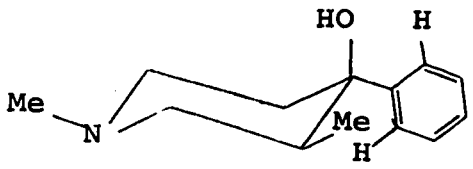


36

This established the stereochemistry of the racemate prodines in the solid state. This may not, however, reflect the conformation in solution as would be the case under physiological conditions.

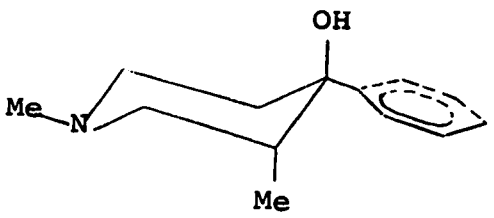
In 1966 Casy attempted to use proton magnetic resonance

spectrometry to establish the configuration and conformation of the prodine alcohols in solution. The 4-phenyl group in (33) is expected to be in a plane approximately at right angles to that of the piperidine ring, the equatorial 3-methyl group and aromatic ortho hydrogen interaction being minimal in this conformation (37). This arrangement is in agreement with a series of cyclohexanes examined by Allinger



37

(1962) who showed that an equatorial phenyl group normally orients perpendicular to a cyclohexane ring in its most favoured conformation. In β-prodine alcohol the same orientation would create an axial 3-methyl-ortho aromatic hydrogen interaction. Therefore it is more likely that the 4-phenyl ring will be oriented in a plane parallel to the piperidine ringe (38).



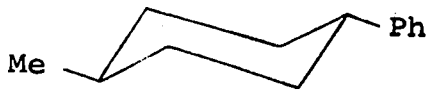
38

Proton magnetic resonance spectral analysis shows these differences quite clearly. The aromatic signal of the α-isomer is expected to be more complex since the ortho hydrogens are in distinctly different environments and thus chemical shift and coupling values with the meta protons, which also differ from each other, are expected to give rise to a large multiplet.

The β-alcohol, on the other hand, is expected to display evidence of more symmetrical environment for the aromatic protons due to the latter's parallel orientation. The aromatic signals for the two isomers in $CDCl_3$ were found to verify these expectations; the expected multiplicity of the α-4-phenyl signal is clearly evident, and the base width (30 Hz.) indicative of differing chemical shifts, while the β-4-phenyl signal is considerably more simplified and with a base width of 24 Hz.

The equatorial 3-methyl group in the α-isomer (35) is expected to fall within the diamagnetic shielding zone of the benzene nucleus (Johnson and Bovey, 1958) when the latter is oriented perpendicular to the piperidine ring. Likewise, the axial 3-methyl group is expected to fall within the same aromatic shielding zone due to the parallel conformation of the benzene ring. Thus both methyl groups are expected to fall upfield of those of 3-methyl cyclic analogues in which a phenyl ring is not adjacent to the methyl group. The chemical shift positions of the 3-methyl doublets for α- and β-prodine alcohols occur at δ0.63 and δ0.73, respectively, as

compared to the methyl doublet of 4-phenyl methylcyclohexane (39), which appears at δ1.01 (all observed in $CDCl_3$).

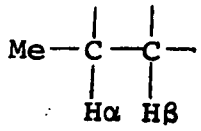


39

The small difference between the chemical shifts of the 3-methyl groups of the prodine alcohol isomers may be due to the deshielding of the lone electron pair of the nitrogen; this influence is expected to be greater in the β-isomer because, in this case, the 3-methyl group has a 1,3-diaxial relationship with the lone pair.

When the basic centre is protonated the α-3-methyl signal experiences only a small downfield shift (0.03 ppm) whereas the corresponding β- signal displays a larger (0.24 ppm) downfield shift which is indicative of the diaxial arrangement of the positive nitrogen and the axial 3-methyl group of the β-alcohol.

Peak multiplicity of the α-3-methyl signal for the α-isomer (J = 5.5 Hz.) is displayed by the appearance of a third peak midway between the main peaks, especially noticeable when examined in CCl_4. This distortion is a result of virtual long range coupling. Virtual coupling is seen between a methyl group and α- protons (40), when the coupling constant between the α- and β- protons is of the same order as the chemical shift difference between the two.



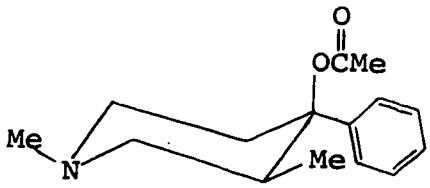
40

This arrangement is likely to prevail in the α-prodine type where the equatorial 3-methyl group is coupled to an axial C-3- proton which will be strongly coupled to an axial C-2- proton. The β-isomeric form, on the other hand, is coupled to an equatorial C-3- proton which will have a small coupling value with the axial C-2- proton, hence virtual coupling is not expected.

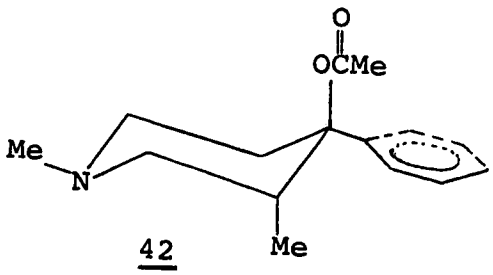
Subsequent PMR studies of the acetate, propionate and n-butyrate of the α- and β-1,3-dimethyl-4-phenyl-4-piperidinol hydrochlorides in $CDCl_3$ indicated that the conformations present in the alcohol analogues also exist in the ester derivatives.

The 3-methyl signal of α-prodine base appears at δ0.68, and at δ0.73 for the hydrochloride in $CDCl_3$; while the same group in the β-isomer exhibits a doublet at δ0.73 and δ1.03 for the base and hydrochloride respectively. These are close to the chemical shift values for the alcohol analogues and indicate a similarity of conformation.

Signals displayed in the PMR spectrum of α- and β-1,3-dimethyl-4-phenyl-4-acetyloxypiperidine (41, and 42 for the ester function) would be expected to show a difference due to the differing orientations of the 4-phenyl group. The 4-acetyloxy group is free to rotate around the O-C bond and hence will spend some time over the aromatic ring. However,



41



42

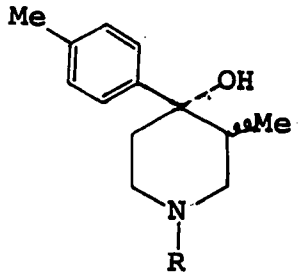
in the α-isomer the 4-phenyl group is preferentially oriented perpendicular to the piperidine ring and hence the methyl signal of the ester function will tend to be deshielded due to the diamagnetic current present at the "edge" of the benzene ring. Conversely, the β-4-acetyloxy group will be screened as it passes over the aromatic plane due to the latter's parallel arrangement with respect to the piperidine ring.

Chemical shift values observed in the present work for the acetates of α- and β-prodine alcohols appear near δ2.18 and δ2.00 respectively for the bases and hydrochlorides in $CDCl_3$. The β-acetate being upfield from the α- form due to the reasons outlined.

Similar chemical shift values for the propionates of the α- and β-1,3-dimethyl-4-phenyl-4-propionyl piperidines were observed ($OCOCH_2\underline{CH}_3$ triplets for α- and β-prodines near δ1.23 and δ1.08 respectively for bases and hydrochlorides in $CDCl_3$, and $OCO\underline{CH}_2CH_3$ quartets near δ2.62 and δ2.39 for the α- and β-hydrochlorides in the same solvent).

The PMR characteristics of a series of N-alkyl-3-methyl-4-p-tolylpiperidine-4-ols (43) have also been investigated

by Casy (1966) who noted that the same signal variations were displayed. The aromatic signal is broader and more complex in the α-isomer, the chemical shift upon protonation

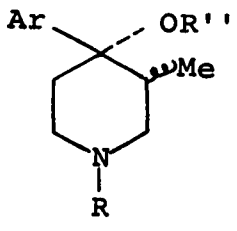


43

of the α-3-methyl group (δ0.63, base; δ0.67, hydrochloride) in $CDCl_3$ is small while the β-3-methyl signal difference (δ0.74, base; δ0.94, hydrochloride) in the same solvent is significantly large. It was therefore assumed that a similar stereochemistry must exist for these analogues; namely, the α-3-methyl group is equatorally oriented and the β-3-methyl group is axial, again assuming the piperidine ring to be in the chair form with the 4-aryl group equatorial.

The analgesic potency of a number of 4-acyloxy esters has been determined (Casy, 1968) and in all cases the β-isomer which has the cis 3-Me/4-Ph configuration and an axial 3-methyl conformation (in $CDCl_3$) is the more potent (see Table VII).

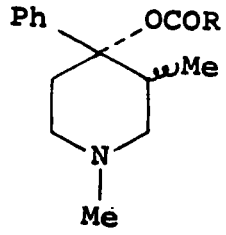
Casy et al. (1961) investigated the chemistry and analgesic potency of a series of 4-alkoxy piperidines (44) related to



44

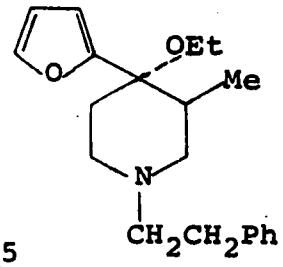
TABLE VII. ANALGESIC POTENCY OF SOME 1,3-DIMETHYL-4-ACYLOXY-4-PHENYLPIPERIDINE HYDROCHLORIDES

(HOT PLATE TEST, SUBCUTANEOUS INJECTION)



R	Isomer	Relative Potency
Me	α	0.4
Me	β	2.2
Et	α	2.0
Et	β	8.7
n-Pr	α	1.3
n-Pr	β	2.9
		morphine = 1.0

the prodines. In these compounds the 4-aryl group was changed to a number of heteroaromatic rings, and the 4-oxygen function altered to an ether group. The most active member of the series was found to be N-phenethyl-3-methyl-4-(2-furyl)-4-ethoxypiperidine (45). PMR data (unpublished) again showed that

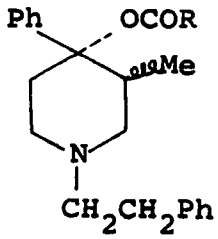


45

ED_{50} = 5.9 mg./Kg.
(Pethidine = 20 mg./Kg.)

the active diastereoisomer had the β- configuration (cis 3-Me/4-furyl).

Beckett and coworkers in 1959 synthesized a series of N-phenethyl-3-methyl-4-phenyl-4-acetyloxypiperidine derivatives (46) which were shown earlier to be significantly



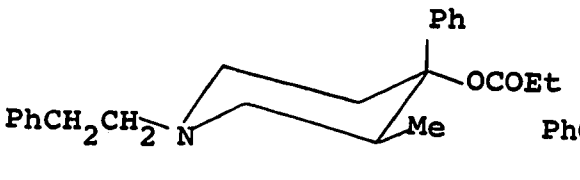
46

potent analgesics (see Table IV).

The configuration was established by the relative ease of hydrolysis of the ester function. Their findings led them to believe that the ester function which hydrolyzed fastest must be oriented equatorially, and that the more stable ester

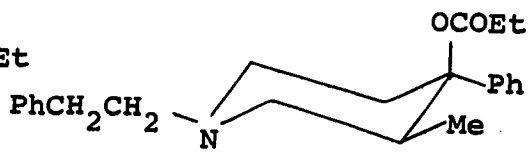
group was due to an axial, or less accessible, orientation. They assumed that the 3-methyl group would remain equatorial in both cases and that the piperidine ring maintained the chair conformation.

The ultimate conclusion therefore was that the cis 3-Me/4-Ph isomer and the trans 3-Me/4-Ph isomer had the configuration and preferred conformation as shown in (47) and (48).



cis 3-Me/4-Ph

47



trans 3-Me/4-Ph

48

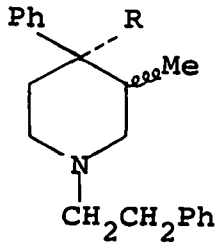
Although only the propionyloxy esters were subjected to hydrolysis, the configuration of the other isomers was related to these by the appearance, in the trans form, of a band near 1000 cm^{-1} in the IR spectrum that was absent in all the cis isomers.

The cis isomer was thus related to β-prodine and was given the β-isomer designation.

To ascertain that the β-isomer did have the cis 3-Me/4-Ph geometry, Casy et al. (1967) subjected both diastereoisomers to PMR analysis (see Table VIII).

The cis 3-Me/4-Ph configuration is evident from the larger downfield shift of the 3-methyl signal upon protonation of the basic centre. Also the ester signal positions of the cis isomer are upfield from those of the trans form

TABLE VIII. PMR CHARACTERISTICS OF SOME DIASTEREOISOMERIC N-PHENETHYL-3-METHYL-4-PHENYL-4-PIPERIDINOLS AND THEIR ESTERS IN $CDCl_3$



Form	R	Configuration	(PMR Signals)[a] 3-Me[b]	CH_2Me[d]	CH_2Me[c]
Base	OH	trans	0.63		
HCL	OH	trans	0.67		
Base	OH	cis	0.80		
HCl	OH	cis	1.05		
HCl	OCOEt	trans	0.73	2.62	1.22
HCl	OCOEt	cis	1.08	2.37	1.08

(a) chemical shifts in δ from TMS, spectra being measured at a frequency of 60 MHz

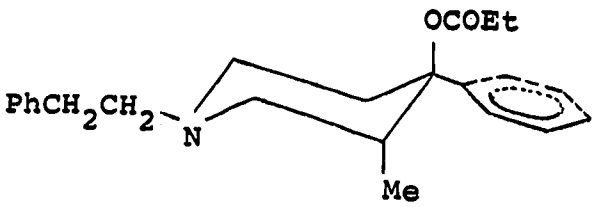
(b) doublet

(c) triplet

(d) quartet

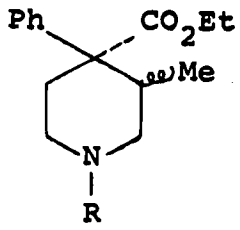
which is indicative of a parallel arrangements of the aromatic ring in the cis isomer. Therefore the probable configuration and conformation of α- and β-N-phenethyl-3-methyl-4-phenyl-4-propionyloxypiperidine (and the alcohol analogues) are as shown in (49) and (50) respectively.

49



50

3-Methyl analogues of pethidine (51) have been investigated by Casy et al. (1969) using techniques already outlined for the prodines. PMR data obtained are presented in Table IX.



51

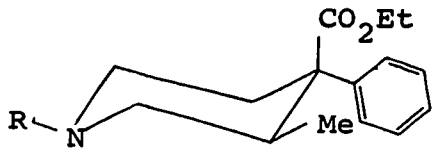
The chemical shifts of the β-3-methyl signals move downfield by approximately 0.3 ppm upon protonation, whereas the corresponding α- signals are much less affected by the same change. This has been shown to indicate that the α-isomer has an equatorial 3-methyl group while the β-isomer has an axial 3-methyl function. The ester signals of the α-isomer were found to be consistently lower field than those of the corresponding β-isomer. This has also been shown previously

TABLE IX. PMR CHARACTERISTICS OF SOME 4-ETHOXYCARBONYL-3-METHYL-4-PHENYLPIPERIDINES IN $CDCl_3$

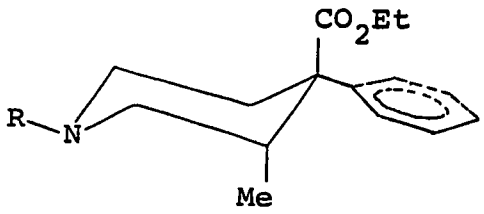
Form	R	Isomer	(PMR Signals)[a] 3-Me[b]	CH_2Me[d]	CH_2Me[c]
Base	CH_3	α	1.07	4.30	1.27
HCl	CH_3	α	0.93	4.30	1.27
Base	CH_3	β	0.75	4.18	1.13
HCl	CH_3	β	1.05	4.17	1.12
Base	$PhCH_2CH_2$	α	1.07	4.25	1.23
HCl	$PhCH_2CH_2$	α	1.00	4.35	1.30
Base	$PhCH_2CH_2$	β	0.75	4.13	1.13
HCl	$PhCH_2CH_2$	β	1.08	4.18	1.13

N.B. Notations used here have the same meaning as described in the footnotes of Table VIII.

to indicate a preference of the 4-phenyl group in the α-isomer to be oriented perpendicular to the piperidine ring (52) and in the β-isomer to be oriented parallel to it (53). Both forms are shown in the chair conformation with the phenyl ring equatorial.



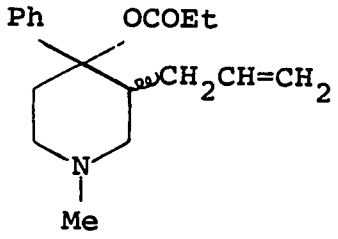
α trans 3-Me/4-Ph



β cis 3-Me/4-Ph

52 where R = Me or $PhCH_2CH_2$ 53

Ziering et al. (1957) reported the synthesis of 1-methyl-3-allyl-4-phenyl-4-propionyloxypiperidine(54). The analgesic activity of the α-isomer in this case was found to be eleven



18

times as active as morphine while the β- form was the less active isomer being only three times more active than morphine (β-prodine is seven times more active than morphine in the same test). This compound may therefore provide an exception to the finding that the minor isomers are more active than the major forms in the 4-phenylpiperidine

derivatives; however, the stereochemistry of the 3-allyl derivatives has not been unequivocally established.

ISOMERIC PROMEDOLS AND THEIR CORRESPONDING ALCOHOLS

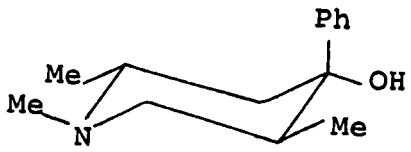
In the 1,2,5-trimethyl-4-phenyl-4-piperidenols, there exist four (±) diastereoisomeric pairs designated as α, β, γ, and δ. The original workers, Nazarov et al. (1949), assigned the configuration (55) and (56) to the γ- and α-forms respectively. The gamma isomer was postulated as having

55

56

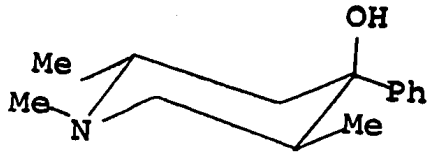
a trans disposition of the 2- and 5-methyl groups and a trans arrangement of the 4-phenyl ring with respect to the 5-methyl group. The α-isomer was stated as also having the 2- and 5-methyl groups trans, but with a cis configuration of the 4-phenyl ring with respect to the 5-methyl group.

In 1959 Shvetsov and Kucherov claimed to have isolated all four (±) diastereoisomers of 1,2,5-trimethyl-4-phenyl-4-piperidinol. The configurational assignments were reversed for the α- and γ-isomers from those of Nazarov. Thus, according to Shvetsov, the γ-isomer had the configuration (57), and



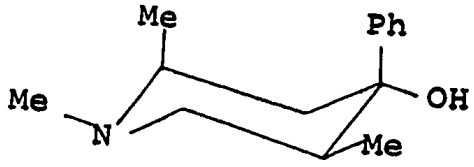
57

α-promedol alcohol was then assigned the structure (58).



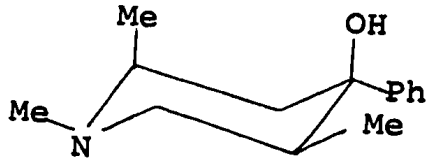
58

Isopromedol alcohol, the β-isomer, was assigned the cis 2,5-dimethyl arrangement and a cis 4-Ph/5-Me disposition (59) by Shvetsov in the same paper.



59

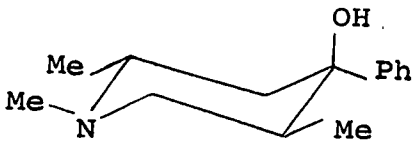
The same workers concluded that the δ-isomer must have the only configuration remaining, that is, a cis 2,5-dimethyl and a trans 4-Ph/5-Me arrangement (60).



60

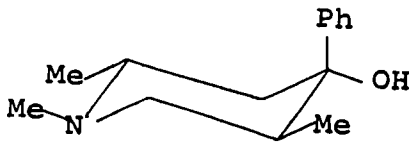
In order to resolve these conflicting views, several workers in Russia attempted to establish conclusively the stereochemistry of the isomeric 1,2,5-trimethyl-4-phenyl-4-piperidinols and their esters. Prostakov and Mikheeva (1961) applied the principles of column chromatography on the alcohols

and found that the γ-isomer was eluted first from an alumina column, followed by the β-form and finally the α-alcohol. The γ-isomer was thus thought to have an axial hydroxyl group since it was bound the least on the column; conversely the α-isomer was bound most strongly and hence should have an accessible equatorial hydroxyl group. In both these forms the C-methyl groups were assumed to have a trans diequatorial arrangements (55) and (56).



(γ-promedol alcohol)

55



(α-promedol alcohol)

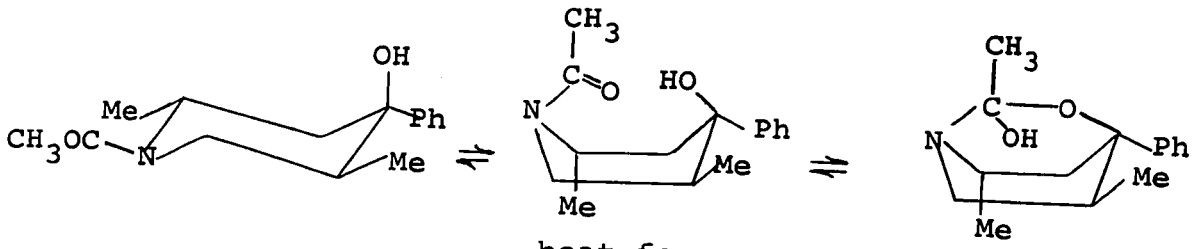
56

No stereochemical conclusions were reached about the β-isomer in this paper.

Ester hydrolysis was used in the prodines to determine the steric hindrance of the ester function (see earlier). Using comparable conditions, the α- 1,2,5-trimethyl-4-phenyl-4-propionoxypiperidine was found to hydrolyze much faster than the γ-isomer (Prostakov and Mikheeva, 1962). This result again indicated, to these authors, that the hydroxyl group is equatorial in the α-isomer and axial in the γ- form.

In 1958, Nazarov and coworkers studied N→O acyl migration using the method introduced by Fodor and Nador (1953). In order for N→O acyl migration to occur the 4-hydroxy must be "syn", or on the same side and pointing to, the N-acetyl

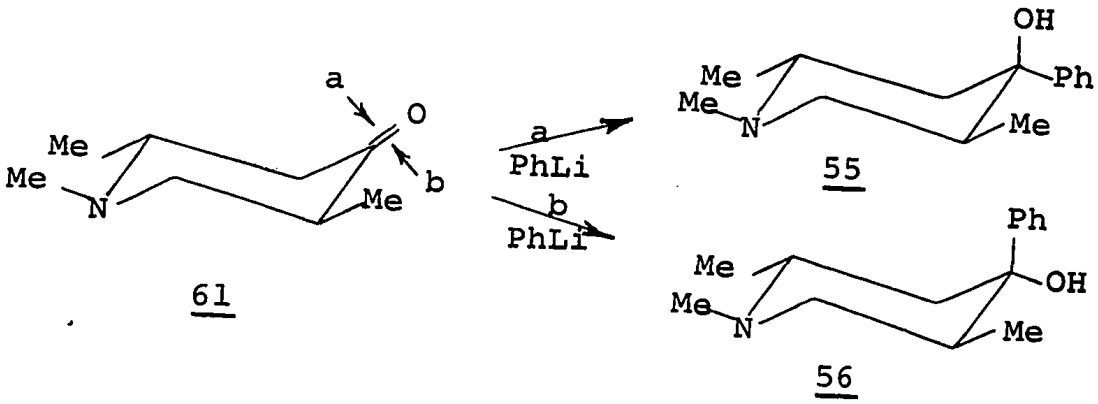
moiety. The γ-N-acetyl isomer below readily undergoes acid catalyzed acyl migration to give the γ-4-acetyloxy compound, and base catalyzed acyl migration to give the γ-N-acyl isomer back again. This is thought to occur via the boat conformer which will facilitate the N→O acyl migration.



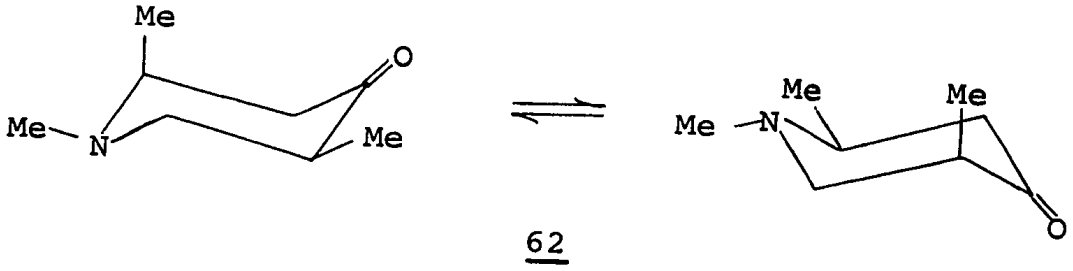
boat form

The α-isomer would not be thought to undergo acyl migration since the OH is not in an axial position; however, under severe conditions the α-isomer does in fact undergo N→O acyl migration, and this was explained as occurring via an inversion of configuration at C-4, thus giving the γ-isomer of 2,5-dimethyl-4-phenyl-4-piperidinol N-acetate, as the reverse O→N acyl migration in the γ- form does also.

Since 1,2,5-trimethyl-4-piperidone (the precursor of the promedol alcohols) consists largely of the trans isomer (61) (Nazarov and Shvetsov, 1959), which, in its most favoured conformer, will have the methyl groups equatorial, then aryllithium attack should give rise to the γ-isomer (55) predominantly, and a minor amount of the α- form (56). The cis 2,5-dimethyl isomer (62) will therefore give rise to the β- and δ-isomeric forms.

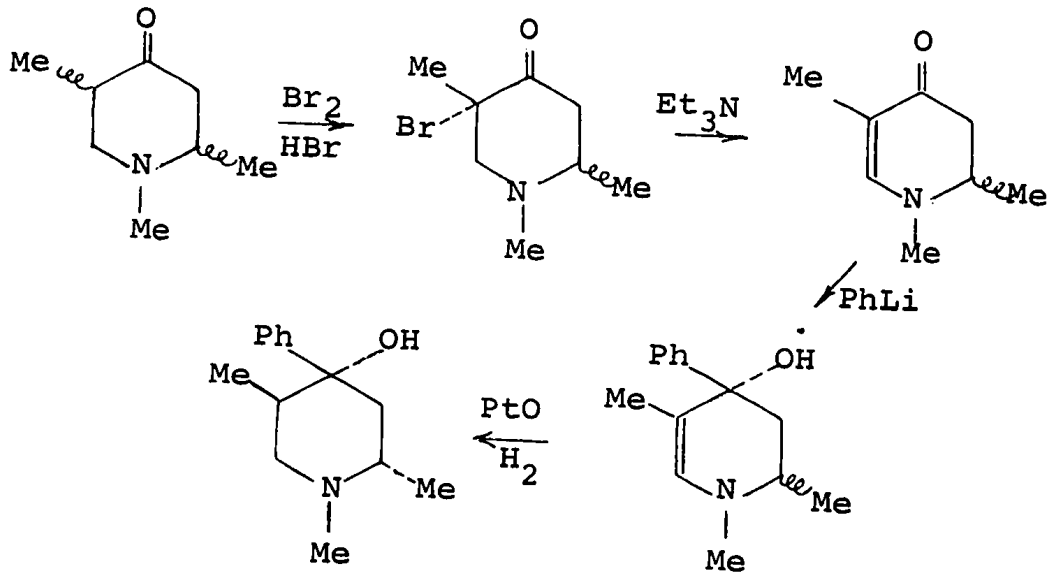


61



62

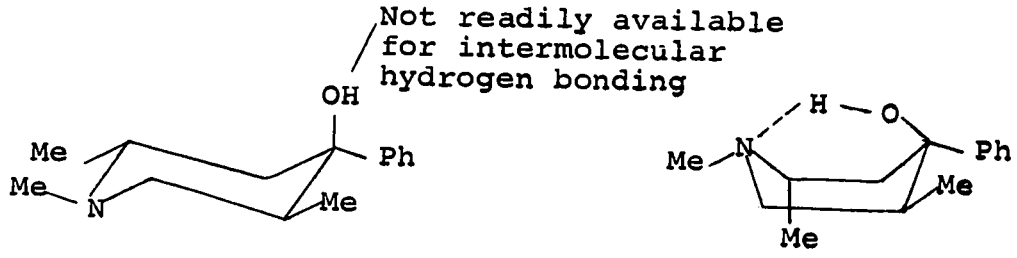
In order to make the α- and β-promedol more accessible, since these are formed in small amounts during a normal synthesis, a stereospecific synthesis was proposed by Nazarov and Shvetsov (1959). The sequence shown below (Scheme I) was



Scheme I

not supported by any proof, and will be the subject of further investigation later.

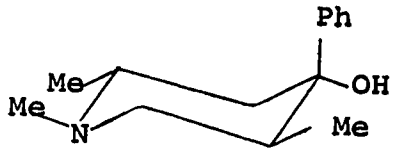
Infrared evidence of the spatial arrangement of the 1,2,5-trimethyl-4-phenyl-4-piperidinols was studied by Prostakov et al. (1964) who reasoned that the infrared absorption bands in the 2800 to 2900 cm^{-1} region and a band at 3200 cm^{-1} were due to vibrations of the hydroxyl groups, which will form inter- and intramolecular hydrogen bonds. With dilution studies, the band at 3200 cm^{-1} diminished, and hence must be due to intermolecular hydrogen bonding. The difference in absorption upon dilution was greatest in the γ-isomer as compared to α- and β- forms, while on the other hand the α- and β-isomers show weaker intramolecular bonding. They concluded, therefore, that the γ- isomer must have an axial hydroxyl group capable of strong intramolecular hydrogen bonding but sterically hindered from intermolecular bonding (55).



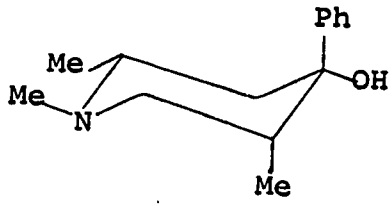
55

The α- and β-isomers, because they behave in an opposite manner to the γ- form, were said to have equatorial hydroxyl groups and were assigned the structures (56) and (63).

56



63



It has been suggested by Prostakov (1962) that β-promedol and β-prodine have identical steric configurations of the 3- and 4- substituents in the piperidine ring and therefore are expected to have almost identical physiological activities. This view is not without merit; however, the conformation as well as the configuration of the promedols will be shown later to be an important feature from a structure-activity standpoint.

It may be fairly stated from the evidence proposed that the stereochemistry of the 1,2,5-trimethyl-4-phenyl-4-piperidinols and their esters (which are known as the promedols) has not been conclusively established.

The analgesic properties of the promedols have been investigated and, as is often the case, the minor isomers are the most active (see Table X). Since the promedols are so potent, precise knowledge of their stereochemistry is of importance and will be the subject of much of this thesis.

TABLE X. ANALGESIC POTENCY OF
1,2,5-TRIMETHYL-4-PHENYL-4-PROPIONYLOXYPIPERIDINE IN RATS

(Route of Administration Not Given)

(Nazarov et al., 1956)

(Shvetsov and Kucherov, 1959*)

Name	Isomeric Designation	Relative Potency
Morphine		1
Promedol	γ	2-3
Isopromedol	β	4
Alphapromedol	α	8
Delta Promedol*	δ	4-6

AIMS AND OBJECTIVES OF THE PRESENT WORK

The 3-methyl 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 corresponding 1,2,5-trimethyl derivatives (the promedols), compounds which are not only potent, but which show considerable activity variation amongst the various forms.

The prime aim of this thesis, therefore, is to obtain further data upon the promedol isomers with a view:

(1) to establish the configuration and conformation of each isomer and to relate the result to the prodines; and

(2) to investigate certain structure-activity relationships in the class, such as the ester groups and the N-methyl substituents.

To this end, work was also planned on 3-methyl analogues to correlate the influence of the methyl group adjacent to the 4-Ph, 4-OCOEt unit, and upon 2-methyl analogues to obtain data about the 2-methyl influence.

This work entailed the following aspects:

(1) synthesis;

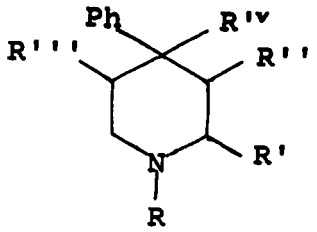
(2) separation of isomers;

(3) assignment of configuration and conformation using chemical and physical methods;

DISCUSSION OF RESULTS

DISCUSSION OF RESULTS

The bulk of the work in this thesis involves the synthesis of 4-arylpiperidine derivatives with methyl groups substituted at various positions on the ring:



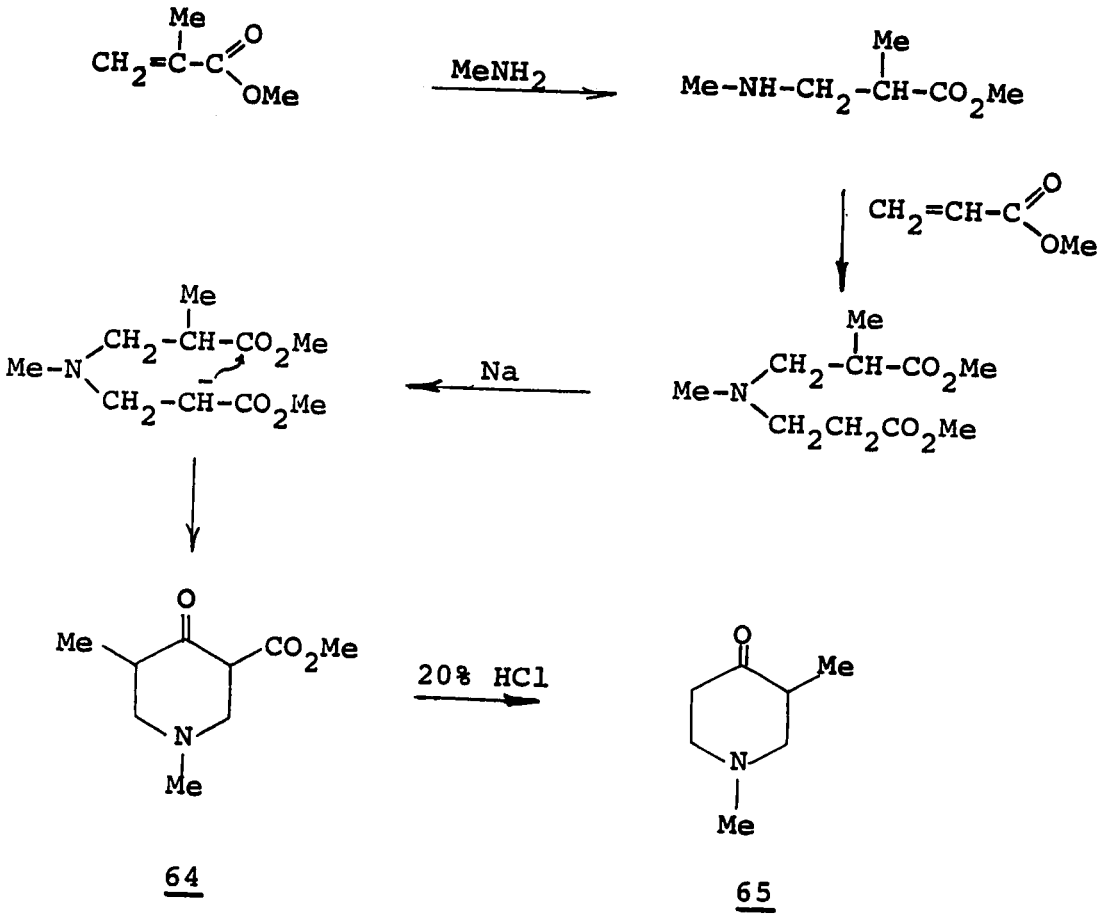
where	R =	R', R'', R''' =	R'''' =
	Me	CH_2-CH=CH_2	H
	Et	CH_3	OH
	CH_2Ph	H	OCOMe
	CH_2CH_2Ph		OCOEt

4-PIPERIDONE SYNTHESIS

4-Piperidones (65) are the key intermediates in the synthesis of the above 4-arylpiperidines and therefore a description of the various ketones produced will be presented. The general procedure for the synthesis of the 3-substituted-4-piperidones was first investigated by Howton (1945), whose procedure is shown in Scheme II.

The N-methyl-3-carbomethoxy-5-methyl-4-piperidone (64) was not identified and is quite likely that N-methyl-3-carbomethoxy-3-methyl-4-piperidone was also formed during the Dieckmann cyclization (see Schaefer and Bloomfield, 1967).

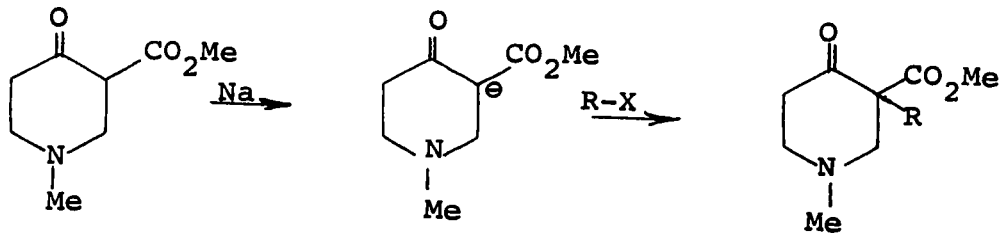
It would be of interest to alkylate, with various alkyl



64 65

Scheme II

halides, the commercially available 1-methyl-3-carbomethoxy-4-piperidone (66) thereby producing any number of 3-substituted piperidones.



66 67

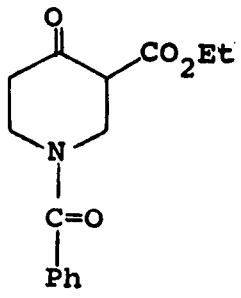
Scheme III

The normal method of alkylating an α-keto ester is by treatment with a strong base to produce the carbanion (67) which is readily alkylated with most alkyl halides (Scheme III).

Several attempts to alkylate the anion (McElvain, 1946 and 1956, and refs therein) resulted in the quaternary salt rather than the substituted piperidine.

Although exact proof that the latter fact was not offered, the solubility characteristics and non-volatility of the product indicated that the salt had been formed. It is quite possible that the quaternary salt and the substituted piperidine were produced at the same time; however, the quaternary salt, once formed, cannot be readily converted back to the free base and therefore the desired products could not be isolated and the method was not pursued.

Baty (1967), and McElvain and Stork (1946), successfully alkylated N-benzoyl-3-carbethoxy-4-piperidone (68) with various alkyl halides, since this compound no longer carries a basic nitrogen and hence is not vulnerable to salt formation.

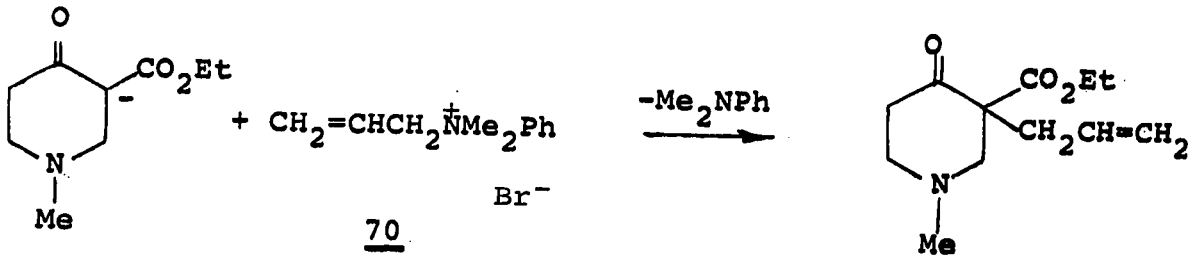


68

Attempts to repeat the route outlined by Baty did not meet with success in several trials and was not pursued

further, since the desired products were available in relatively good yields by a modification of Howton's method.

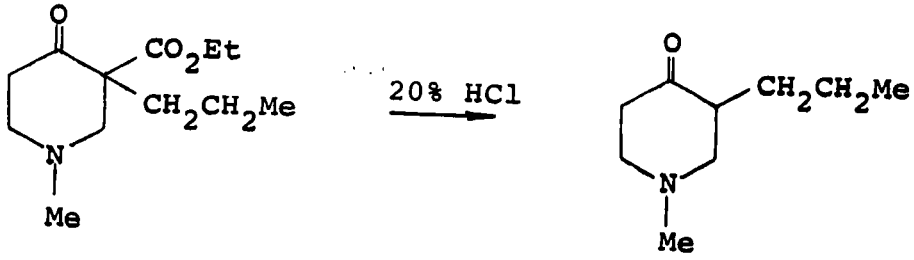
In order to circumvent the production of the amine salt, McElvain and Barnett (1956) proposed the use of allyl dimethylanilinium bromide (70) as an alkylating agent (Scheme IV) to produce N-methyl-3-allyl-3-carboethoxy-4-piperidone (71) from the anion derived from N-methyl-3-carboethoxy-4-piperidone (69). The product (71) was distilled and a



69 70 71

Scheme IV

significant amount of decomposition was noticed. The 3-allyl-3-carboxy-derivative was not decarboxylated at this point, but rather the allyl function catalytically reduced to give the n-propyl analogue (72).

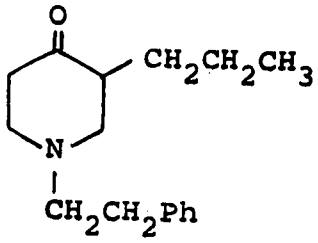


72 73

This product was then decarboxylated to give N-methyl-3-n-propyl-4-piperidone (73).

In 1958 Kirk used this method to make the N-phenethyl

analogue (74).

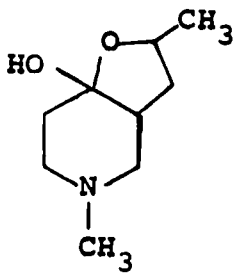


74

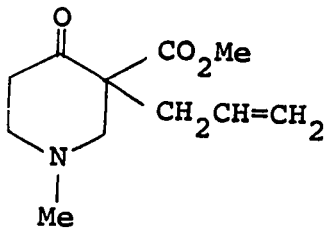
It appeared that if decarboxylation was affected after alkylation with allyl dimethylanilinium bromide that this would be a good method to produce N-methyl-3-allyl-4-piperidone. As mentioned earlier, the 4-phenyl alcohol and esters of this compound have high activity and according to Zeiring et al. (1957), the most active isomer differs in configuration from the more active form of the 3-Me analogues.

Attempts in our laboratories to produce the 3-allyl analogue met with failure when the decarboxylation of (71) was tried. McElvain and Barnett (1956) also obtained the same results in an identical experiment. They isolated a hemiacetal (75) which later was also isolated as a distillable solid in this work after decarboxylation of N-methyl-3-carbomethoxy-3-allyl-4-piperidone (76)

In order to identify the suspected hemiacetal (75) that

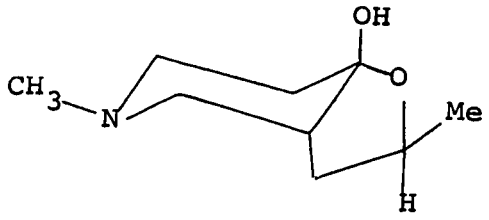


75

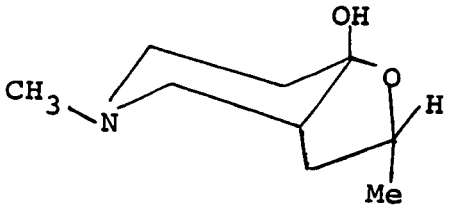


76

was obtained in this work, mass spectrometry was employed. The spectrum showed a molecular ion peak $(M)^+$ at m/e 171 which corresponds to the molecular formula $C_9H_{17}NO_2$, the $\frac{(M+1)^+}{M^+}$ and $\frac{(M+2)^+}{M^+}$ ratios verified the existence of one nitrogen and two oxygens which could not be the case if decarboxylation had occurred. The PMR spectrum of the product showed a pair of methyl doublets at δ1.40 and δ1.36 due to the two possible orientations of the methyl group next to the ether oxygen (77 and 79).



77

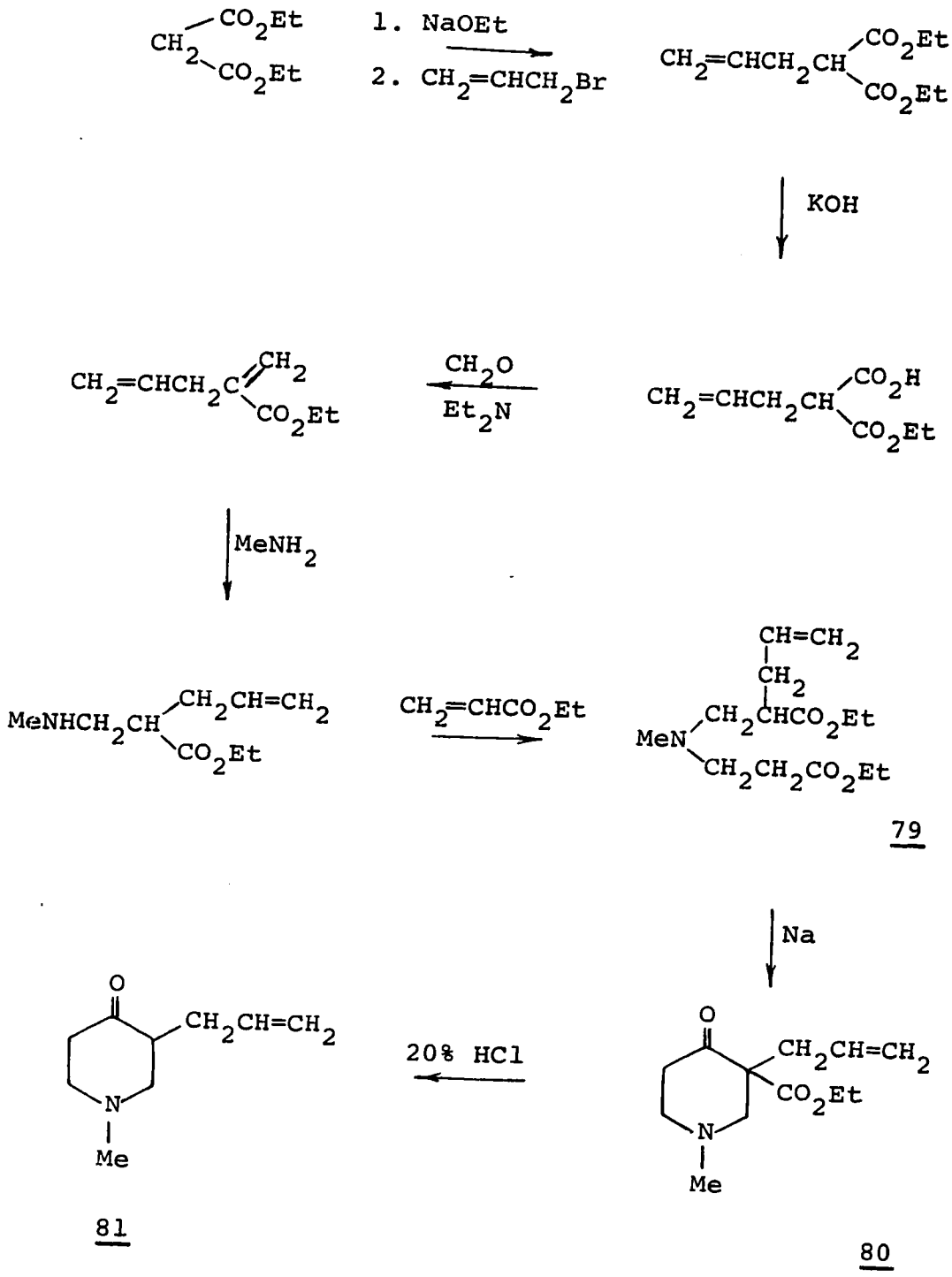


78

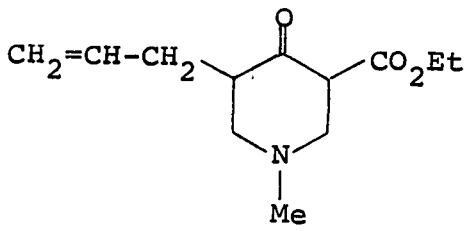
In 1957, Zeiring claimed to produce N-methyl-3-allyl-4-piperidone employing the ester condensation developed by Howton (Scheme V).

The isomeric nature of the N-methyl-3-carboethoxy-3-allyl-4-piperidone (80) was not proven to be as shown, and

Scheme V


1. NaOEt
2. CH2=CHCH2Br
KOH
CH2O
Et2N
MeNH2
CH2=CHCO2Et
Na
20% HCl
Me
Me
79
80
81

it is likely that the 5-allyl derivative (82) was also formed (evidence from later work substantiates this possibility).



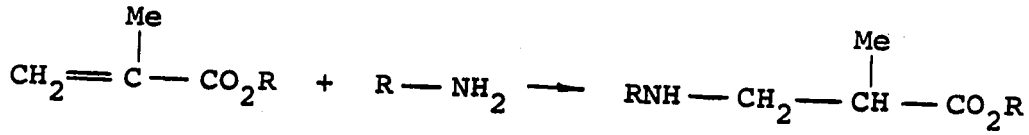
82

It would seem, therefore, that N-methyl-3-allyl-4-piperidone (81) can be produced by Howton's procedure; however, several attempts in the course of this work to reproduce Zeiring's route resulted in formation of the hemiacetal (76) upon decarboxylation of the intermediate (80) rather than the 3-allyl analogue.

3-METHYL-4-PIPERIDONES

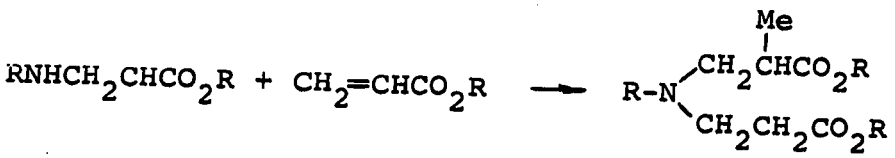
In this group of N-alkyl-3-methyl-4-piperidones, the method of synthesis was either the same as that used by Howton (1945) or one of several modifications.

The condensation of α-, β-unsaturated esters (83) with amines (84) is known to be reversible (McElvain, 1946; Harper, 1960). The initial condensation usually proceeds smoothly when the reactants are gently refluxed together for several hours. In at least one case, however, the best yields were obtained by letting the reactants sit at room temperature for a long time (see later). The adducts of the type (85) were



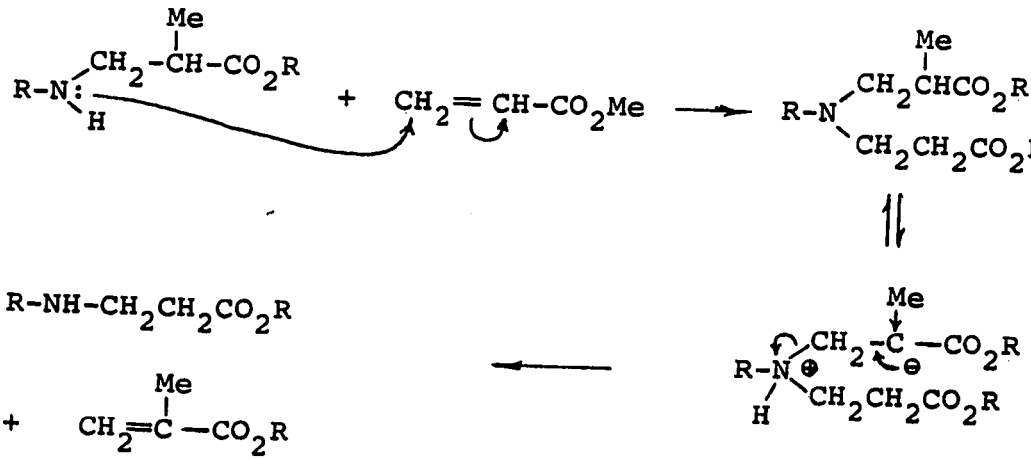
83 84 85

distilled at relatively low temperature (below 120°) and pressure (0.5 mm). When the product of the second addition (86) is distilled, however, there is a tendency for the tertiary amine to break down, particularly if high temperatures need to be employed. The direction of elimination occurring



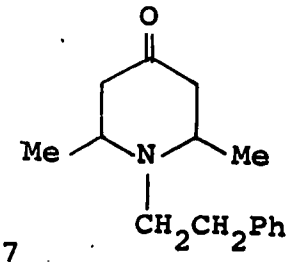
86

during distillation of the diester (Scheme VI) will likely be towards the unsubstituted ester moiety since the methyl group will tend to stabilize the incipient double bond.



Scheme VI

These factors are most likely responsible for the failure of Harper et al. (1960) to prepare N-phenethyl-2,6-trimethyl-4-piperidone (87) by the acrylate condensation route, for



87

when the second ester addition occurs, the tertiary amine produced is not only electronically unstable but steric crowding will also increase the likelihood of breakdown (particularly during distillation at higher temperatures).

Once the diester has been formed (and isolated), the significant step in the synthesis is the success (or failure) of the Dieckmann condensation, or cyclization. The yields of this particular reaction vary greatly depending on the molecule to be cyclized and the base catalyst employed. Since the anion, once formed, is very reactive, it is able to condense with ester functions in the same or different molecules. That is, intermolecular condensations as well as intramolecular cyclizations may occur.

Refering to Scheme II, the anion should react with its own "tail" preferentially if high dilution with solvent is employed. Although studies in this respect were not complete, they did show that increases in the molar ratio of solvent to solute past a ten molar excess resulted in no significant trends toward higher yields.

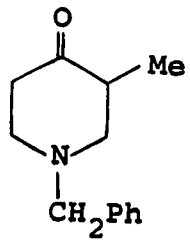
The base used to form the anion is normally an alkaline earth element, with sodium the usual choice. Yields of the piperidones produced by this method vary, depending on the workers, but are normally between thirty and sixty percent, based on the amount obtained from the diester after a two-step process, namely cyclization and then decarboxylation.

In the present work for the preparation of 1,3-dimethyl-4-piperidone (65) (Scheme II), several variations of the cyclization step were employed in an effort to increase the yields of this ketone.

When sodium sand in toluene or xylene was the base catalyst, the piperidone was isolated in yields up to forty-five percent. Sodium hydride emulsion in mineral oil was somewhat easier to handle but gave low yields: twenty-three percent in one trial and thirty-eight in another. The variability may be attributed to inconsistencies in the emulsion or hydrolysis of the NaH to NaOH since the total exclusion of atmospheric water is difficult under normal storage conditions. Sodium amide is much the same as sodium hydride; unfortunately yields of the piperidone were found to be very poor when the amide was employed. Again this may be attributed to contamination by atmospheric water.

When sodium methoxide in toluene was employed in the synthesis of 1,3-dimethyl-4-piperidone (65), the reagent was made fresh and the remaining methanol evaporated completely at low pressure before toluene was added. Yields obtained from this reaction were only thirty percent; yet when the

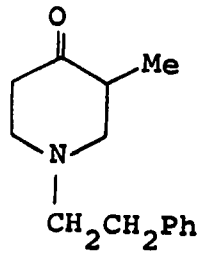
same reagent was used to produce N-benzyl-3-methyl-4-piperidone (88), the yields were very good (sixty-one percent).



88

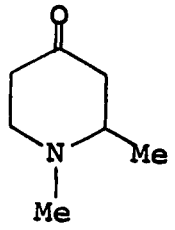
Normally the cyclized product is poured onto twenty percent hydrochloric acid and decarboxylated directly. However, this particular ketone was initially insoluble in this mixture and separated as a fluffy white solid. The total weight of this solid, which proved to be a mixture of N-benzyl-3(and 5)-carbomethoxy-3-methyl-4-piperidone, indicated good yields at this point. Therefore it is possible that the decarboxylation step is at least partially responsible for lowering the total yields (see later).

N-phenethyl-3-methyl-4-piperidone (89) was produced, using sodium sand in toluene, in varying amounts, the least of which was seventy-five percent, obtained from a small scale synthesis.



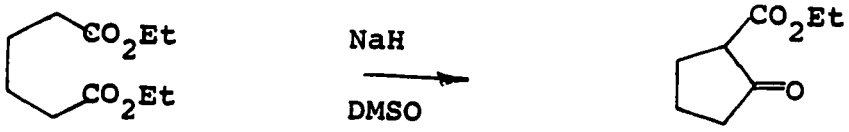
89

The use of potassium ethoxide in toluene, produced in the same way as sodium methoxide, resulted in comparatively good yields of thirty-seven and forty-three percent of 1,2-dimethyl-4-piperidone (90) obtained from two trials (see later).



90

The possible effect of solvent was then investigated using 1,3-dimethyl-4-piperidone (65) as a model in an attempt to determine the contribution of this variable towards higher yields. Bloomfield and Fennessey (1964) used dimethyl sulfoxide and sodium hydride in the cyclization of diethyl-adipate (91) to produce sixty-five to seventy-five percent yields of 2-carboethoxypentanone (92).



91 92

Using the same method, only thirty-five percent yields of 1,3-dimethyl-4-piperidone (65) were obtained. Hence the yields appear to depend more on the nature of the diester to be cyclized rather than the solvent.

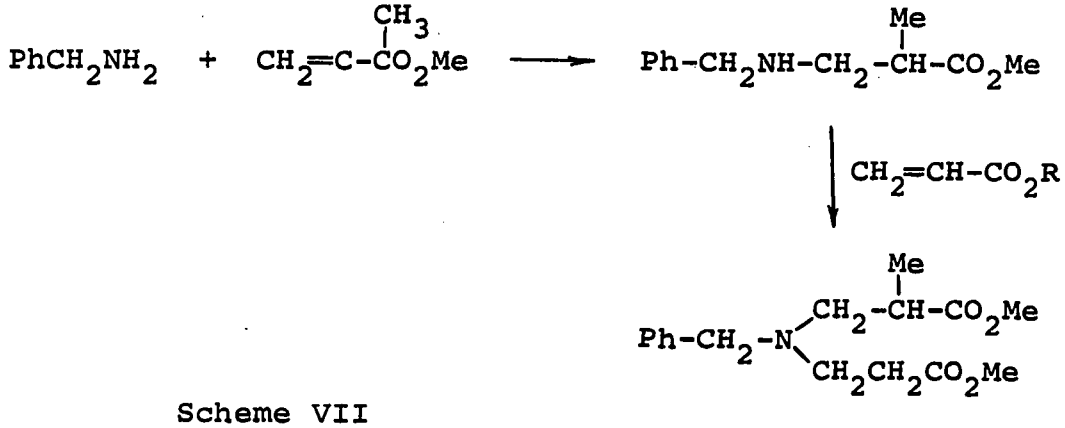
Mistryukov et al. (1961) employed sodium in liquid ammonia

(essentially fresh sodium amide) to produce 1,3-dimethyl-4-piperidone and claimed yields of up to seventy percent. However, as was frequently the case, yields in the present work were lower, and of the order of forty-seven percent, using the same method. This particular procedure, although reasonably good yields result, is lengthy and inconvenient and therefore was used only twice.

Perhaps the best consistently dependable method of producing the variety of piperidones required was that employing freshly prepared sodium (or potassium) methoxide and toluene as a solvent.

In the synthesis of 1,3-dimethyl-4-piperidone, it was found that yields could be increased by five percent or more if continuous extraction of the slightly water soluble base with chloroform was employed. Normal salting out techniques did not decrease the water solubility to a significant amount to allow regular extraction procedures.

Although the synthesis of N-benzyl-3-methyl-4-piperidone is reported in the literature (Carabateas and Grumbach, 1962), the method described presented severe problems. No difficulty was encountered in preparation of the mono ester (Scheme VII); however, when the addition of methyl acrylate to the mono ester was thought to be complete, and the product distilled, the only product isolated appeared to be the unreacted secondary amine and methyl acrylate. Several attempts to effect addition of the second acrylate ester by varying the conditions met with the same failure. Finally,



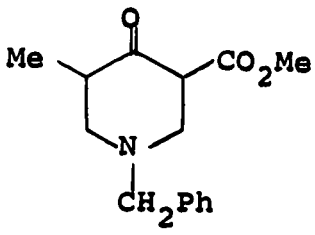
Scheme VII

PMR analysis of the distillate from the reaction showed that the initial fractions contained both unreacted methyl acrylate and methyl methacrylate. The only possible means for the latter to appear in the initial distillate would be from breakdown of the initial mono ester during distillation. This reversibility has been mentioned earlier (p. 64) as a possibility in all acrylate additions; however, it had never been observed before.

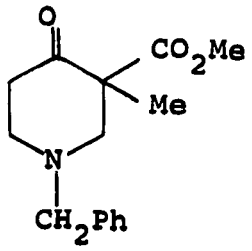
In the literature the diester has been reported as distilling at 140-145°/0.3 mm; however, other workers have reported a pressure of 0.01 mm. is required to prevent breakdown (Iorio, 1970). Unfortunately, this high vacuum could not be attained so that the distillation temperature could not be kept low, therefore the excess of methyl acrylate was removed at 20 mm. and room temperature on a rotary evaporator. The residue was examined by PMR and displayed a spectrum completely devoid of the characteristic vinylic multiplet of methyl acrylate (δ5.5 - 6.1). The entire spectrum was consistent with the diester product (δ1.08, 2-methyl

doublet; δ3.60 and 3.64, methyl ester singlets; multiplet between δ2.30 and 3.0 integrating for 7 protons; the benzyl methylene protons were found under the ester signals, and the phenyl ring itself, a singlet at δ7.25).

This diester was then cyclized using NaOMe in toluene, and as mentioned previously, the N-benzyl-3-carbomethyl-5-methyl-4-piperidone intermediate (93) was initially insoluble when poured onto twenty percent hydrochloric acid. PMR analysis showed (by the absence of a singlet for a tertiary 3-methyl group) that no detectable amount of N-benzyl-3-carbomethoxy-3-methyl-4-piperidone (94) was formed during the synthesis.



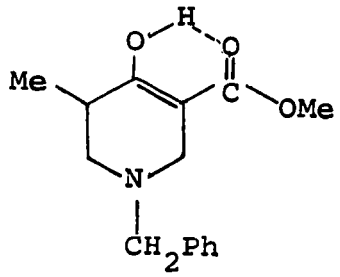
93



94

As might be anticipated from the structure of the α, β-keto ester, the IR spectrum showed the existence of tautomeric forms. If the form (95) exists in the hydrochloride then it would be expected that the IR spectrum should show an absorption band in the OH region and as well bands for the ester function and the double bond but no ketonic absorption. This was indeed found to be the case; a broad OH band appeared between 3400 and 3100 cm^{-1} and as well the bonded ester appeared at 1695 cm^{-1}, the longer wave length

position being indicative of hydrogen bonding. The double bond appeared at 1620 cm^{-1}.



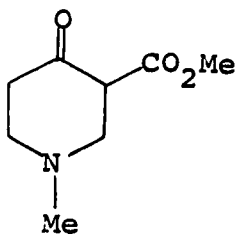
95

The spectrum of the free base (film) also had a small OH band centered at 3400 cm^{-1}, but four almost equally intense bands between 1800 and 1600 cm^{-1}. Absorption at 1750 cm^{-1} and 1725 cm^{-1} was thought to be due to the non hydrogen bonded species (93) while the band at 1665 cm^{-1} was likely due to the bonded ester (95) and the double bond was therefore assigned to the peak at 1625 cm^{-1}. Since, in the spectrum of the base, the absorption due to the carbonyl groups were nearly equally intense, it was reasoned that the enol form exists to the extent of 50%, while in the hydrochloride the lack of any ketonic absorption band indicates that the enol form is the only one present.

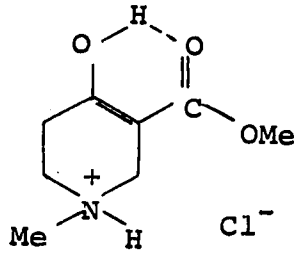
In order to ascertain that the hydrogen bonding was intramolecular and not between two molecules, dilution studies (in CCl_4) were undertaken. These showed conclusively by the consistency of the ketone to enol ratio that no detectable amount of intermolecular bonding occurred.

Comparison of this sample was made with another analogue:

N-methyl-3-carbomethoxy-4-piperidone (kindly supplied by the Smith, Kline and French Laboratories, Philadelphia). The IR spectrum of this α, β-keto ester (96) displayed absorption bands at positions that very nearly corresponded to those of the previous analogue for both the hydrochloride salt and its free base.



96



97

Again, it was clear that the hydrochloride existed entirely in the enol form (97) since only an OH band (broad absorption between 3500 and 3100 cm^{-1}) and a band due to the bonded ester (1685 cm^{-1}) and the conjugated double bond (1620 cm^{-1}) appeared. The absence of any ketonic absorption precluded the presence of the "free" species in this salt.

The spectrum of the base (film) displayed on OH band at 3400 cm^{-1} and as well absorption at 1665 cm^{-1} for the bonded ester and at 1625 cm^{-1} for its conjugated double bond. A peak at 1750 cm^{-1}, then, was due to the presence of the ketone group, and a band at 1725 cm^{-1} was assigned to the double bond of the free keto ester species (96).

The PMR spectrum of the N-benzyl-3-carbomethoxy-5-methyl-4-piperidone hydrochloride (93) was of interest from two

points of view:

1. The doublet nature of the ring methyl signal establishes the product as a 5-methyl derivative and excludes the possibility of any of the 3-methyl form (94) being present (see earlier).
2. The 5-methyl signal appeared as a pair of doublets rather than a single doublet in a variety of solvents and in both base and salt forms (see Table XI). The relative intensities of the pair of doublets were nearly equal in all solvents.

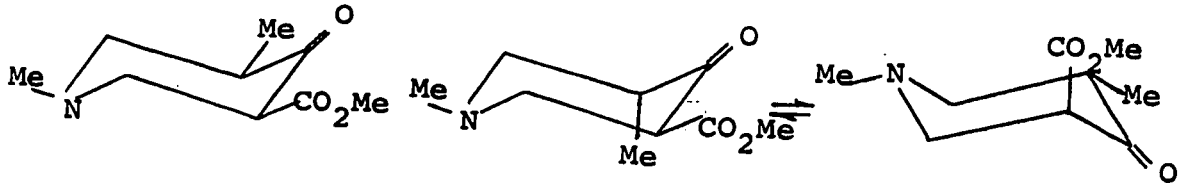
TABLE XI. PMR CHEMICAL SHIFT VALUES OF N-BENZYL-3-CARBOMETHOXY-5-METHYL-4-PIPERIDONE

Solvent	Form	PMR Signals [a]	
		5-Me [b]	3-OCOMe [c]
$DmSO-d_6$	base	0.98, 0.87	3.73
	HCl	1.13, 0.93	3.73
$CDCl_3$	base	1.17, 0.98	3.73
	base + TFA [d]	1.20, 1.12	3.67
D_2O	HCl	1.25, 1.00	3.79

(a) Chemical shifts in δ units from TMS, being measured at a frequency of 60 MHz. (b) Doublet. (c) Singlet. (d) The hydrochloride was insoluble in $CDCl_3$.

This result is evidence that (93) exists in solution as a

mixture of cis and trans stereoisomers (99) and (100). The lack of duplication of the COOMe signal suggests that the

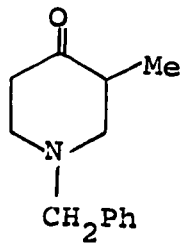


99 100

preferred conformation of the trans isomer is that with an equatorial ester function since the environments of COOMe in the two isomers are then about the same. The 5-methyl group is equatorial in cis and axial in trans, in this case, and hence would be expected to exhibit different chemical shifts. The lower field doublet is probably due to the trans form since an axial 5-Me will be deshielded by the nitrogen lone pair (in the base) and an N^+-H function (in the protonated form) in this isomer (see page 76). The deformed nature of the higher field 5-Me doublet seen in the spectrum of the base in $CDCl_3$ substantiates these assignments since the effect (virtual coupling, see page 38) is more likely to arise when the methyl substituent is equatorial than when it is axial.

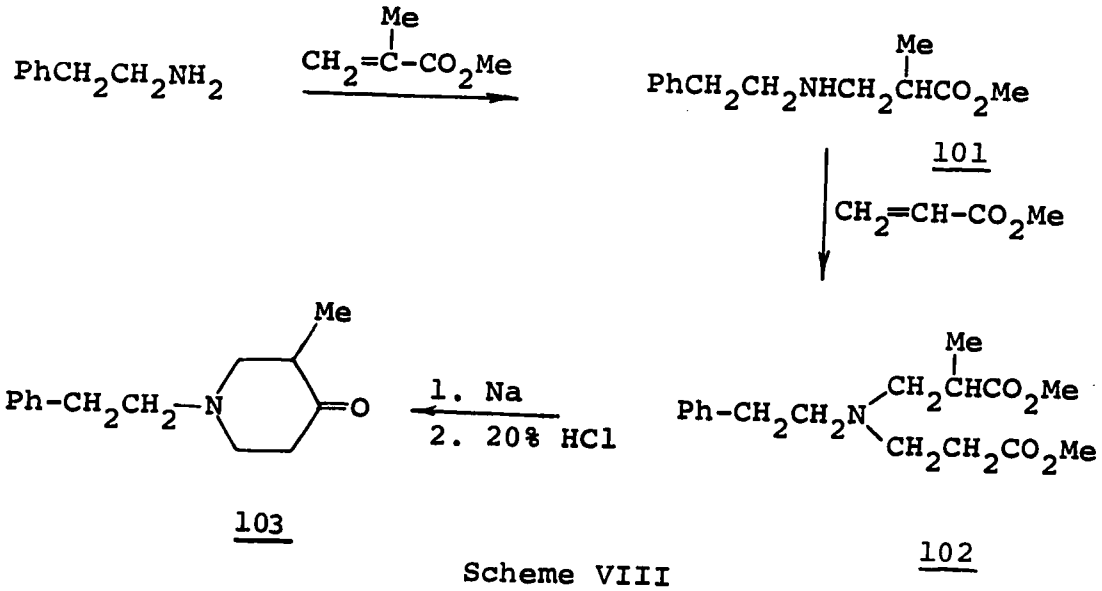
N-benzyl-3-carbomethoxy-5-methyl-4-piperidone (93) was finally decarboxylated by suspending the solid in concentrated HCl and refluxing vigorously for twelve hours to give N-benzyl-3-methyl-4-piperidone (88). PMR spectrum of the product displayed the 3-methyl doublet at δ0.93 which shifted downfield by a small amount (0.05 ppm) after protonation

of the basic centre, thus substantiating the equatorial orientation of this group.



88

Preparation of N-phenethyl-3-methyl-4-phenyl piperidone (103) was approached via the usual acrylate additions (Scheme VIII).



103 102

Scheme VIII

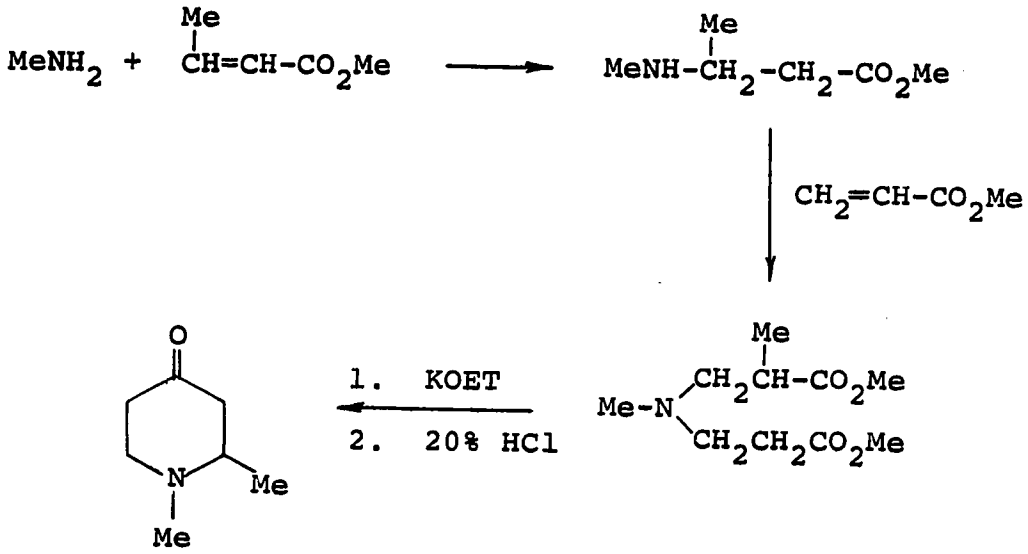
In the literature method (Beckett et al., 1959), the monoester addition occurred in forty-two days at room temperature resulting in fifty-one percent yields. By extending this time to three months (arbitrarily) the yield was increased to sixty-five percent. The yield of diester was

increased from fifty percent after refluxing the reactants for eight hours, to ninety-two percent after eight days of reflux (no solvent). The literature method used refluxing condition for forty-eight hours from which sixty-five percent of the diester could be recovered.

In an attempt to increase the yields of diester in a shorter space of time, the reactants were heated at 105° for six hours under nitrogen at 850 lbs./sq.in. Unfortunately only trace amounts of the desired diester could be recovered and the pressure method was abandoned. Apparently the mono ester and diester are best obtained using long reaction times at room temperature or moderate reflux temperatures.

Unlike the N-benzyl analogue, the N-phenethyl diester in this series was readily distilled at moderate vacuum; 150-155°/0.25 mm. Since distillation temperature was fairly high and yet the diester was recovered in good yields, it was felt therefore that the N-benzyl analogue may represent an increased instability of the tertiary amine.

The synthesis of another piperidone analogue, 1,2-dimethyl-4-piperidone (90), was accomplished by the usual acrylate addition shown in Scheme IX. This particular ketone synthesis represented the first attempt at using a metal other than sodium as the base catalyst. In two separate runs, the 4-piperidone was decarboxylated directly and the 3-carbomethoxy intermediate not isolated. The yields of 1,2-dimethyl-4-piperidone (mentioned earlier) were

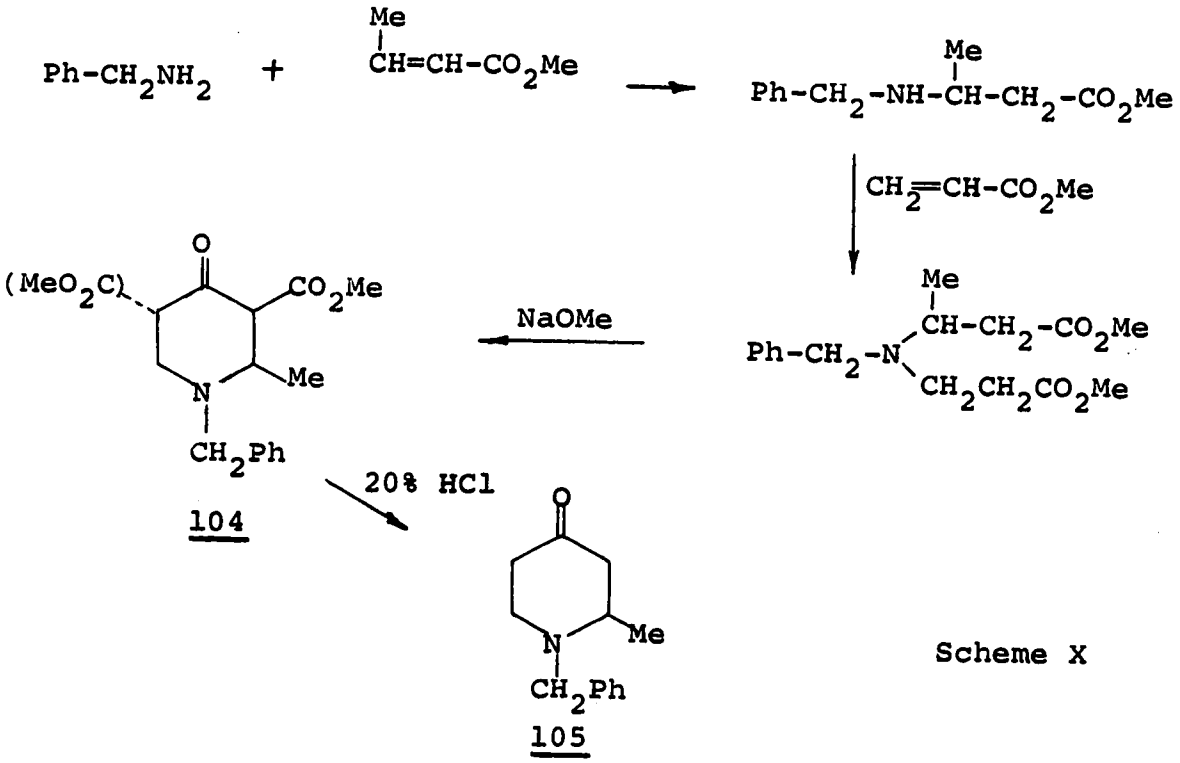


90

Scheme IX

close to forty percent using this technique.

N-benzyl-2-methyl-4-piperidone (105) was synthesized initially using the acrylate condensation route (Scheme X).



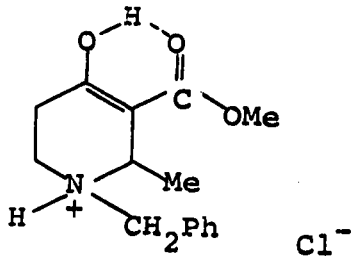
104

105

Scheme X

The mono ester formed was readily distilled at 120-123/0.5 mm., and the diester was distilled in small quantities (50 g.) at 140-145°/0.5 mm. However, when a larger synthesis was attempted and a total of nearly five hundred grams of diester distilled, some breakdown was noticed because methyl acrylate appeared in the pump traps and monester distilled over, yet examination of the crude diester after removing unreacted methyl acrylate at room temperature had shown, by the two equally intense singlets for the two COOMe groups at δ3.64 and δ3.60, that the diester was originally present in nearly quantitative yields. Therefore it was concluded that the N-benzyl diester analogues were subject to decomposition during distillation and at best should be distilled at high vacuum (so that distillation temperature can be kept low) and in small quantities, for prolonged heating even at 120° (0.5 mm.) gave some diester breakdown.

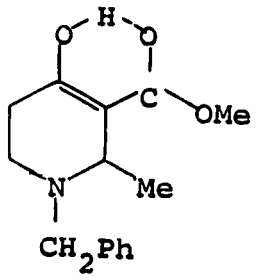
Cyclization of the diester was effected with sodium methoxide in toluene, and then subsequent isolation of the 3-carbomethoxy compound (104), by pouring the mixture onto ice and dilute HCl and collecting the white fluffy solid that separated. The IR spectrum of the hydrochloride thus isolated showed two absorption bands at 1695 and 1630 cm^{-1} and a broad band at 3150 cm^{-1} which were shown earlier to be due to the presence of a lone tautomeric form (106) in the salt. The band at 1695 cm^{-1} was therefore assigned to the hydrogen bonded ester function and the double bond assigned to the band at 1630 cm^{-1}. The OH, then, absorbs at 3150 cm^{-1}



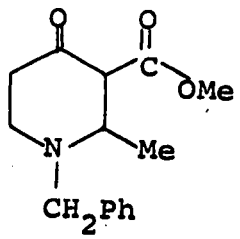
106

and is again at a lower wave number than would be expected.

The free base (film) displays a band between 3200 and 3500 cm^{-1} of very weak intensity and two peaks at 1670 and 1625 cm^{-1}; these are assigned to the OH, the ester and the double bond respectively of tautomer (107).



107

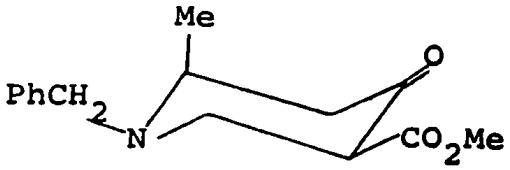


104

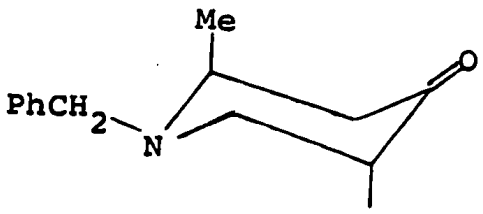
Two bands of weaker intensity than the preceding peaks appeared in the carbonyl region at 1750 and 1725 cm^{-1}; these are assigned to the free keto-ester form (104). From relative intensities it would appear that in the base the enol form also predominates.

The PMR spectrum of the salt showed two doublets at δ1.52 and δ1.68 for the 2-methyl group which indicated that two isomers had formed. The spectrum also displayed two COOMe singlets near δ3.65 which overlapped with some of

the ring protons. In the base in $CDCl_3$, the two 2-Me signals collapsed to a single doublet at δ1.50, and, as well, the ester groups appeared as a large singlet at δ3.65. The benzylic methylene protons, which are known to appear as a quartet if adjacent to an equatorial 2-methyl group and as a singlet when adjacent to an axial 2-methyl group (Lyle and Thomas, 1969), appear as two singlets at δ4.28 (major) and δ4.62 (minor). The PMR evidence indicates that two possible configurations are (108) and (109). Consideration of the conformational free energy of (109), however, would indicate that this form is highly unlikely. Skewing of this conformer is a more likely possibility.

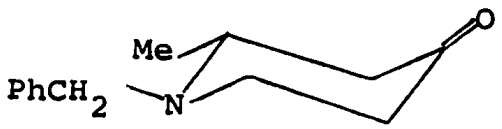


108



109

Decarboxylation of this intermediate was readily affected using twenty percent hydrochloric acid to yield N-benzyl-2-methyl-4-piperidone (110). The PMR spectrum of this piperidone displayed a quartet for the benzylic methylene protons centered at δ3.69 and a single doublet for the 2-methyl group at δ1.13, indicating that the conformation and configuration is as shown (110) with the methyl group equatorial (see later).

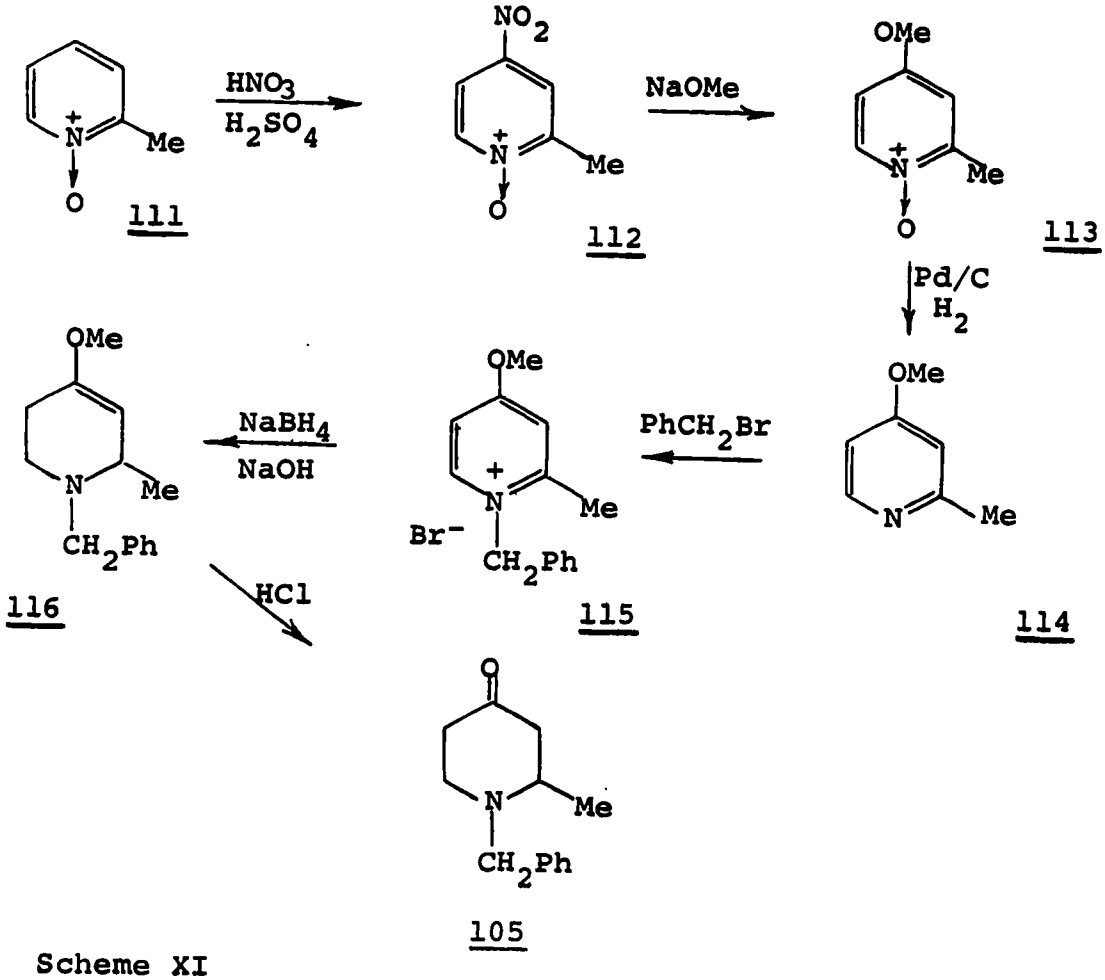


110

PREPARATION OF N-BENZYL-2-METHYL-4-PIPERIDONE VIA 2-METHYL PICOLINE-N-OXIDE

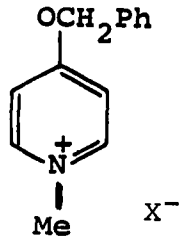
The synthesis of N-benzyl-2-methyl-4-piperidone (105) previously described was somewhat unsatisfactory in that the overall yields were low. Therefore an adaptation of a procedure based on some work of Lyle et al. (1959) was attempted in an effort to increase the yields of this ketone and also as a possible route to a variety of other 4-piperidones.

The synthetic route is shown in Scheme XI.

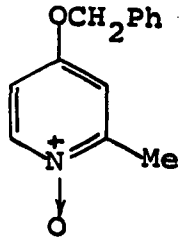


Scheme XI

It should be pointed out that Lyle and his coworkers synthesized the N-methyl-4-benzyl ether (117) analogue of (115); however, attempts to prepare benzyl ether analogue (118)



117



118

were not successful and instead some unidentifiable by-products resulted (Hassan, unpublished results). It was thought that the methyl ether (113) might offer a better intermediate since a compound of this type had been prepared by Ochiai (1953) in good yields.

The first step involves the mono nitration of the commercially available α-picoline-1-oxide (111) with the normal nitrating mixture of nitric and sulphuric acids. The product, 4-nitro-2-methylpyridine-1-oxide (112) had a m.p. which agreed with the same product originally prepared by Ochiai (1953).

PMR analysis in $CDCl_3$ showed that the nitration had produced essentially the mono-4-nitro compound since the spectrum displayed a lone singlet at δ2.57 for the tertiary 2-methyl group. The aromatic region, a multiplet between δ7.7 and δ8.5, integrated for three protons and was significantly different from the starting material, but the coupling constants could not be readily identified.

The 4-nitro derivative (112) was then reacted with sodium

methoxide in methanol to yield 4-methoxy-2-methylpyridine-4-oxide (113) and sodium nitrate as a by-product. The sodium nitrate was only partially insoluble in methanol and the bulk of the salt formed was filtered off. Upon distillation of the methanol more sodium nitrite separated out, this was removed by a series of filtrations and then further reducing the volume of methanol and filtering again.

Analysis of the pure product indicated that the compound had crystallized out with a molecule of water. The IR spectrum showed an OH band at 3480 cm^{-1}.

The PMR spectrum displayed a 2-methyl singlet at δ2.37 and a 4-methoxy singlet at δ3.84. The aromatic signal was split into two major signals; a one-proton quartet appeared at δ8.25 (J=7 and 1.5 Hz.), this was assigned to the C-6-proton since it is next to nitrogen and the values are in line with ortho and para couplings. The higher aromatic signal between δ6.7 and δ7.0 was therefore assigned to the two remaining C-3 and C-5 protons. Coupling constants for these could not be determined. A signal at δ3.57 (2 protons) was due to the molecule of water crystallizing out with the compound.

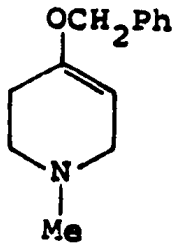
Reduction of the N-oxide in a mixture of acetic acid and a small amount of acetic anhydride as a catalyst using palladium charcoal and hydrogen at atmospheric pressure was found to proceed smoothly to produce 4-methoxy-2-methylpyridine (114). However, when an impure sample that contained residual amounts of sodium nitrate was reduced it was found that

the nitrogen dioxide evolved from the mixture and severely hampered reduction. The nitrogen dioxide so released caused a build-up of back pressure and prevented the hydrogen from reaching the surface of the mixture. It was thought that the gas may also be absorbed onto the surface of the palladium charcoal and thereby inactivate it. Therefore hydrogen was bubbled through these impure samples in an attempt to displace all the nitrogen dioxide from the mixture. When this was done reduction proceeded smoothly once more.

The PMR spectrum of the reduced product displayed a 2-methyl singlet at δ2.5 and a 4-methoxy singlet at δ3.82. The aromatic signal appeared little changed from that of the N-oxide with a quartet at δ8.17 (J=7 and 1.5 Hz.) and a multiplet between δ6.55 and δ6.75.

The bulk of the product was then converted to N-benzyl-2-methyl-4-methoxy-pyridinum bromide (115) by reaction with excess benzyl bromide.

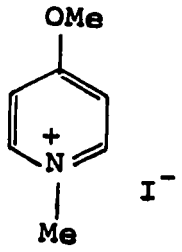
The reduction of the above compound (115) was initially attempted at room temperature following the procedure of Lyle and his coworkers (1959) who prepared 1-methyl-1,2,3,6-tetrahydro-4-pyridylbenzyl ether (119), which was originally felt



119

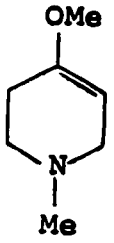
to be an analogous product to the present case. Unfortunately the desired product (116) was only recovered in trace amounts (Hassan, unpublished data). It was decided, therefore, to follow a recent procedure that Takeda et al. (1969) have reported.

These workers reduced 4-methoxy-1-methyl-pyridinum iodide (120) by dissolving the quaternary salt in a mixture of 1 N



120

sodium hydroxide and sodium borohydride and using low temperature (-15°) conditions, and thereby were able to isolate in good yields 4-methoxy-1-methyl-1,2,3,6-tetrahydropyridine (121).

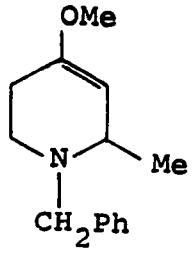


121

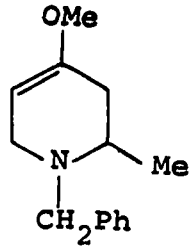
Reduction of 1-benzyl-4-methoxy-2-methyl-pyridinium bromide (115) using the above conditions resulted in reasonable yields (52%) of 1-benzyl-4-methoxy-2-methyl-1,2,5,6-tetrahydropyridine (116).

PMR analysis of the total product displayed two singlets for the 4-methoxy group at δ3.45 (major) and δ3.44 (minor).

The 2-methyl group also appeared as two close doublets at δ1.17 (major) and δ1.15 (minor). Relative signal intensities showed an approximate ratio for the two signals of 12:5. Two products are possible from the sodium borohydride reduction, that is (116a) and (116b). It was reasoned that the lower field



116a



116b

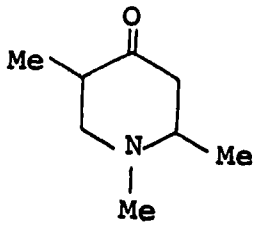
signal for the 2-methyl group should be due to (116a) since in this isomer the nearness of the double bond will tend to deshield the methyl group more so than the isomer with the double bond one carbon further removed.

The preceding methyl ethers were readily hydrolysed with hydrochloric acid using the same conditions as Lyle and his coworkers (1959) to give N-benzyl-2-methyl-4-piperidone (110) which proved to be identical to the sample of the same compound prepared previously. The total overall yield of this compound was found to be 7% which was considerably lower than the yields of the same product (40%) prepared by the condensation of acrylates (see earlier).

1,2,5-TRIMETHYL-4-PIPERIDONE

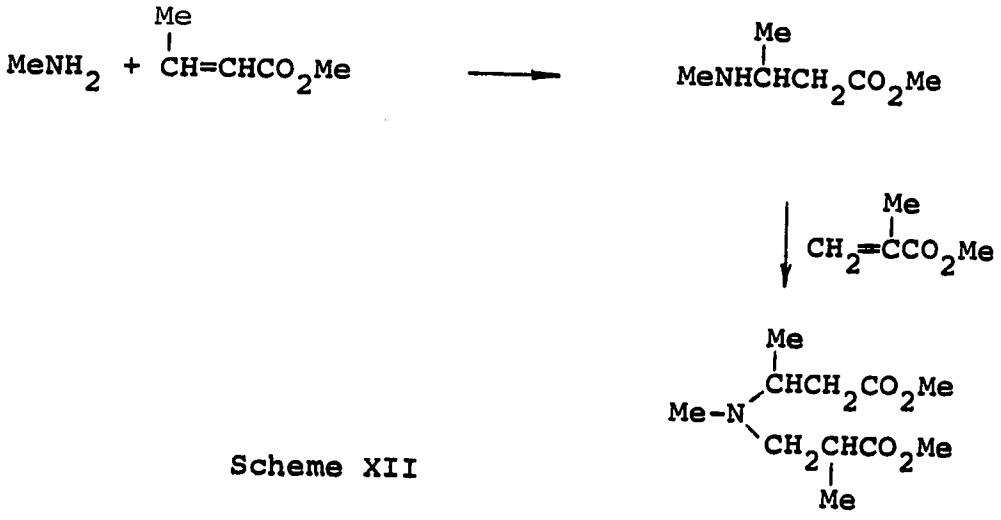
Midway through this investigation, we were recipients of a generous give of 1,2,5-trimethyl-4-piperidone (122) from Dr. N.S. Prostakov of the Lomonosov Institute of Fine

Chemical Technology, Moscow, USSR.



122

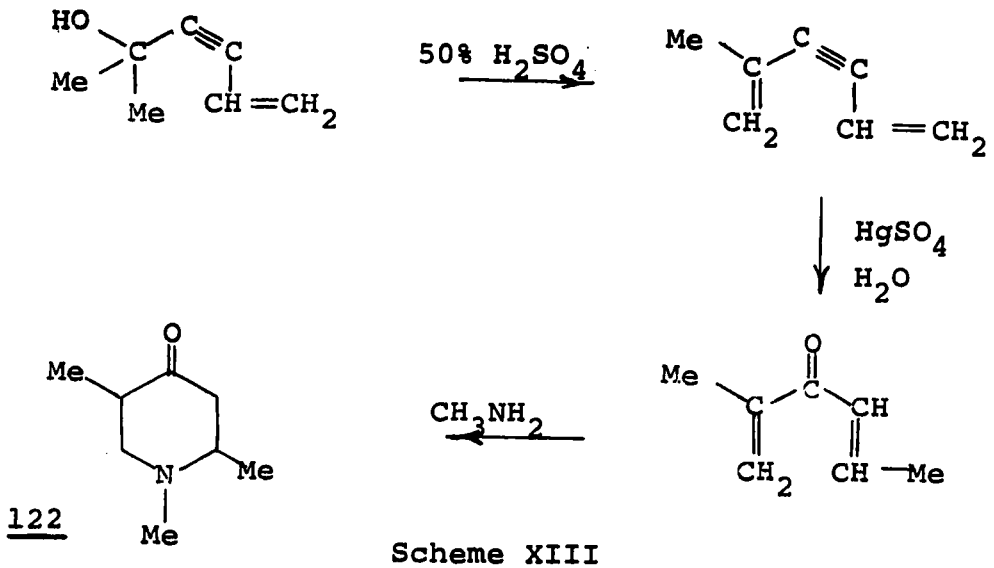
Although we had applied the usual acrylate addition method (Scheme XII) in the preparation of this compound, the diester shown could not be isolated.



Scheme XII

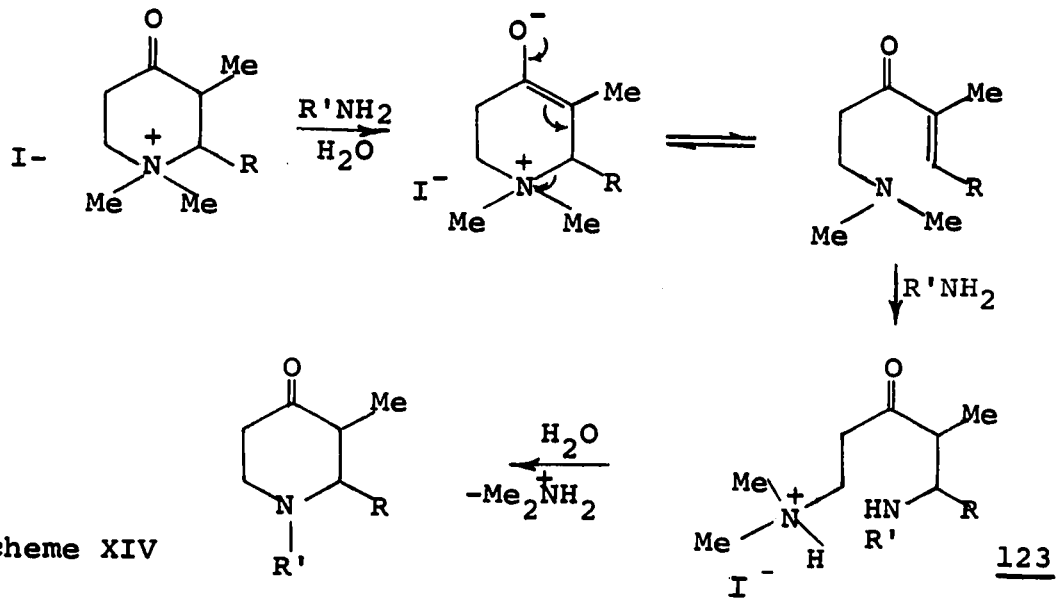
It is possible that the diester is formed but is extremely heat labile and thus was broken down during distillation. The matter was not pursued further since we had an ample supply of the desired ketone.

At present the Russian industrial preparation of (122) is as shown in Scheme XIII, the product being a mixture of cis and trans dimethyl isomers (Nazarov and Rudenko, 1948).



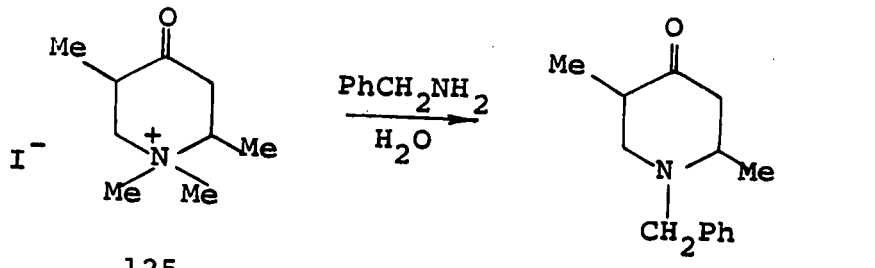
Scheme XIII

Mistryukov et al. (1961) pioneered a rather unusual method for the synthesis of N-alkyl piperidones based on an exchange reaction between the methiodide of an N-alkyl-4-piperidone and a primary base. The probable mechanism is shown in Scheme XIV.



Scheme XIV

This procedure has been examined in the present work on several occasions and it has been found that the amount of water used is important, the original authors having used a six molar excess of water as compared to the amount of methiodide derivative. When a one to one molar proportion of 1,2, 5-trimethyl-4-piperidone methiodide to water was used, and the base employed was benzylamine, the reaction failed and the product, although not identified since extensive decomposition occurred when distillation was attempted, was likely a mixture of the open chain diamine plus unreacted methiodide.



125 126

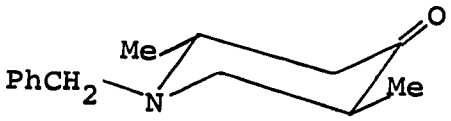
When a ten molar excess of water to methiodide was used in the preparation of the same compound (126), the method again worked. However, since a six molar excess of water appeared from this work and that of Mistryukov's to be the ratio that gave consistently good results, it was the amount employed in all subsequent reactions.

The reaction itself is relatively simple; the reactants are mixed, let stand overnight, and an oily, basic layer separates which is removed and distilled.

The PMR characteristics of N-benzyl-2,5-dimethyl-4-

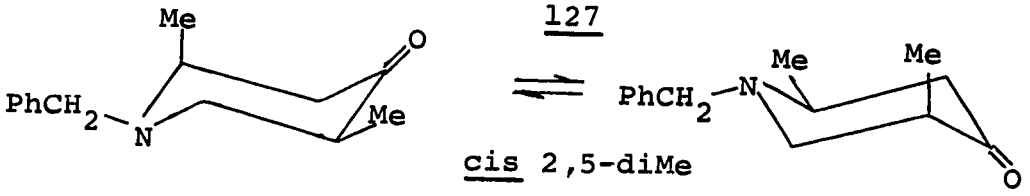
piperidone (125) produced by this method have been used by Hassan and Casy (1970) to establish the stereochemical nature of the ketone. The benzylic methylene protons show nonequivalence in a particular stereochemical arrangement.

In the trans form (127), the N-CH_2Ph signal forms an AB quartet characteristic of protons in an asymmetric environment (Hill and Chan, 1965), while in the cis isomer (128)



trans 2,5-diMe

127

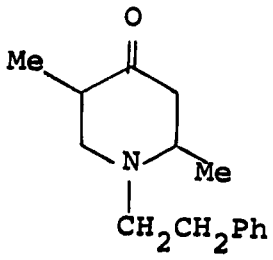


cis 2,5-diMe

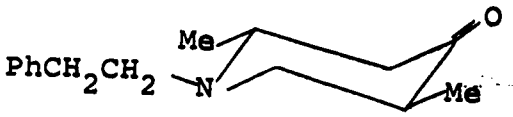
128

it forms a broad singlet. The last result is evidence that the cis isomer prefers a conformation in which the 2-methyl substituent is axial, the isomeric ratios being 16:13 for the trans and cis isomers respectively. Similar cases have been described by Lyle and Thomas (1969).

In another trial, the exchange reaction was used to produce N-phenethyl-2,5-dimethyl-4-piperidone (129). The PMR of this product showed only two doublets at δ1.10 (J=5.5) and δ0.63 (J=5.5) for the 2- and 5-methyl groups thereby indicating that the product is essentially a single isomer. This form is almost certainly the more stable trans 2,5-dimethyl isomer (130).

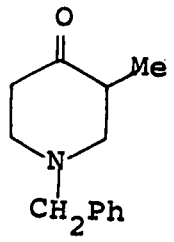


129



130

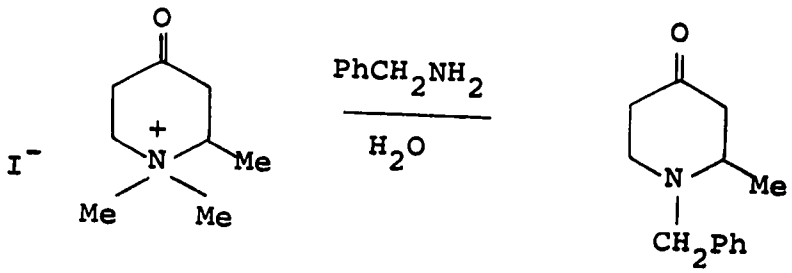
The exchange reaction was used again to prepare N-benzyl-3-methyl-4-piperidone (88).



88

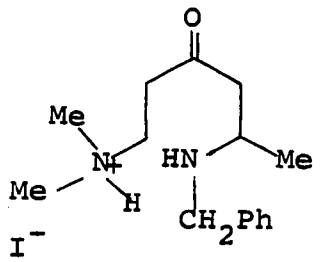
The product was identical with that prepared by the acrylate condensation method. The 3-methyl group is too far away from the N-substituent in this case to have any influence on the environment of the benzyl methylene protons and thus they appear as a singlet at δ2.78 in the PMR spectrum.

Using the same reaction to produce N-benzyl-2-methyl-4-piperidone (110) from the 1,2-dimethyl-4-piperidone methiodide (131) considerable difficulty was encountered and two

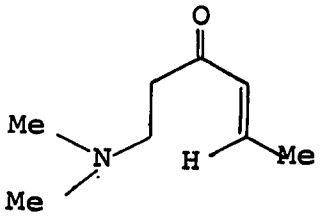


131 110

attempts met with failure. PMR analysis of the total products isolated indicated a mixture, and the possibility that ring closure had not occurred giving (132) and (133). Although the open chain compounds were not isolated, tentative PMR analysis showed no significant sec-methyl signal but instead



132

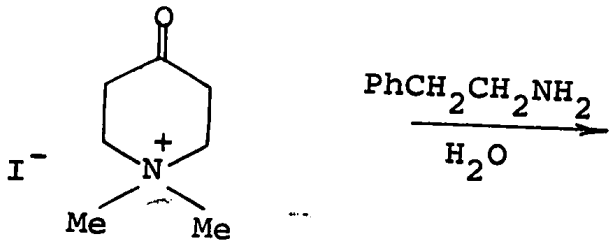


133

the spectrum displayed several peaks for the N-methyl groups, an aromatic signal for the benzyl group and a signal in the vinylic region, which the above two compounds would account for.

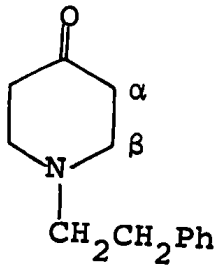
It was therefore thought possible that the substitution on the 3 or 5 position of the piperidine ring was necessary for success in the reaction. (Mistryukov et al. always had this type of substitution in all the compounds they worked with).

When the exchange reaction was tried (Hassan, unpublished results) using N-methyl-4-piperidone methiodide (134) and phenethylamine to produce N-phenethyl-4-piperidone (135), in order to test our theory that substitution on the piperidine ring in the 3- position is a necessity for success, the desired reaction did not occur, and the product could not be identified with certainty. It was concluded therefore that



134

$PhCH_2CH_2NH_2$ / H_2O



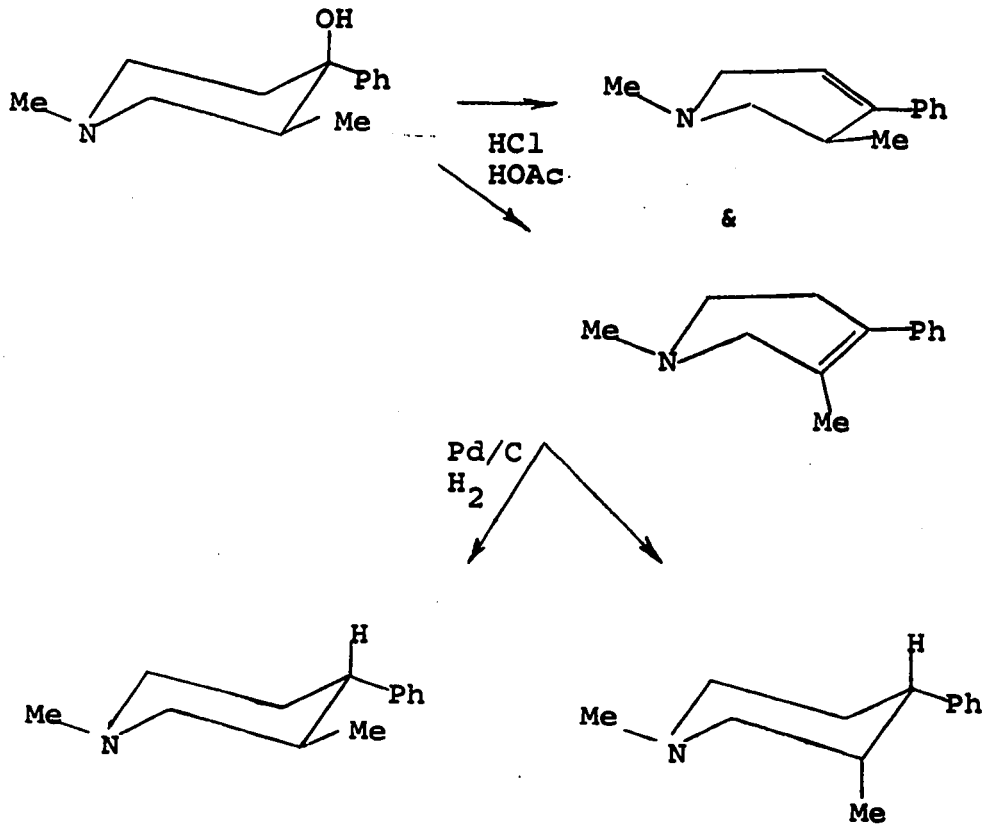
135

this exchange reaction will proceed only in the presence of substituents on the α- position of the piperidine ring. Mistryukov et al. (1961) had suggested that the important feature was substitution on the β carbons; this may be true, but only as a steric factor in the introduction of bulky groups since the exchange occurs readily with 1,3-dimethyl-4-piperidone methiodide (see p. 94) where no substituent is on the β carbons.

4-PHENYLPIPERIDINE DERIVATIVES LACKING AN OXYGENATED FUNCTION

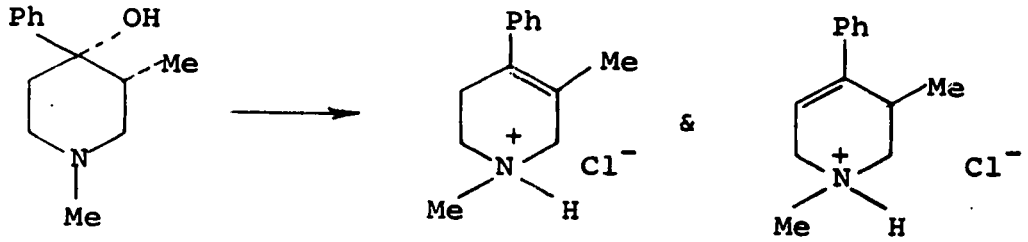
The preceding section has dealt with the synthesis of various ketones and their properties. These compounds are very reactive to phenyl lithium treatment, and allow subsequent treatment of the lithium complex with a variety of reagents in order to prepare the alcohols and esters that were required in this investigation.

Treatment of 1,3-dimethyl-4-piperidone (65) with phenyl lithium and then decomposing the lithium complex with either water or an acid anhydride results in the production of the 1,3-dimethyl-4-phenyl-4-piperidinol isomers and their corresponding esters, the stereochemistry of which has been



Scheme XV

piperidinols of type (33) gave rise to a mixture of tri (138) and tetra (139) substituted alkene forms, the relative proportions of the two forms depending on the duration of the



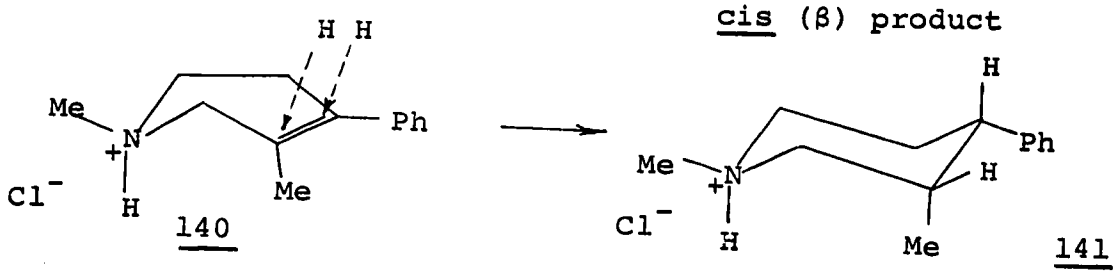
33 139 138

dehydration procedure. Pure isomers could be separated but

isomeric mixtures of alkenes were used for the present reduction experiments.

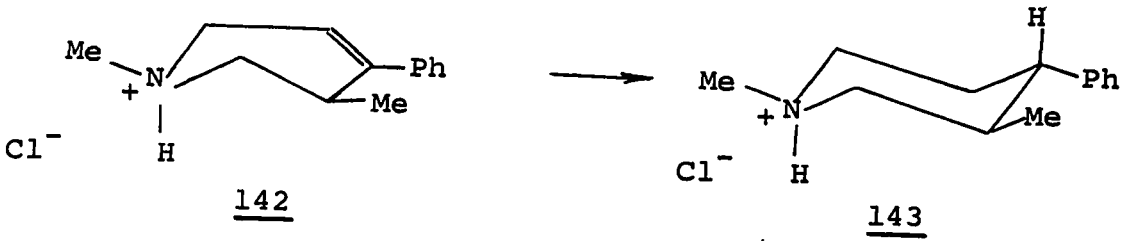
When the mixture of products (138) and (139), as hydrochloride salts, were subjected to hydrogenation using a palladium-charcoal catalyst in a hydrogen atmosphere at normal pressure and room temperature, two possible products were expected. It is customary to consider that Pd/C hydrogenations occur by a cis addition of hydrogen across the double bond from the least hindered site (House, 1965, and refs therein). There are, however, references in the literature where trans addition of hydrogen or inversion of configuration occur when alkenes are reduced over metals (Siegal and Smith, 1960; Mitsui et al., 1967; Howard and Morley, 1967), but the generally accepted view is that reduction occurs by adsorption (or chemisorption) of the π cloud of electrons on the surface of the catalyst and then transfer of two atoms of hydrogen from the catalyst surface to the same side of the double bond.

Cis addition of hydrogen to the tetrasubstituted alkene component of the dehydrated product obtained from α-prodinol (1,3-dimethyl-4-phenyl-4-piperidinol) (33) must give rise to a cis 3-Me/4-Ph hydrocarbon as shown below.



140 141

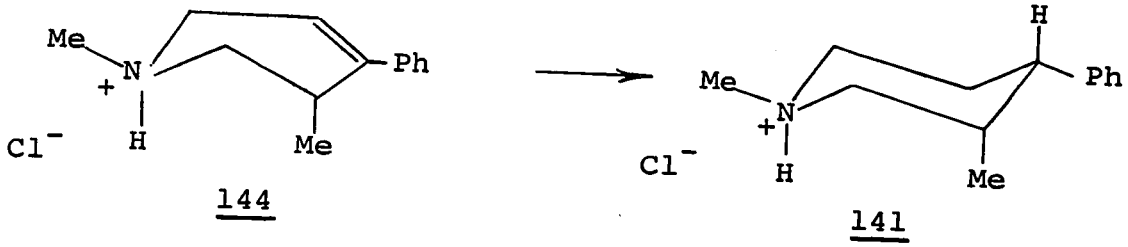
The product of cis addition to the protonated trisubstituted alkene will depend on the preferred conformation of the conjugate acid. If it is (142) a trans product (143)



142 → 143

trans (α) product

will result, but if it be (144) then a cis derivative (141)



144 → 141

cis (β) product

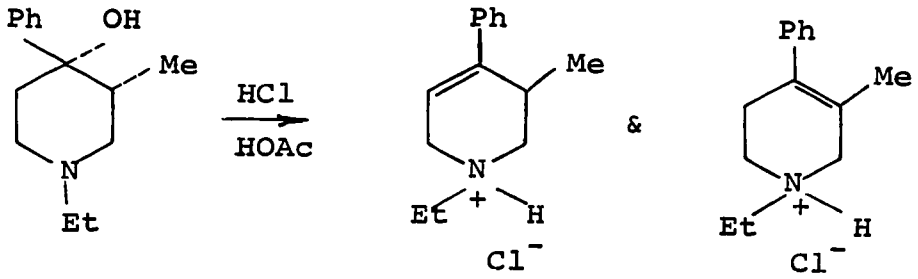
will again be formed. There is good evidence that (144) is a preferred conformation for 5-methyl-4-phenyl-1,2,5,6-tetrahydropyridines (Casy et al., 1965).

In the last two reductions hydrogen addition is considered to be from the side anti to the pseudo axial 3-methyl group (or from the least hindered side).

In fact, reduction of the total tetrahydropyridine mixture of (139) and (140) yielded a single isomeric form of 1,3-dimethyl-4-phenyl piperidine as shown by the fact that the PMR spectrum of the total product displayed sharp, non-duplicated signals. The configuration of the product is

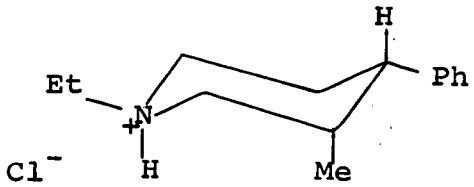
clearly cis (141) since the 3-methyl signal in the base in $CDCl_3$ showed a significant downfield shift (0.41 ppm) after the ring nitrogen had been protonated (see Table XI).

In another series, reduction of the trisubstituted alkene (146) (supplied by Dr. A.P. Parulkar, Edmonton) derived from dehydration of N-ethyl-3-methyl-4-phenyl-4-piperidinol (145) gave only one isomer, which proved to be



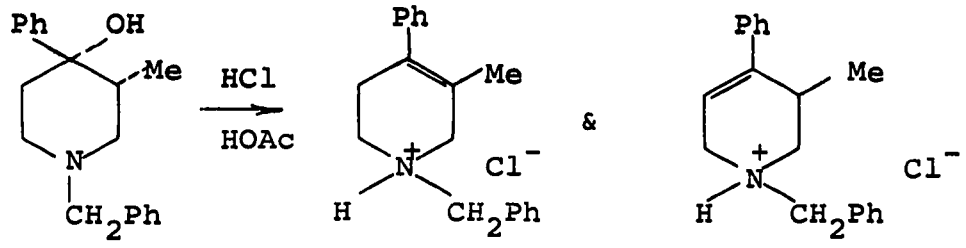
145 146 147

the β- form (148) from PMR analysis, since the 3-methyl signal shifted downfield significantly (0.17 ppm) when the basic centre was protonated. Reduction of the tetra-substituted alkene (147) yielded an identical product (148), as shown by its PMR spectrum (as well as IR and mixed m.p.), which was therefore also assigned the cis 3-Me/4-Ph configuration.



148

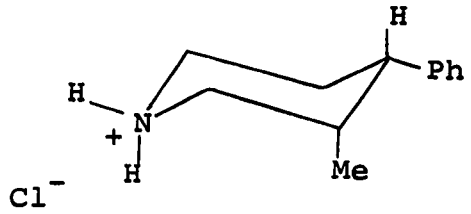
Reduction of the alkenes (also supplied by Dr. A.P. Parulkar) derived from dehydration of N-benzyl-3-methyl-4-phenyl-4-piperidinols (149) was attempted in order to determine if the β-cis 3-Me/4-Ph isomer would again be the



149 150 151

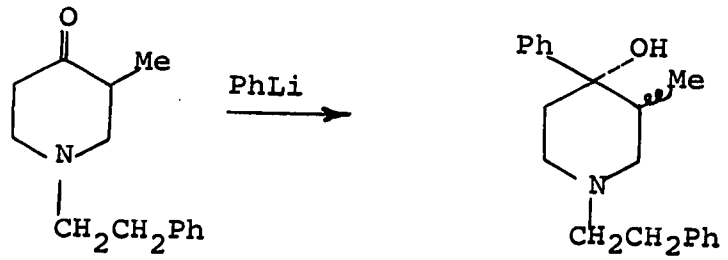
solitary product.

When both alkenes (150) and (151) were reduced separately over 10% palladium charcoal a single product was isolated from each. This proved, by PMR evidence and mixed melting point (216-217°), to be a single isomer (Table XI) and, from the chemical shift difference between the base and hydrochloride in $CDCl_3$, was assigned the cis 3-Me/4-Ph configuration. The reduction in this case removed the N-benzyl group as well as hydrogenating the double bond to leave β-3-methyl-4-phenylpiperidine hydrochloride (152).



152

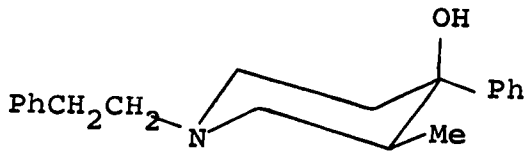
N-phenethyl-3-methyl-4-phenyl-4-piperidinol (153) was prepared by treatment of the N-phenethyl-3-methyl-4-piperidone (102) with phenyllithium. From this mixture, Beckett



102 153

et al. (1959) were able to isolate the cis and trans isomers by fractional crystallization of the corresponding ester hydrochlorides.

In this investigation only the α-isomer (154) could be isolated from the mixture of alcohols. This proved identical

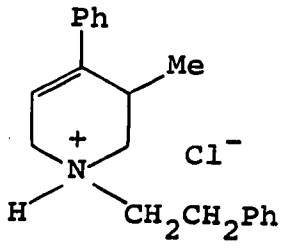


154

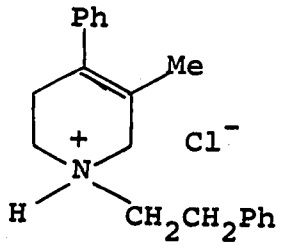
to an authentic sample (m.p., mixed m.p.) of the α-isomer. The PMR spectrum in $CDCl_3$ displayed a doublet at δ0.62 which shifted to δ0.68 upon protonation. This small shift, along with evidence of virtual coupling of the 3-methyl signal of the base spectrum substantiated the α-trans-3-Me/4-Ph- configurational assignment of this alcohol.

Subsequent dehydration of the α-alcohol (154) with a refluxing mixture of hydrochloric and acetic acids yielded

a mixture of the trisubstituted (155) and tetrasubstituted (156) alkenes:

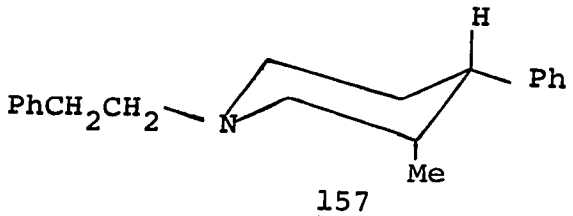


155



156

PMR analysis of the base showed it to consist of a 30:70% mixture of (155) and (156) respectively. This was in contrast to the usual ratios obtained by Casy and coworkers (1966), who normally found the trisubstituted alkene to be produced in larger amounts. Fractional crystallization gave the major form (156) which was subsequently hydrogenated to yield β-N-phenethyl-3-methyl-4-phenylpiperidine (157) as the



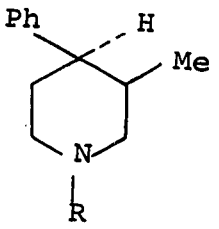
157

sole product. Reduction of the total mixture of alkenes remaining after isolation of (156) again gave the β-isomer as the sole product. PMR analysis of both reduced products confirmed the cis configuration since the 3-methyl signal was significantly shifted upon protonation (see Table XI).

The PMR data collectively presented in Table XI show

a series relationship. Each analogue of N-alkyl-3-methyl-4-phenylpiperidine displays a significant shift for the 3-methyl signal when the base is protonated. This has been shown to represent the cis 3-methyl-4-phenyl configuration with the 3-methyl group axial.

TABLE XI. PMR CHARACTERISTICS OF N-ALKYL-3-METHYL-4-PHENYLPIPERIDINES IN $CDCl_3$



Form	R	PMR Chemical Shifts[a] 3-Me[b]	Configuration (3-Me/4-Ph)
Base	Me	0.73	cis
HCl	Me	1.14	
Base	Et	0.95	cis
HCl	Et	1.12	
Base	H	0.95	cis
HCl	H	1.05	
Base	$PhCH_2CH_2$	0.78	cis
HCl	$PhCH_2CH_2$	1.11	

(a) Chemical shifts in δ units from TMS (60 MHz)

(b) doublet, deformed in all cases due to virtual coupling

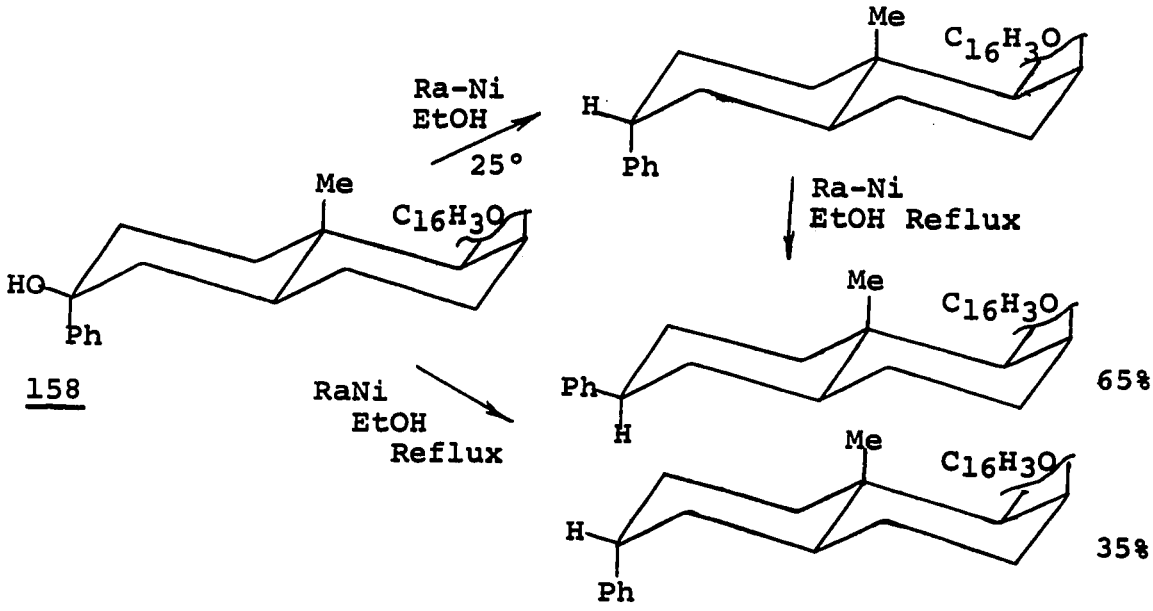
Since hydrogenation of the above alkenes did not provide

the trans 3-Me/4-Ph analogues it was decided to reduce the 4-oxygenated function directly. The literature contains many reports that the reduction of alcohol groups over metals is a facile method of producing the hydrocarbon. Some authors report that hydrogenolysis over Raney Nickel catalyst occurs with inversion of configuration (Bonner and Zderic, 1956) and at least one group of workers have employed Raney Nickel as an agent to facilitate inversion of one alcohol to another (Eliel and Schroeter, 1965, and Eliel and Gilbert, 1969). However, in other reports hydrogenolysis of a hydroxyl group over Raney Nickel has been found to proceed with retention of configuration (Garbisch, 1967; Mitsui, 1969).

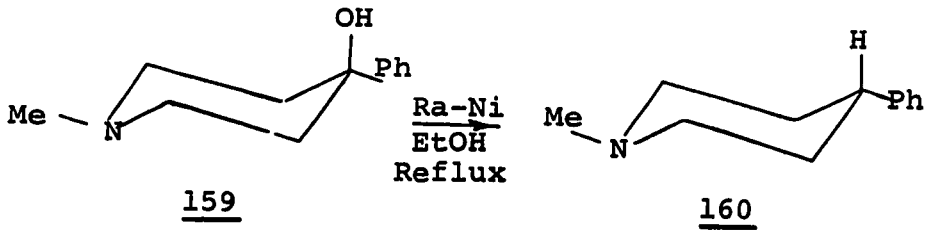
From an analysis of these sometimes conflicting reports a general trend was noted. Hydrogenolysis of hydroxyl groups, unhindered by other competitive reduction pathways, was found to proceed with retention of configuration at room temperature but frequently some inversion of stereochemistry was noted at elevated temperatures.

Garbisch (1962) found this to be the case in the cholestane derivatives (158), where hydrogenolysis at room temperature occurred with retention of stereochemistry but at elevated temperatures inversion occurred.

In order to investigate the possibility of hydrogenolysis of the tertiary alcohols isolated in the present work a model compound was first prepared: N-methyl-4-phenyl-4-piperidinol (159). When this alcohol was stirred for twelve hours at room temperature over Raney Nickel no reaction

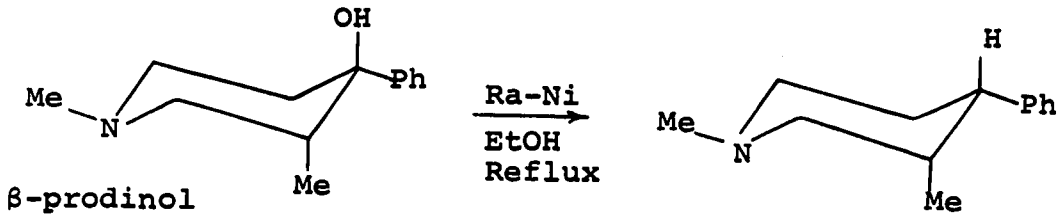


occurred and the unchanged alcohol was recovered. It was then refluxed in ethanol over the same type catalyst and after four hours nearly quantitative yields of N-methyl-4-phenylpiperidine (160) resulted.



Turning then to the isomer 1,3-dimethyl-4-phenyl-4-piperidinols (33) and (34): the ability to reduce these alcohols stereospecifically with Raney Nickel was investigated as a convenient route to both the α- and β-1,3-dimethyl-4-phenyl piperidines (143) and (141). Since a sample of the

hydrocarbon which has been assigned the β-configuration was available from previous reduction studies (see earlier), the β-prodine alcohol was treated first with Raney Nickel in refluxing ethanol for four hours after which time reduction was found to be complete. The product proved to be identical with that obtained previously, and the reaction had therefore proceeded stereospecifically.



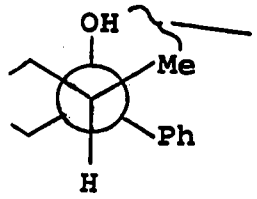
β-prodinol

34 141

PMR analysis of the total product showed one isomeric form which displayed a single 3-Me doublet at δ0.73 shifting to δ1.14 in the salt. This large shift (0.41 ppm) is indicative of an axial C3-methyl group (see earlier). Treatment of the β-isomer (141) with Raney Nickel in refluxing ethanol for twenty-four hours failed to produce any inversion of configuration. We therefore tentatively concluded that Raney Nickel would reduce the tertiary alcohols stereospecifically under mild reflux conditions.

When α-prodinol (33) was treated in a similar manner only the unreacted alcohol could be recovered. Lengthening the reflux times produced no change in the substrate and hence it was concluded that the α-isomer was not subject to hydrogenolysis. A possible reason for this failure may

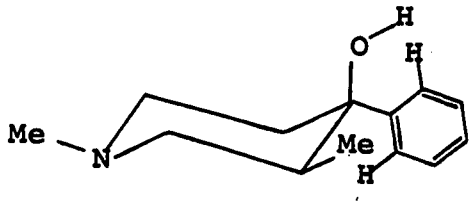
be due to steric hindrance of the hydroxyl function by the gauche 3-methyl group (161) which will impede the approach



gauche interaction

161

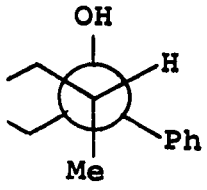
of the molecule onto the surface of the catalyst. It is also possible that the 4-phenyl group, which has been postulated earlier to be preferentially oriented perpendicular to the piperidine ring in the ester analogues, may also be similarly oriented in the alcohol (37) and will interfere



37

with the 4-OH binding at the catalyst's surface.

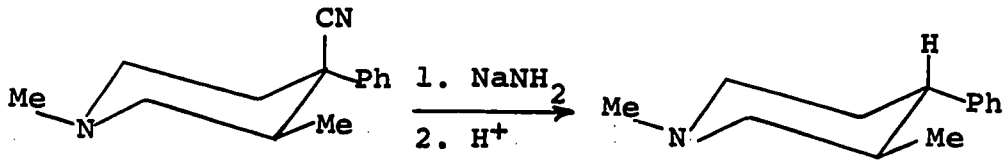
On the other hand the β-prodine alcohol has a trans (anti) 3-Me/4-OH arrangement (162) which will allow close



162

approach to the nickel surface.

Thus far we have not been able to produce α-1,3-dimethyl-4-phenylpiperidine (137); however, in related research the α-hydrocarbon was prepared by the cleavage of α-1,3-dimethyl-4-phenyl-4-piperidinonitrile (155) with sodamide (Khullar, 1969).



155 137

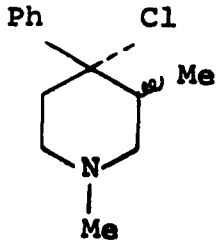
PMR spectral analysis of the α-isomer substantiated the equatorial 3-methyl conformation, since virtual coupling of the 3-methyl signal was noted in the base in $CDCl_3$. Also, the α-3-methyl signal (δ0.68) was slightly higher field than the β-3-methyl signal (δ0.80) for the bases in $CDCl_3$, which was shown earlier to indicate the α- compound has a 3-methyl function further removed from dishielding of the nitrogen lone pair of electrons.

Pharmacological data upon these hydrocarbon analogues will be described later.

REACTION OF THIONYL CHLORIDE UPON α- AND β-PRODINOL

It has previously been observed that isomeric 1,3-dimethyl-4-phenyl-4-piperidinols behave differently toward thionyl chloride (Casy, 1961). α-Prodinol (33) was found to undergo elimination of water to give tetrahydropiperidines

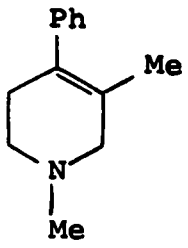
(138) and/or (139) as the sole products. The β-1,3-dimethyl-4-phenyl-4-piperidinol (34) on the other hand gave 1,3-dimethyl-4-phenyl-4-chloropiperidine (163) in good yield.



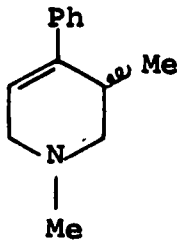
163

This work was repeated in order to establish the isomeric proportions of the dehydrated material and also to establish the configuration of the β-reaction product.

PMR analysis of the base of the total product derived from the treatment of α-prodinol (33) with thionyl chloride showed a 3:2 ratio (determined from the integral trace) of the trisubstituted alkene (138a), whose 5-methyl signal appeared as a doublet at δ1.08; to the tetrasubstituted alkene (139a), the 3-methyl signal of which appeared as a broad singlet at δ1.61. A similar ratio resulted when a refluxing



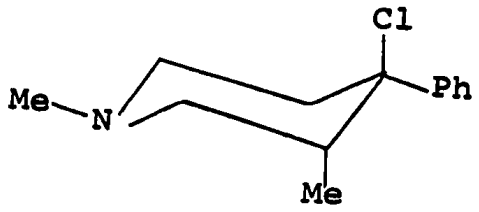
139a



138a

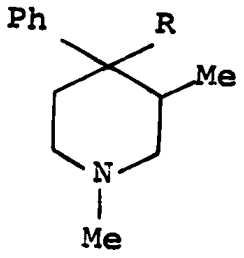
mixture of hydrochloric and acetic acid was employed to dehydrate the α-isomer.

Treatment of β-prodinol (34) with thionyl chloride gave the same product (m.p., IR evidence) as the earlier investigator had found. PMR analysis (see Table XII) confirmed the previous suspicions that the chloro-compound so obtained had retained the β- stereochemistry (164).



164

TABLE XII. 3-METHYL CHEMICAL SHIFT VALUES OF β-PRODINE ALCOHOLS AND CHLORO DERIVATIVES IN $CDCl_3$



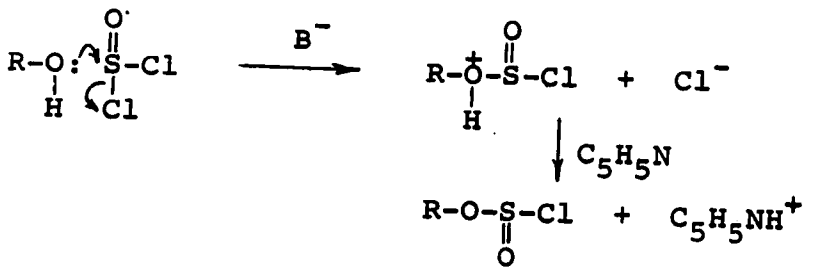
R	3-Me Chemical Shift Base[b]	Salt[b]	Δppm
4-OH	0.76	0.97	0.21
4-Cl	0.97	1.13	0.16

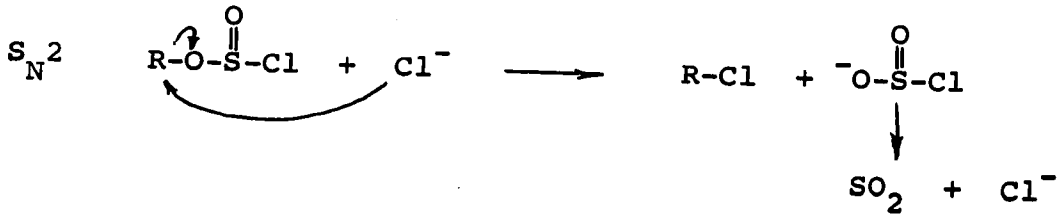
N.B. Notations used here have the same meaning as described in the footnotes of Table VIII.

From the above values it will be noted that the typical large shift of the β-prodinol upon protonation is also shown with the 4-chloro compound thereby establishing the similarity of configuration of the two analogues.

The question arises then as to why the α-isomer (33) should give the dehydration product but the β- form (34) results in quantitative yields of the β-1,3-dimethyl-4-phenyl-4-chloro-piperidine (164).

Normally reactions with thionyl chloride are performed in pyridine, since a strong base will promote the loss of Cl from the (protonated) HOSOCl function, thereby leaving the necessary chloride ion (Cl^-) for S_N2 reaction.

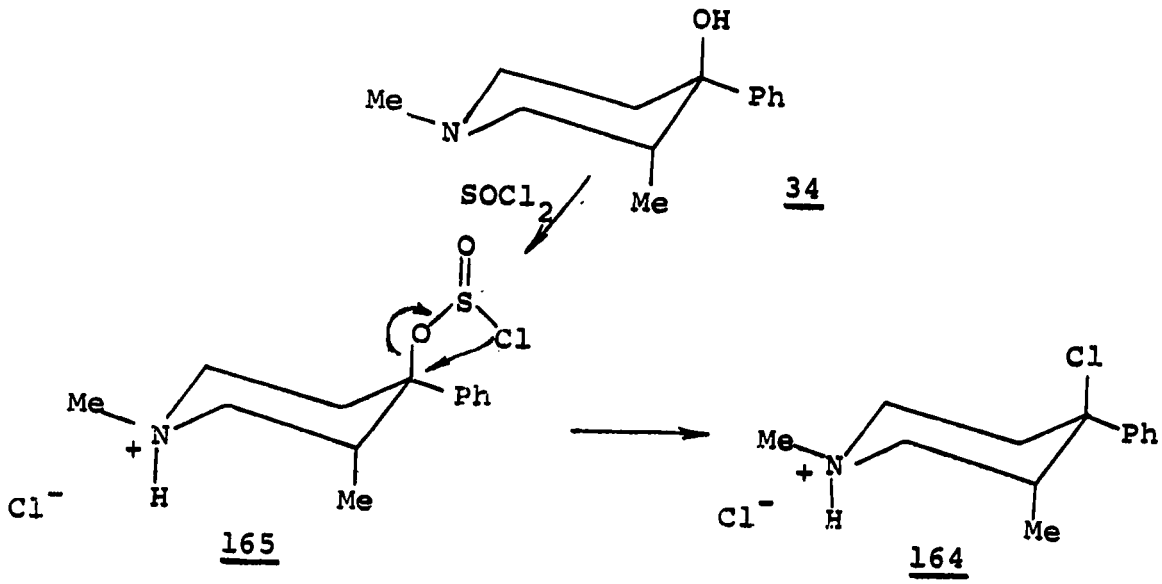




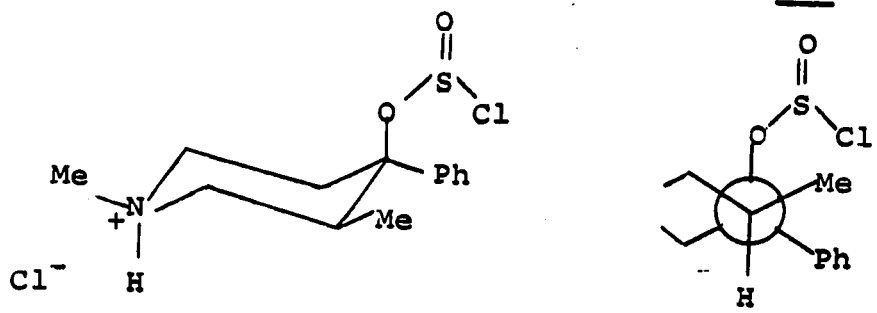
With piperidine compounds one molecule of piperidine is acting as the base to accept the proton from the reaction (the HCl salt is isolated from the reaction).

β-Prodine alcohol likely forms the chlorosulfite (165) which rearranges by an Sni process with retention of

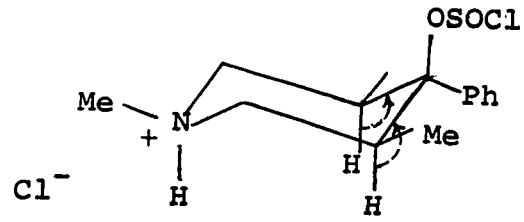
configuration.



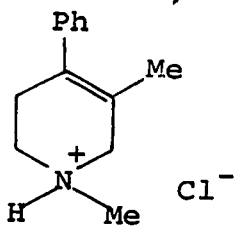
In the β-isomer the axial 3-methyl group will offer no steric hindrance to the intramolecular process depicted in compound (165). However, with the α- form, the chlorosulfite (166) probably forms as before but in this case S_Ni attack by Cl is hindered by the gauche 3-methyl substituent (167).



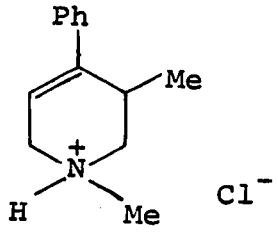
Therefore elimination via an E1 type mechanism is more likely by a trans diaxial pathway whereby two products result, in agreement with the experimental results.



166



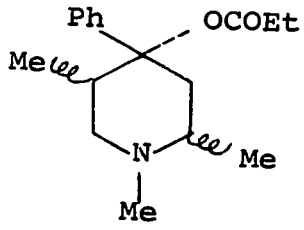
139



140

ISOMERIC 1,2,5-TRIMETHYL-4-PHENYL-4-PIPERIDINOLS AND THEIR DERIVATIVES

As pointed out in the introduction of this thesis, the inconclusive and conflicting evidence about the stereochemistry of the analgesic promedol and its isomers (27) was



27

considered to warrant further investigation of this group of compounds. The techniques employed rest upon experience

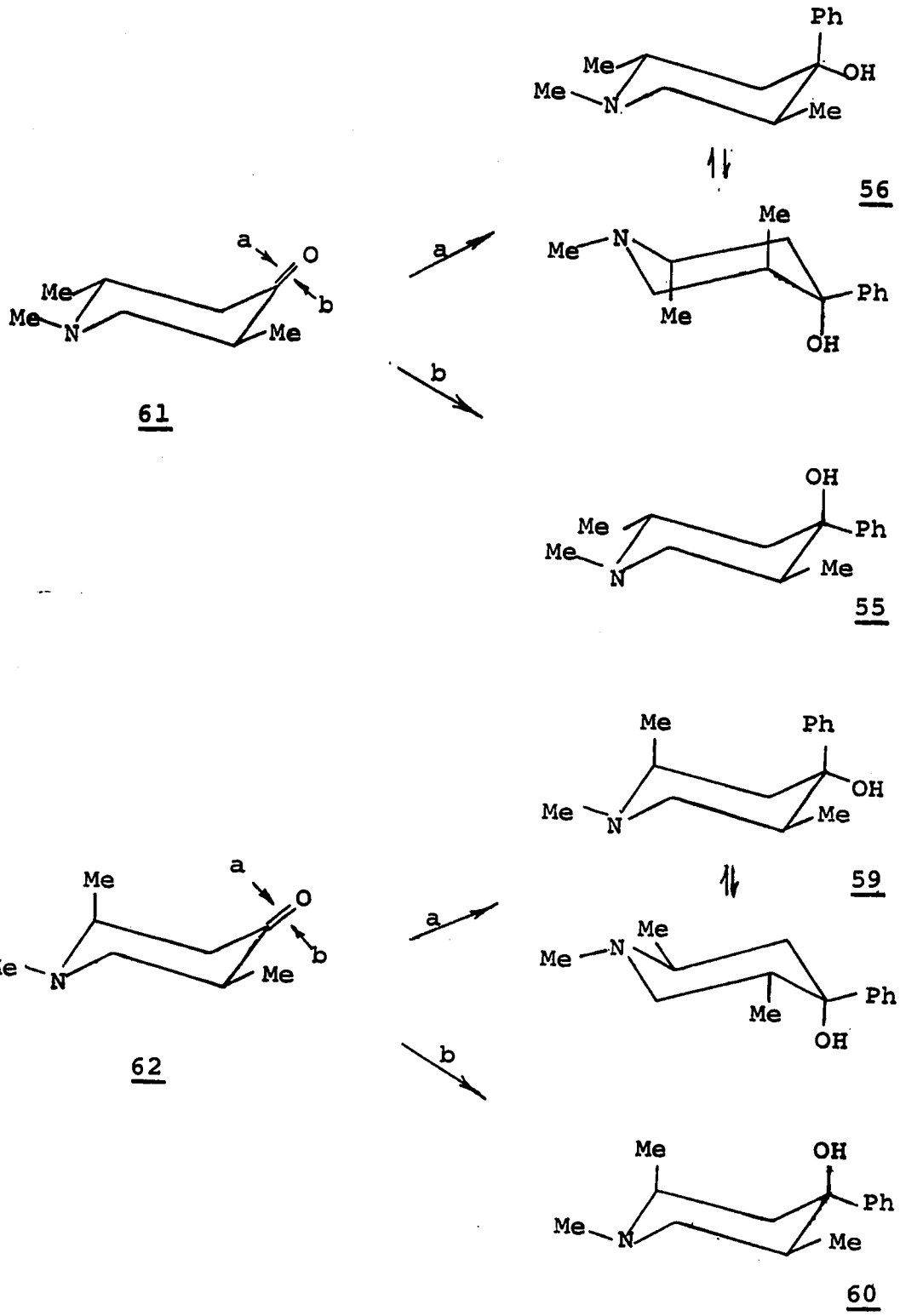
gained in the chemical properties and PMR analysis of α- and β-prodine and their derivatives.

Four racemic diastereoisomeric alcohols may arise from the addition of phenyllithium to the precursor ketone, 1,2,5-trimethyl-4-piperidone (see Scheme XVI). This ketone is composed of a mixture of trans and cis 2,5-dimethyl isomers with the former stereoisomer preponderating as established by a recent PMR study (Hassan and Casy, 1970). The trans ketone (61) has been shown previously (p. 52) to yield the two forms (55) and (56), with (55) as the major product because it involves PhLi attack upon the least hindered side of the piperidone ring. Addition of PhLi to the cis ketone (62) will yield the isomers (59) and (60); these should be minor components since only a small amount of their precursor is present in the 4-piperidone mixture. (Note that preferred conformations are not necessarily as depicted in these structures and remain to be established at this point).

Nazarov et al. (1956), the original workers in this field, isolated three of the four possible 4-piperidinols: one major (55) and two minor (56) and (59) products. Later Shvetsov and Kucherov (1959) reported the fourth derivative (60). The two groups of workers disagreed on the configurational assignment of the γ- and α- forms.

Initially, after the reaction of the ketone with phenyllithium, only two of the four isomers could be isolated; the physical characteristics (m.p.) of these alcohols corresponded to literature data upon the γ- and β-promedol alcohols. The

Scheme XVI


Ph
Me
OH
Me
N
Me
56
a
O
b
Me
Me
N
Me
61
a
Me
N
Ph
Me
OH
b
OH
Me
Ph
Me
N
Me
55
Me
Ph
Me
OH
N
Me
59
a
O
b
Me
Me
N
Me
62
a
Me
N
Ph
Me
OH
b
Me
OH
Me
Ph
N
Me
60

γ-form was readily isolated as the crystalline base from petroleum ether while the β-form was isolated from the remaining mother liquors as the hydrochloride salt from acetone.

PMR analysis of these two forms showed the γ-2- and 5-methyl doublets (base in $CDCl_3$) were at δ1.09 and δ0.62 while the β-isomer 2- and 5-methyl doublets appeared at δ1.13 and δ0.75.

In an effort to obtain the missing isomers, column chromatography was employed. This technique was not a new approach but had been used earlier by Prostakov and Mikheeva (1961) to separate the γ- and α-promedols in a pure state and a mixture enriched in the β-isomer which subsequently gave crystals of pure β- as the hydrochloride.

In the present case, however, it was decided that progress of the elutions be monitored by PMR spectroscopy since spectral characteristics of two of the isomers (γ- and β-) were already known. Fifteen grams of the total alcohol mixture (IR spectrum showed no detectable ketone remained) was chromatographed on 750 g. of neutral alumina (Woelm) and elution carried out with dry chloroform. Two hundred fractions of 20 ml. each were collected. Each tenth fraction was examined by PMR in the chloroform used for elution (the aromatic region was not recorded) and evidence of its composition being derived from the appearance of its 2- and 5-methyl resonance signals. Fractions flanked by samples having essentially identical PMR spectra were bulked. Details are

shown below:

Column Chromatographic Separation of Isomeric 1,2,5-Trimethyl-4-Phenyl-4-Piperidinols

Fraction	Weight	Isomeric Nature
1 - 30	0.2	-
31 - 83	5.8	γ only
84 - 110	2.2	γ (and perhaps δ)
111 - 130	1.2	α, β
140 - 190	5.0	α, β and γ
	total 14.4	

Fractions 31 - 83 clearly comprise the γ-isomer since samples had spectra displaying sharp doublets at δ1.09 and δ0.62 characteristic of the pure isomer.

The spectra of samples in the range 84 - 110 indicated that the γ- form still preponderated but minor doublets at δ1.25 and δ0.73 showed another isomer to be present. A pure sample of 4-piperidinol having these PMR characteristics was never isolated.

The spectra of samples in the range 111 - 130 lacked both γ- signals and those at δ1.25 and δ0.73. Two new sets appeared, however; one corresponded with those of the pure β- form (δ1.13 and δ0.75) and the other (δ1.17 and δ0.74) was later established to arise from the α-isomer.

The last group (140 - 190) was composed of an α, β and γ ternary mixture. Signals for the δ form were not discernible.

Pure γ from fractions 31 - 83 was recovered as the base

after crystallization. Crystallization of fractions 84 - 110 yielded only the γ-isomer and the other isomer (which may be the δ- form) could not be isolated.

Crystallization (as the hydrochloride) of fractions 111 - 130 gave pure β-promedol alcohol. Combination of these mother liquors with the remaining fractions yielded the α-promedol alcohol hydrochloride. The isomeric purity of all samples was followed by PMR spectral analysis of both the base and hydrochlorides.

TABLE XIII. PHYSICAL CHARACTERISTICS OF ISOMERIC PROMEDOL ALCOHOLS (BASES AND HYDROCHLORIDES)

Isomer	Form	m.p.	Lit. m.p.
γ-	base	106 - 107°	107 - 108°[a]
γ-	HCl	150 - 160°	158 - 159°[a]
β-	base	106 - 109°	106 - 107°[a], 102 - 103°[c]
β-	HCl	233 - 235°	233 - 235°[a]
α-	base	99 - 101°	102 - 103°[a], 106 - 107°[b]
α-	HCl	127 - 129°	173 - 174°[a], 230 - 231°[b]
δ-	base	-	109 - 110°[c]
δ-	HCl	-	264 - 265°[c]

(a) Nazarov et al. (1956); (b) Prostakov and Mikheeva(1960); (c) Shvetsov and Kucherov (1959).

(The m.p. of the α-isomer was found to differ from one crystal

crop to another yet the PMR spectra were identical and the analyses were good.)

It was considered that use of a sample of 1,2,5-trimethyl-4-piperidone enriched in the cis isomer (62) might lead to improved yields of at least one of the minor promedol alcohols. Nazarov and Shvetsov (1959) reported a method of increasing the amount of the minor (cis) isomer in the normal mixture by isomerization over alumina. They equilibrated the normal ketone mixture over alumina for thirty minutes at 100° and subsequently distilled the product; unfortunately the final composition of the products was not given.

It was decided, therefore, to investigate the amount of isomerization and the length of time required to effect this isomerization. Changes in the isomeric ratio were monitored by PMR as follows. In the PMR spectrum of the normal mixture of piperidones the 5-Me signal of the trans ketone (major) appears as a prominant doublet at δ0.91, while that of the cis form is a doublet falling slightly lower field (δ0.95) and of much reduced intensity, as shown in Figure I. The 2-Me doublets of the two forms are not separately resolvable and are centered near δ1.11. An increase in the intensity of the δ0.95 doublet relative to that at δ0.91 is evidence of an increased cis component. Treatment over alumina at 100° for forty-five minutes produced a product whose PMR signals for the 5-methyl group showed almost the same ratio of the cis to trans isomer as the original ketone. Heating another sample of the ketone for two hours

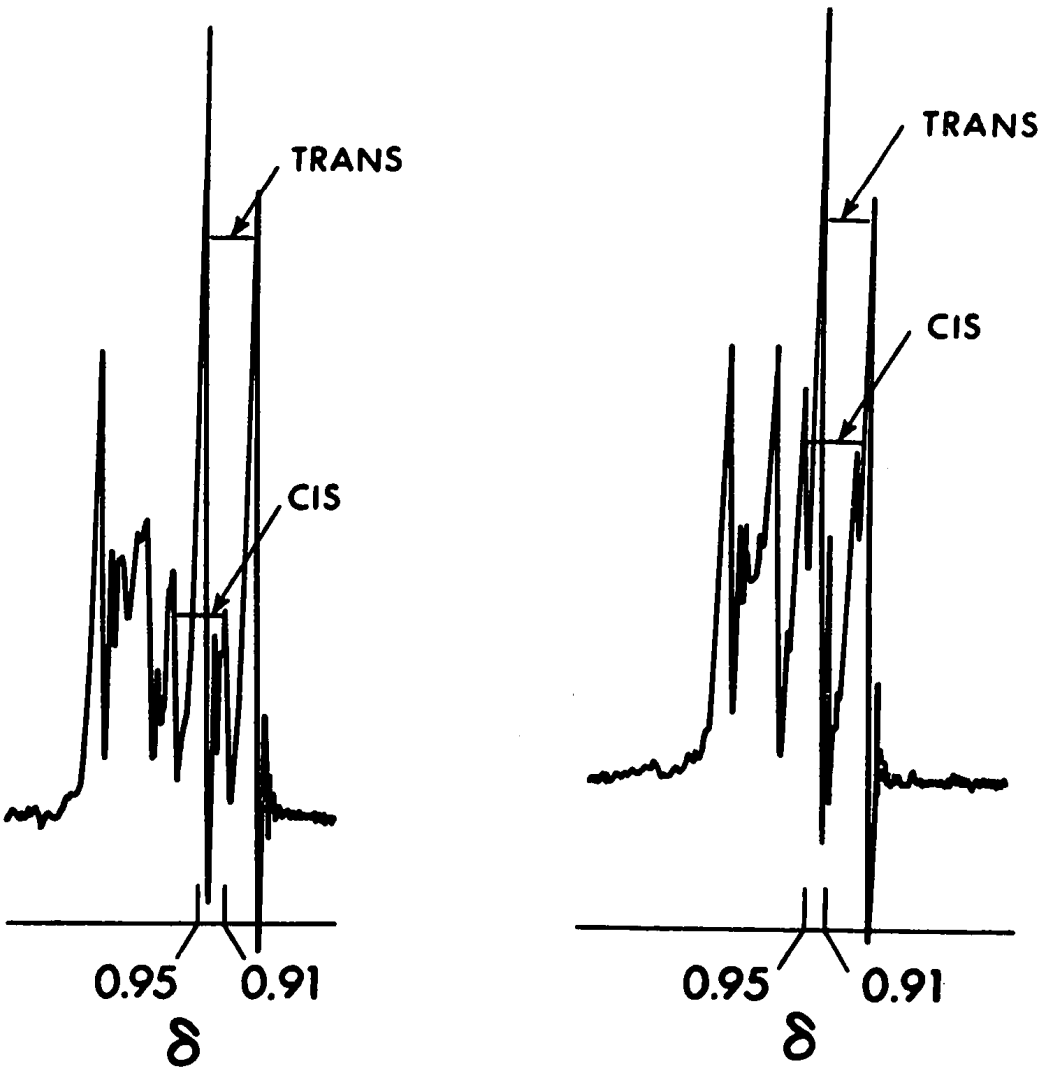


Figure I. Part of the PMR spectrum of 1,2,5-trimethyl-4-piperidone before and after treatment with alumina, recorded at 60 MHz in $CDCl_3$. (Sweep width 500 Hz)

produced a considerable increase in the PMR signal ratio of the cis isomer. Finally, heating yet another sample for twelve hours gave a product whose PMR signals were identical to those of the ketone that had been equilibrated for two hours. It appeared therefore that at the most two hour equilibration period gave an optimum amount of the cis isomeric form.

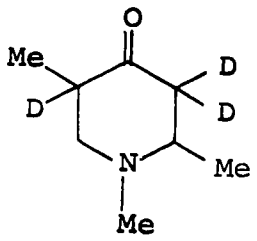
Column chromatography of the mixture of alcohol isomers resulting from treatment with PhLi of the ketone enriched in the cis isomer using the same procedure as before, but on a smaller scale, resulted in poor separation. The enrichment of isomeric alcohols derived from the cis piperidone apparently caused it to overlap into the γ- and α-isomer fractions and therefore only mixtures of the three isomers were obtained as seen from PMR evidence of random samples of the eluate. The isomers were separated subsequently by fractional crystallization as previously described.

PMR ANALYSIS OF ISOMERIC 1,2,5-TRIMETHYL-4-PHENYL-4-PIPERIDINOLS (PROMEDOL ALCOHOLS)

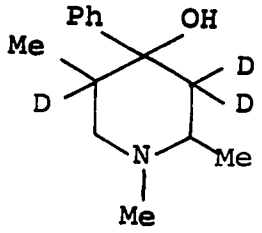
Arguments are based initially on the assumption that the piperidine ring of these isomers adopts a chair conformation with the 4-phenyl group equatorial.

The unambiguous assignment of signals in the following analysis has been achieved by comparing the spectra of the normal alcohols with those corresponding isomers in which the 3-methylene and 5-methine protons have been replaced by

deuterium as in (166). The deuterated forms were obtained from the α-trideuterated ketone (167).



167



168

The α-protons of a 4-piperidone ring are acidic enough to exchange with deuterium (Brignell et al., 1968), and the result of this exchange, using 1,2,5-trimethyl-4-piperidone, is shown in Figure II.

Hydrogen-deuterium exchange was accomplished using NaOD in CCl_4 and shaking this mixture with the ketone for twenty-four hours to produce the α-trideutero compound (167).

PMR analysis in CCl_4 of the secondary methyl region showed a large singlet at δ0.92 which corresponds approximately to the middle of the trans 5-methyl doublet of the normal ketone. The trans 2-methyl doublet appears at δ1.11, unchanged in position from that in the spectrum of the normal ketone. The two signals for the cis isomer appear at δ1.02 (singlet) for the 5-methyl (as compared to δ0.95 for the nondeuterated 5-methyl doublet) while the 2-methyl doublet, centered at δ1.11, overlaps with the major 2-methyl signal (Figure II).

Reactions of the α-trideuterated 4-piperidone with phenyllithium gave a mixture of isomeric 1,2,5-trimethyl-4-phenyl-4-piperidinols. The γ-isomer was isolated as the free base

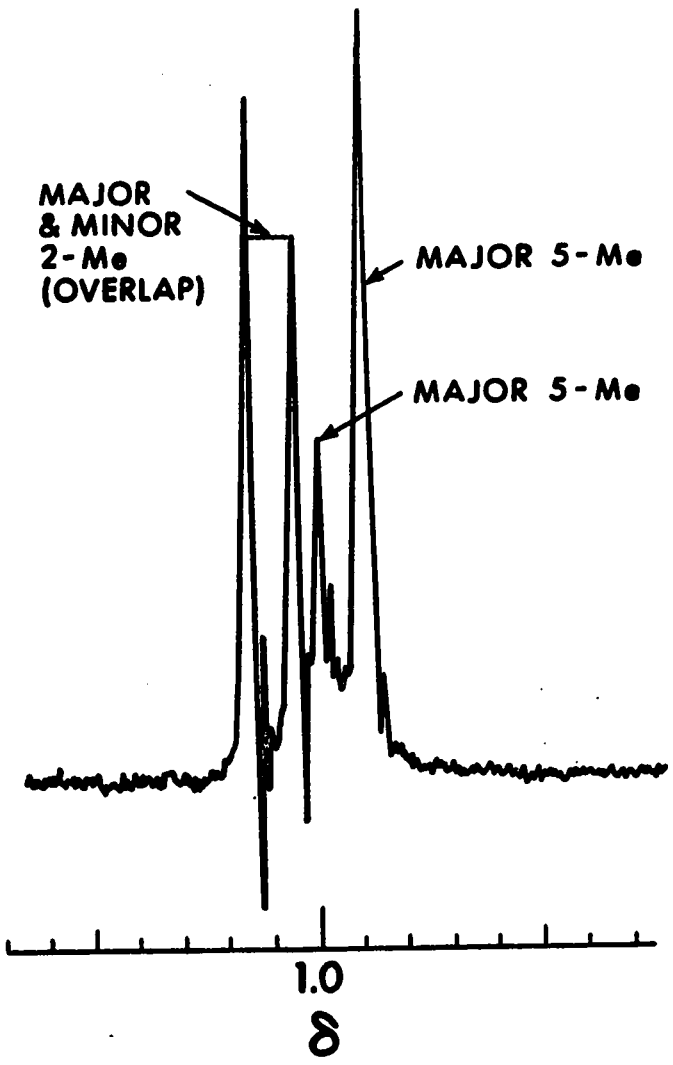


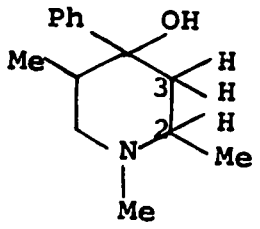
Figure II. Part of the PMR spectrum of 1,2,5-trimethyl-3,3,5-trideutero-4-piperidone, recorded at 60 MHz in CCl_4 (Sweep width 500 Hz).

from petroleum ether and had m.p. 103-104° (base) and m.p. 152-154° (HCl) which compared closely to those of the normal γ-promedol alcohol. The β- form was isolated from the mother liquors remaining as a hydrochloride from acetone with m.p. 90 - 91° (base) and m.p. 228 - 229° (HCl) which again corresponded closely to those of the non-deuterated alcohol. α-Promedol alcohol was isolated from the mother liquors remaining as a hydrochloride from ethanol-ether; m.p. 100 - 101° (base) and m.p. 110 - 120° (HCl).

γ-PROMEDOL ALCOHOL

In the 60 MHz PMR spectrum of the γ-base in $CDCl_3$ a three proton multiplet between δ2.2 and δ1.6 was assigned to the OH proton (a prominent singlet near δ2.03 disappears when D_2O is added) and two of the ring protons (see Figure III).

These protons must be the 3-methylene protons (169) because the signal is absent in the corresponding alcohol



169

prepared from the deuterated ketone.

In the 100 MHz spectrum of the γ-isomer in $CDCl_3$ the OH signal came to resonance at lower field (δ2.09) and did not interfere with the 3-methylene signal which forms a

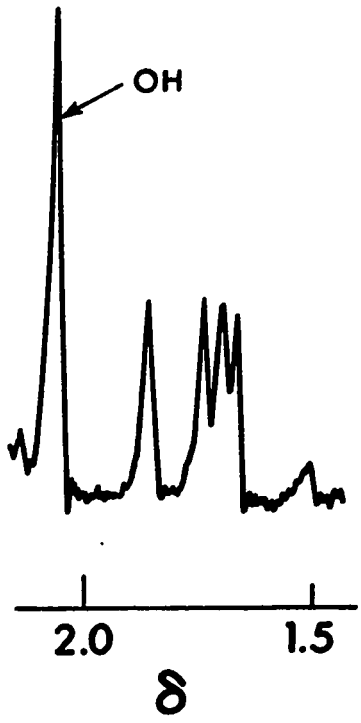


Figure III. Part of the PMR spectrum of γ-promedol alcohol recorded at 60 MHz in $CDCl_3$ (Sweep width 500 MHz).

clear doublet of quartets between δ1.4 and δ2.0 anticipated for the coupled system 3Ha, 3He, 2H (see Figure IV).

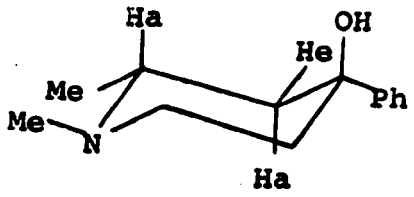
First order treatment gives the approximate coupling constants:

J gem 14 Hz. (identified by its occurrence 4 times within the octet)

J vic (1) 11 Hz.

(2) 3.5 Hz.

The two J vicinal values are typically those of an axial-axial (11 Hz.) and axial-equatorial or equatorial-equatorial (3.5 Hz.) pair of coupling protons (Sternhill, 1969), and show that the arrangement (170) must occur in the γ-isomer.



170

The 2-methyl substituent must therefore be equatorial in the preferred conformation (which is in agreement with the trans ketone producing the trans di-equatorial 2- and 5-methyl functions). The lower field position of the axial 3-H signal (the quartet with the larger J vic value) is probably due to this proton being 1,2-diaxial to the 4-hydroxyl group (in pyranose sugars an axial OH deshields a neighbouring axial proton by about 0.3 ppm) (Lemieux and Stevens, 1966). The lone pair of electrons on the nitrogen will also deshield this proton (Moynehan et al., 1962).

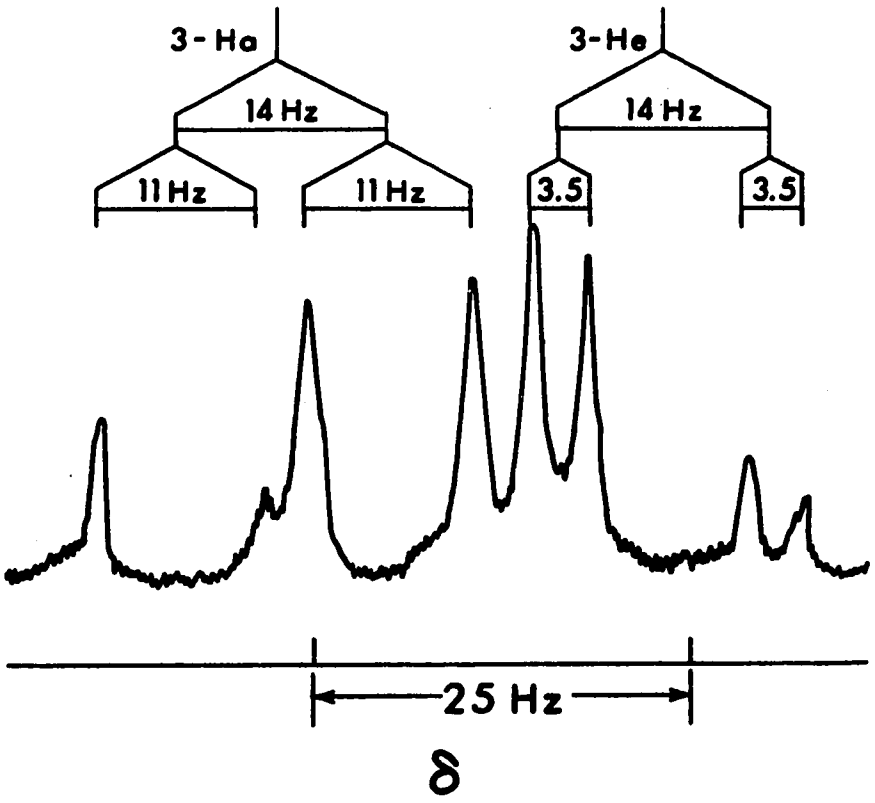
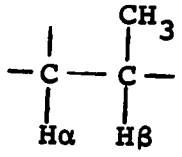


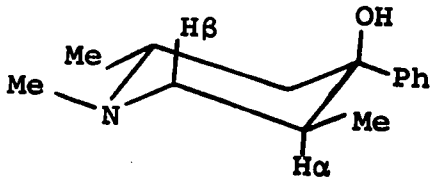
Figure IV. Part of the PMR spectrum of γ-promedol alcohol recorded at 100 MHz in $CDCl_3$ (Sweep width 250 Hz).

The evidence obtained from PMR analysis points to the fact that the 5-methyl group is also equatorial. The 5-methyl signal (identified as the higher field of the two doublets because this signal appears as a singlet in the spectrum of the deuterated ketone) has PMR properties very similar to those of the 3-methyl group in α-prodine alcohol (33) which is known to be equatorial (discussed earlier). Like the 3-methyl signal of α-prodine the 5-methyl doublet of γ-promedol alcohol (55) has the appearance typical of a virtual coupling situation as shown by a deformed doublet and extra peaks (Becker, 1965). This is verified by the increase in separation of the outer lines of the signal when the frequency is changed from 60 to 100 MHz (Lemieux and Stevens, 1965), since true coupling constants are independent of the operating frequency (see Figure V).

Virtual coupling is seen in a system of the type:



when the coupling J $H_\alpha H_\beta$ between two protons is of the same order as the chemical shift difference between the two protons. These conditions are quite likely to arise in (171) because the axial proton Hα is strongly coupled to the axial proton Hβ.



171

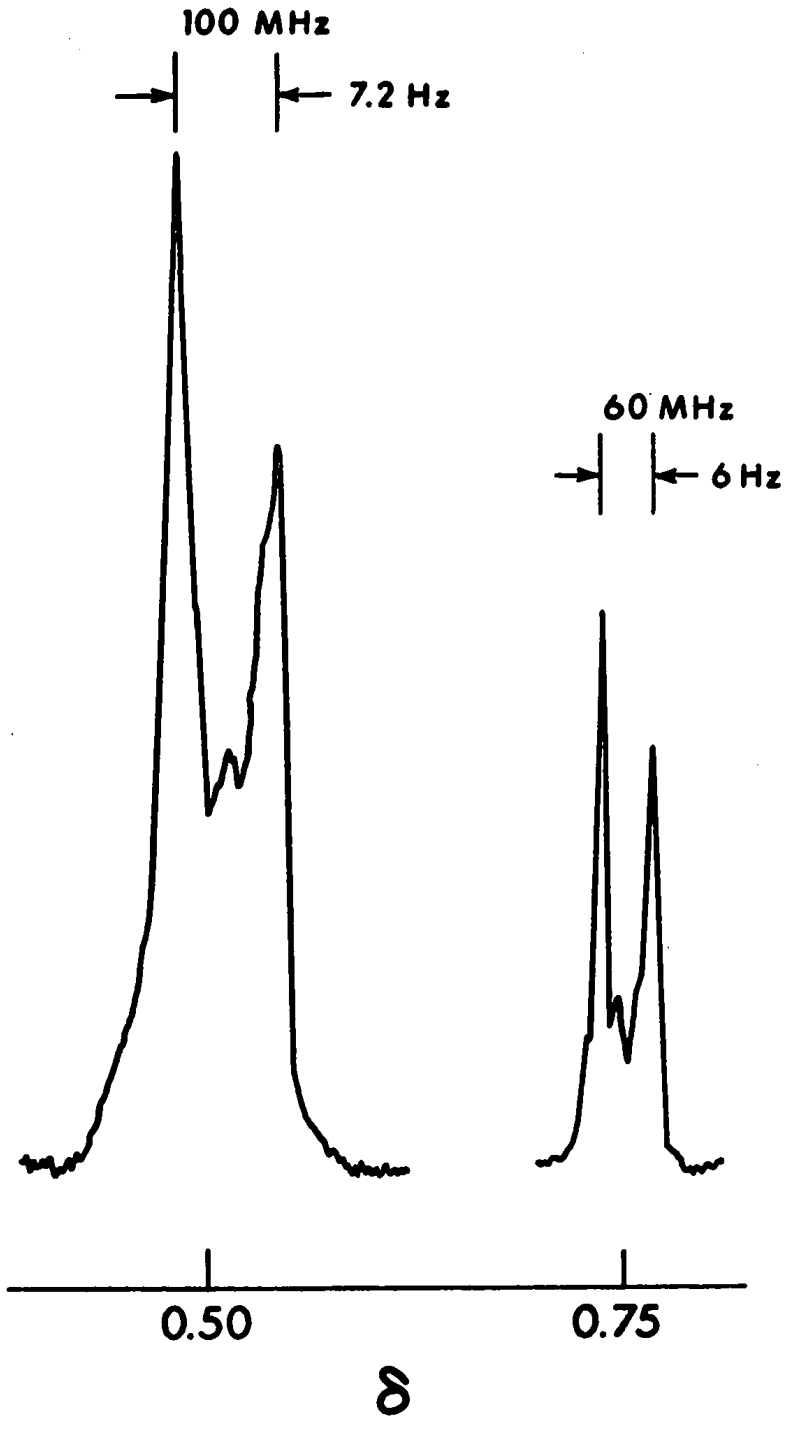


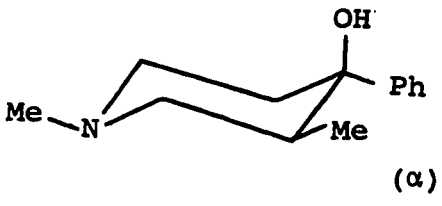
Figure V. Signals due to the 5-methyl group of γ-promedol alcohol at 100 and at 60 MHz. (Sweep width 250 Hz and 500 Hz respectively)

Other evidence that the C5-methyl group is equatorial in its most favoured conformation can be derived from a comparison of the chemical shift data of the base and salts as compared with those of α-prodinol (33) in several solvent systems (Table XIV).

TABLE XIV. CHEMICAL SHIFT DATA OF 3- AND 5-METHYL GROUPS OF α-PRODINE AND γ-PROMEDOL ALCOHOLS[a]

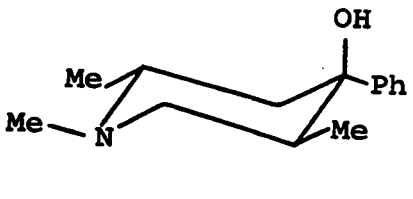
	α-prodine alcohol 3-methyl chemical shift[b]		γ-promedol alcohol 5-methyl chemical shift[b]	
	base	HCl	base	HCl
$CDCl_3$	0.63	0.65	0.63	0.65
DMSO-d_6	0.48	0.52	0.49	0.53
Pyridine	0.78	-	0.78	-

(a) Chemical shifts in δ units from TMS (60 MHz).
(b) Doublet.



(α)

33



(γ)

55

Finally the shift of the 5-methyl resonance which follows protonation of the basic centre (see Table XIV) is small, and typical of an equatorially oriented group.

The OH signal in DMSO-d_6 at δ4.55 corresponds roughly with that of the α-prodinol (δ5.37) and is higher field than

those of β- and α-promedols. The significance of this fact will be discussed later.

The striking similarity of all chemical shift data support the conformational identity of the 3- and 5-methyl groups in the two alcohols (33) and (55).

DECOUPLING OF γ-PROMEDOL ALCOHOL

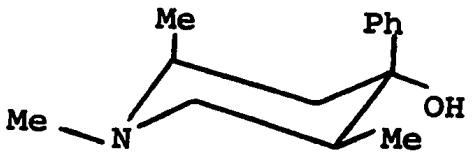
Decoupling, or double resonance, involves the irradiation of one proton or group of protons with a strong radio frequency field corresponding to their resonance frequency while observing the rest of the protons at normal field strength. This technique was employed in the case of the promedol alcohols in an effort to obtain more coupling constant values than could normally be observed.

Irradiation of the signals of the γ-isomer using 100 MHz field HA spectrometer unfortunately produced little new information due to the large overlap of the strong R.F. field used for the decoupling with the protons under observation. It did, however, allow the tentative assignment of the positions of the 3- and 5-H signals of the piperidine ring. Irradiation at δ2.16 (100 MHz field throughout) causes the 5-methyl signal at δ0.49 to collapse to a singlet, therefore the 5-methyl multiplet is centered almost directly under the N-methyl signal at δ2.19 (this signal was found by irradiating the 5-methyl signal at δ0.49 and observing the spectral simplification in the δ2.19 region), due to the overlap of signals no coupling constants could be obtained for the 5-H

signal. Subsequently, irradiation at δ2.48 caused the 2-methyl doublet at δ0.97 to collapse to a broad singlet. Also noticeably affected was the 3-methylene octet in the δ1.4 to δ2.0 region, which collapsed to a doublet centered at δ1.86 (J=14 Hz) and a poorly resolved signal for the other high field doublet at δ1.25 (J=14 Hz). These values unfortunately represent the geminal coupling constants of the 3-methylene protons and hence do not serve to confirm the stereochemistry.

β-PROMEDOL ALCOHOL

We have been unable to locate any experimental evidence about the stereochemistry of this isomer although it has been given the structure (59), of unlikely conformation, in one paper (Shvetsov and Kucherov, 1959).



59

From the spectrum of the normal and deuterated isomers, the 2- and 5-methyl signals and one of the 3-methylene protons are identifiable by principles already outlined for the γ-isomer.

The 100 MHz spectrum of the β-promedol alcohol (see Figure VI) shows one 3-methylene proton as an AB quartet centered at δ1.69 (δ1.72 at 60 MHz) with geminal (J=13.5 Hz)

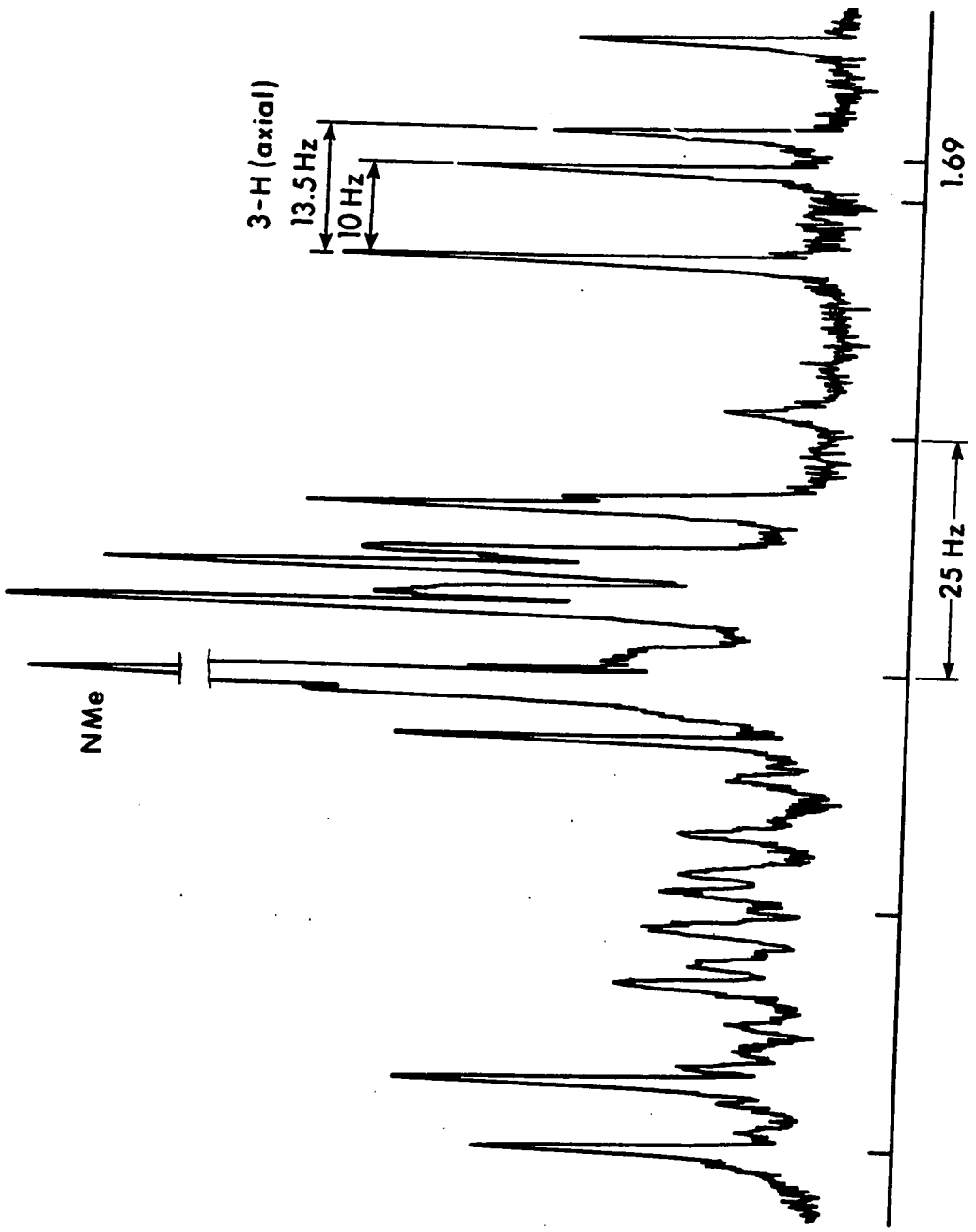
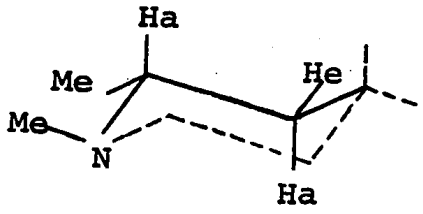


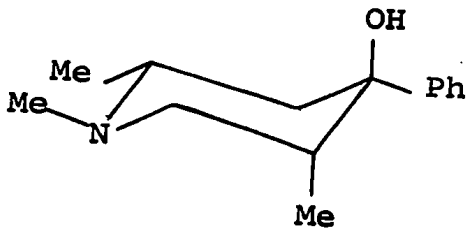
Figure VI. Part of the PMR spectrum of β-promedol alcohol recorded at 100 MHz in $CDCl_3$ (Sweep width 250 Hz).

and vicinal (J=10 Hz) couplings. A coupling constant of 10 Hz is typical of Ja/a coupling, thus the 2-methyl group must be equatorially oriented (as in the γ-isomer) and not axial as the Russian workers proposed. The alcohols must, therefore, have the partial structure (172) and the signal at δ1.69 must be due to the 3-H axial proton.



172

Therefore if the assignment of γ- is correct (55), and the 4-phenyl is taken to be equatorial, the β-5-methyl group must be axial as in (173).



173

The quartet for the γ-3- axial proton (δ1.86 at 100 MHz) was noted to be lower field than the β- axial 3-H signal, which was the reverse of what would be expected, since the β-3-H is opposed by an axial methyl group. This arrangement has been documented by Booth (1966) as causing deshielding of the 1,3-diaxial proton by the methyl function. However,

it is possible that the β-4-phenyl ring shields the β-3-axial proton more so than the γ-4-phenyl shields the γ-3-axial proton because of differing phenyl ring orientations (discussed later).

Other evidence that the β-5-methyl is axial in the preferred conformation can be obtained by chemical shift comparisons (Table XV) with the 3-methyl signal in β-prodinol (34) in which the 3-methyl is known to be axial (Casy, 1966).

TABLE XV. 3-METHYL AND 5-METHYL CHEMICAL SHIFT VALUES OF β-PRODINE AND β-PROMEDOL ALCOHOLS (60 MHz FIELD STRENGTH)[a]

Solvent	β-prodine alcohol 3-methyl chemical shift[b]	γ-promedol alcohol 5-methyl chemical shift[b]
CDCl	0.75	0.75
DmSO-d	0.63	0.68
Pyridine	0.93	0.96

N.B. Notations used here have the same meaning as those described in the footnotes of Table VIII.

Again the similarity of signal position points to the fact that the 3-methyl in β-prodinol (34) has a similar conformation to the 5-methyl in β-promedol alcohol. Also of interest is the fact that the 3-methyl signal of β-promedol is almost free from virtual coupling effects; a clear doublet

of J=6.8 Hz is observed at both 60 MHz and 100 MHz indicating a lack of strong coupling effects.

The O<u>H</u> signal of β-promedol alcohol in DMSO-d_6 at δ4.78 is close to that of O<u>H</u> in β-prodinol, and lower field than the γ-O<u>H</u> signal. In DMSO-d_6 the predominant hydrogen bound species are those formed between solute and solvent molecules and the O<u>H</u> resonance is essentially independent of concentration and small temperature variations (Ouellette, 1964; Rader, 1969), and its chemical shift, dependent largely on the strength of the solute-solvent hydrogen bond, will reflect the steric environment of the OH function. Since hydrogen bonding tends to deshield the OH proton (Pople <u>et al.</u>,1959) then the higher field position of the γ-alcohol, as compared to the β-form, indicates the hydrogen bonding is least effective in the γ-form. The 4-hydroxyl group is considered to be axial in both proposed conformations of the isomers but in the γ-isomer it will be hindered by a gauche 3-methyl group (see Figure VII).

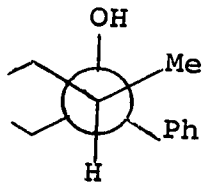


Figure VII. Newman projection of γ-promedol alcohol looking down C_5-C_4 bond.

In the β-isomer, the axial 3-methyl group is removed from the 4-hydroxyl function and hydrogen bonding with the solvent (DMSO-d_6) may be expected to occur more readily

(Figure VIII).

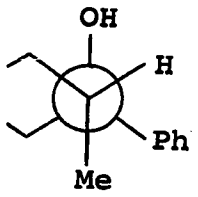
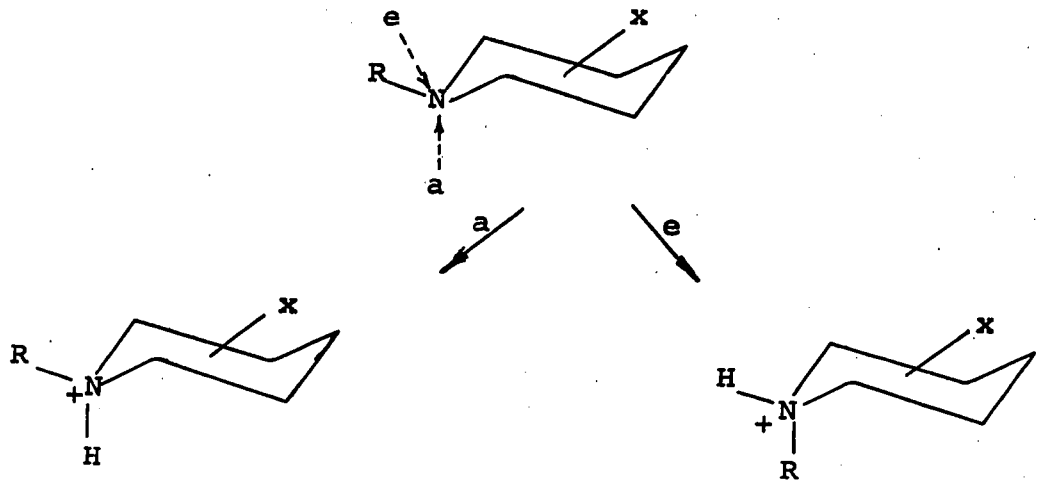


Figure VIII. Newman projection of β-promedol alcohol looking down C_5-C_4 bond.

Previously it has been shown that the evidence for axial 3-methyl orientation in β-prodinol and its esters was provided by the pronounced downfield shift of the 3-methyl resonance signal following protonation of the basic centre. The ideal solvent for observing this shift is $CDCl_3$, for complications arise when polar solvents are employed. Unfortunately the β-promedol alcohol hydrochloride was insoluble in $CDCl_3$; however, in DMSO-d_6 the protonation shift of the 5-methyl signal of the β-form (0.1 ppm) was greater than that seen in the γ-analogue (0.04 ppm), while in the same solvent, shifts for α- and β-prodinol are 0.28 and 0.18 ppm respectively. Therefore differences seen are smaller than in $CDCl_3$ but of the same order.

EPIMERIC CONJUGATE ACIDS

Isomers of this nature arise in cyclic bases as a result of two modes of proton uptake (axial and equatorial) at the nitrogen. Such epimers may be detected in appropriate cases by duplication of the nitrogen substituent signal or the signal of a ring carbon group since the environment of nitrogen



and/or carbon substituents may differ in the two isomers. Detection of epimers generally requires a slow proton exchange rate; if the rate is faster than the PMR time, averaged and not duplicate signals are usually observed since isomers of the type shown above will be rapidly interconverting. Many piperidine salts fail to give PMR evidence of epimer formation even in solution of low pH, and in such cases one epimer (usually that produced by axial protonation) must be extensively favoured over the other. However if the epimer formed as a result of equatorial protonation enables the relief of nonbonded interactions obtained in the product of axial attack, then significant populations of the two forms may be expected.

The spectrum of the β-promedol alcohol hydrochloride in D_2O clearly displayed evidence of the presence of protonated epimers. Both 2- and 5-methyl signals were duplicated, as well as other signals (Figure IX). At the normal operating

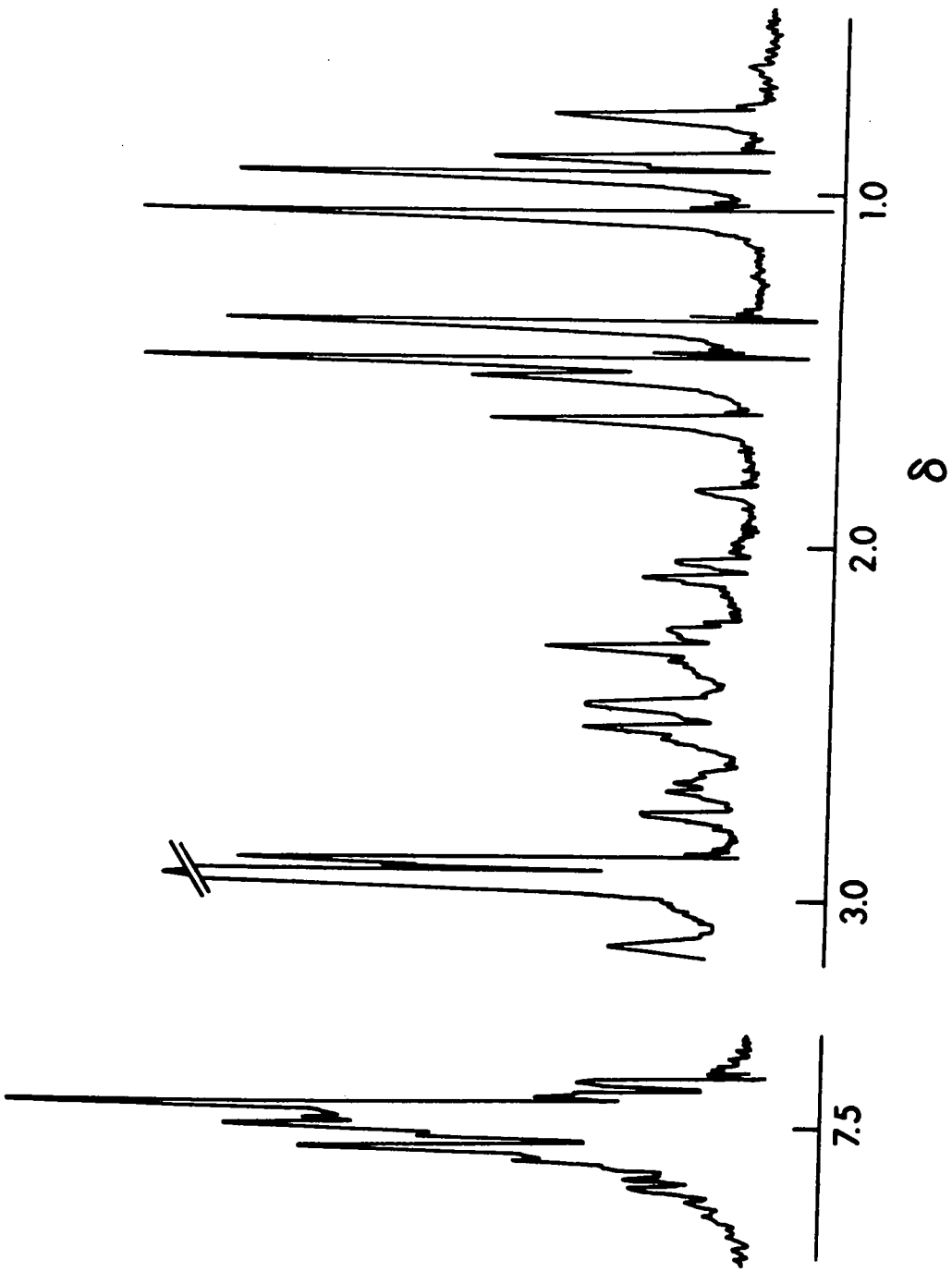
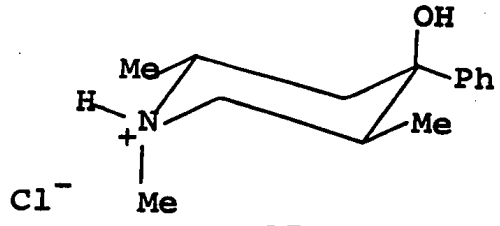


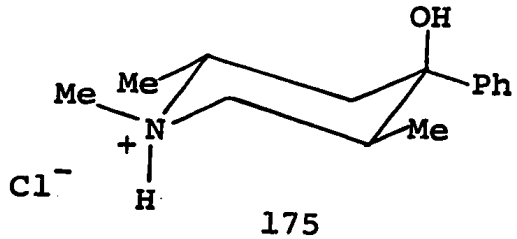
Figure IX. PMR spectrum of β-promedol alcohol hydrochloride showing epimer formation recorded at 60 MHz in D_2O (Sweep width 500 Hz).

temperature of the instrument the higher field 2-methyl and lower field 5-methyl signals had a greater intensity (in several spectral runs it was sometimes found necessary to add a small trace of acid (HCl/D_2O) to effect good resolution).

When the temperature of the probe was raised, the 2- and 5-methyl signals started to collapse (Figure X) and at 90° only two doublets remained and the whole spectrum was greatly simplified (Figure XI). The final chemical shift was found to be a weighted mean of that of the two epimers.

The γ-alcohol hydrochloride in D_2O does not display epimeric forms. This is anticipated since epimers are not expected in the γ-isomer because the product of equatorial protonation (174) may not relieve non bonded interaction of the axial N-methyl by a conformation change, since any departure from the chair form shown must place the equatorial





2,5-methyl and 4-phenyl groups in less favorable orientations. Hence the protonated form must be (175) almost entirely.

In the β-promedol alcohol hydrochloride the product of axial protonation (176) no doubt represents the major epimer in spite of the unfavorable non bonded interaction of the axial 5-methyl group. The product of equatorial protonation

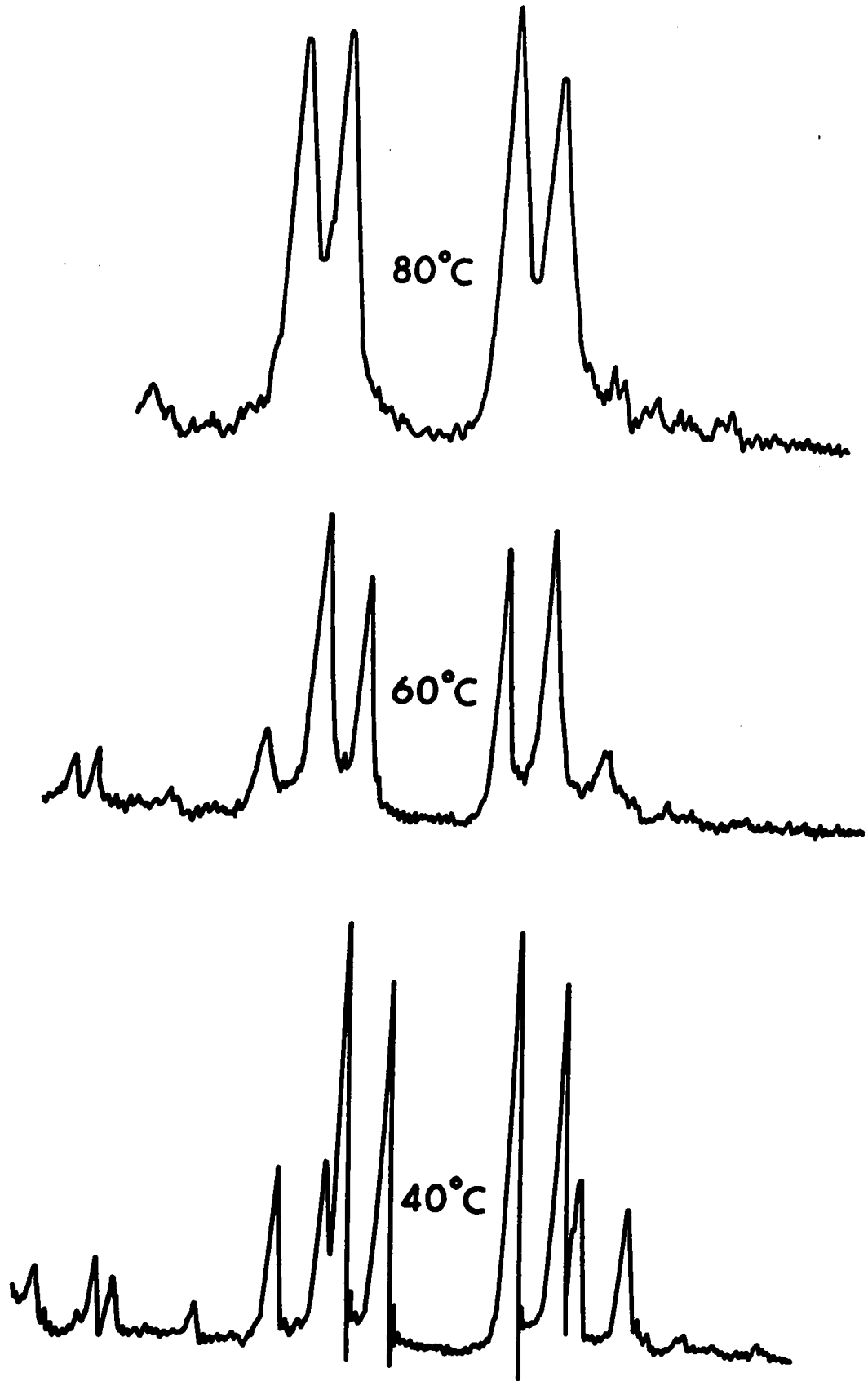


Figure X. Part of the PMR spectrum of β-promedol alcohol hydrochloride showing the effect of variable temperature on the 2- and 5-methyl groups recorded at 60 MHz in D_2O (Sweep width 500 Hz).

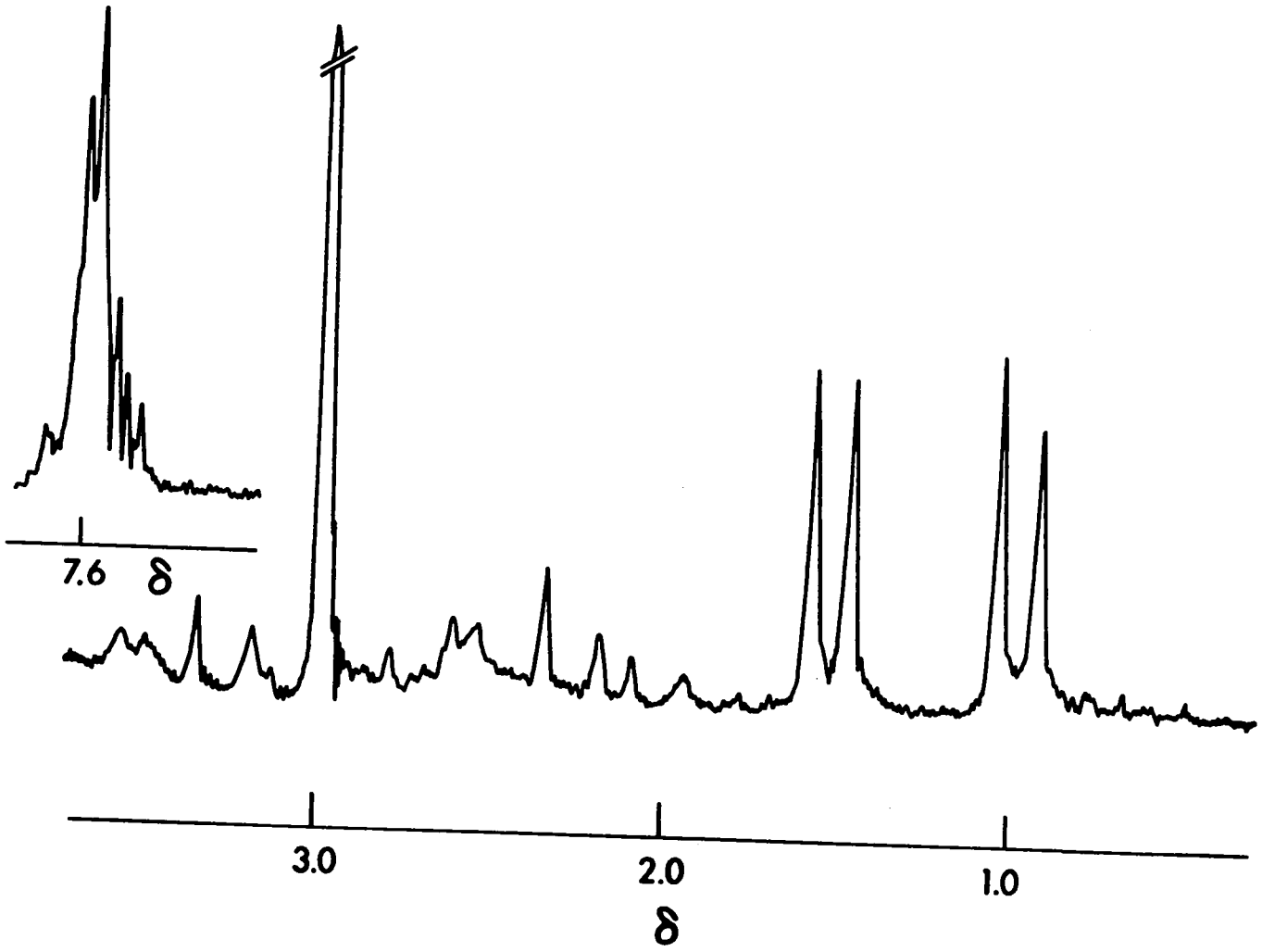
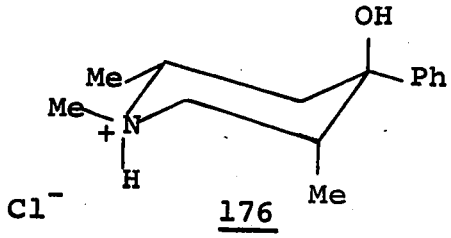
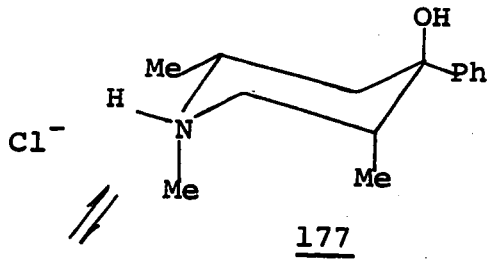


Figure XI. PMR spectrum of β-promedol alcohol hydrochloride at 90° recorded at 60 MHz in D_2O (Sweep width 500 Hz).

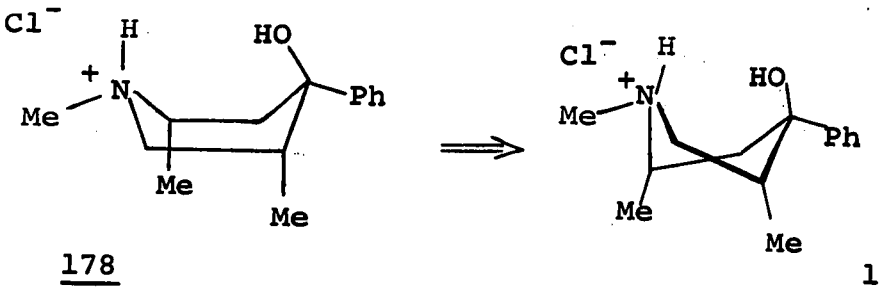


176

(177), on the other hand, although clearly of higher energy in the chair form, may undergo a conformational change which will reduce the non bonded interaction of two axial



177



178 179

methyl groups (N-Me and 5-Me). The boat form (178) relieves this interaction to some extent but the skew boat (179) is most likely; in fact the population of the chair (177) is probably very low because of its diaxial N-methyl and 5-methyl interaction.

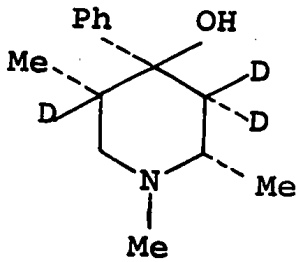
On this basis the lower 5-methyl signal (δ0.95) has been assigned to the major isomer (176), and the higher field (δ0.77) to the minor form (179). The 5-methyl in (176) will be more subject to deshielding by the NH group than will be

the 5-methyl group in (179). The 2-methyl signal in the major epimer (δ1.38) is close to the γ-value of δ1.36 and is in agreement with the major β-epimer (176) and the γ-isomer (175) having similar geometry about the C-2-position of the piperidine ring.

In the minor form of the epimer, the 2-methyl group has a lower field position (δ1.53) and, as expected, lacks any real similarity with the γ-isomer 2-methyl group.

There is evidence that the 3-methyl groups of β-prodinol HCl (Casy, 1966) has a preferred skew boat conformation in D_2O and since its 3-methyl signal (δ0.75) is close to that of the 5-methyl signal (δ0.77) of β-promedol in the same solvent it is feasible that the minor epimer has the same skew boat conformation. Adoption of the same type of conformation by the structure assigned to the major β-promedol alcohol epimer (176), however, is improbable since this would place the 2-methyl substituents in less favorable orientations.

To complete the PMR analysis of the β-isomer, attempts were to identify other ring proton signals by spectral study of the deuterated alcohol at 100 MHz and of the non-deuterated alcohol at 100 and 220 MHz. In general, the spectrum of deuterated β-promedol alcohol (180) is considerably



180

simplified over that of the non-deuterated form. However, at 60 MHz the only signals clearly defined were those for the two methyl groups (2-methyl doublet and 5-methyl singlet).

At 100 MHz the base in $CDCl_3$ displayed a spectrum which was more readily resolvable. Each 6-methylene signal formed a doublet of J gem 12 Hz at δ2.68 and δ2.08. The 2-methine proton appears as a quartet of J=7 Hz centered at δ2.48. All signals were broadened by coupling with deuterium (Figure XII).

Comparison of spectra of the normal (Figure VI) and deuterated alcohol (Figure XII) at 100 MHz shows the resonance lines around the prominent N-methyl singlet comprise quartets due to the equatorial 3-methylene proton (the axial proton has already been assigned to the clear quartet at δ1.68) and one of the 6-methylene protons plus a multiplet due to the 5-methine proton. No reliable resolution of individual signals is possible because of the complex nature of the group and the high degree of overlap. Resolution of the low field 6-methylene proton (near δ2.68) is also not possible because of overlap with the 2-methine proton. The spectrum of the deuterated alcohol (Figure XII) does show that the two 6-methylene protons differ considerably in their chemical shift (Δ0.6 ppm). This result is not inconsistent with the stereochemistry proposed (181), since in this arrangement Ha is deshielded by the axial 4-OH (Carr and Huitric, 1964) and the axial 5-methyl (Booth, 1966) while He is shielded by the latter group.

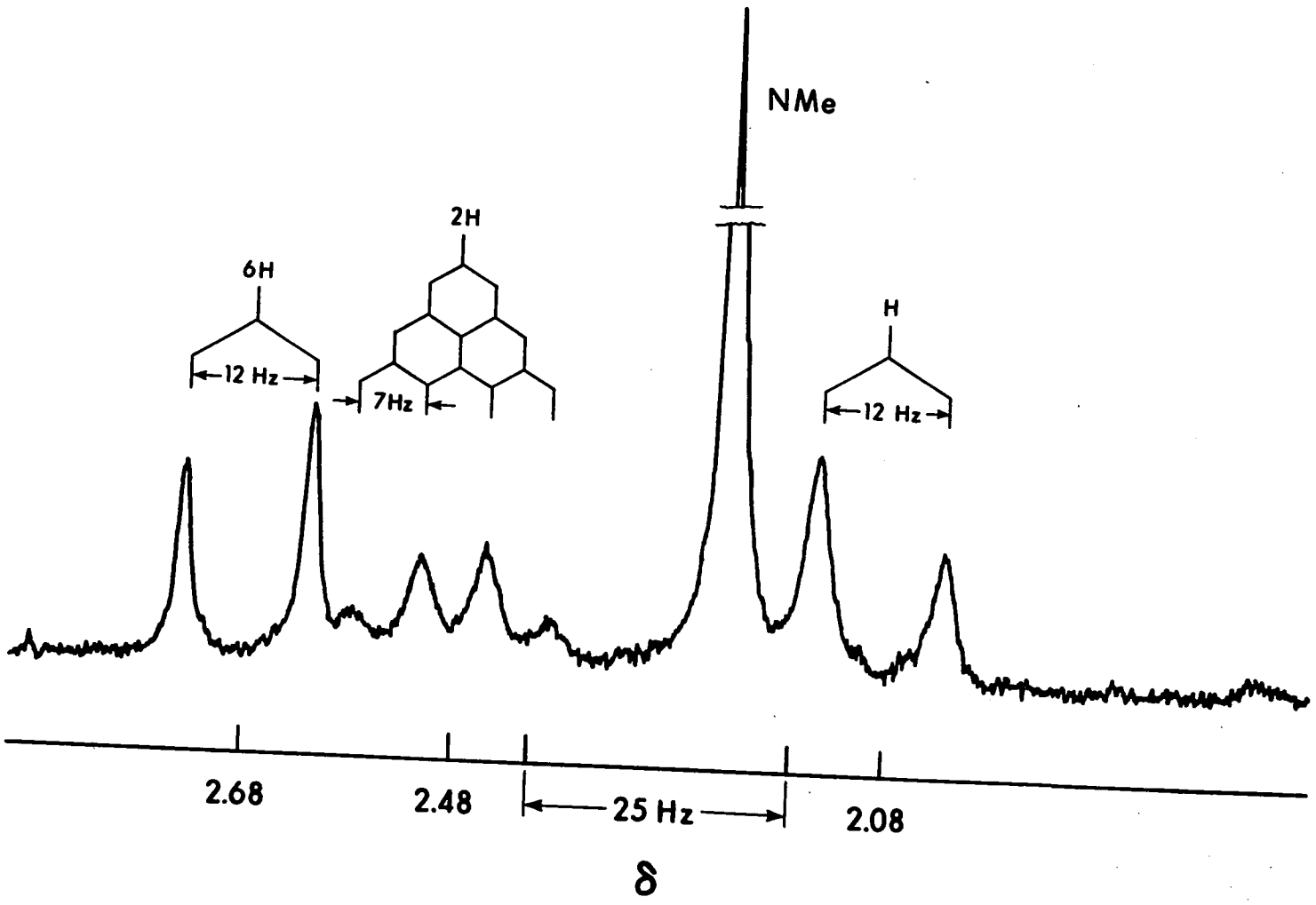
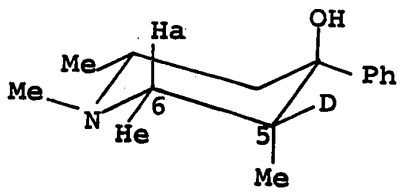


Figure XII. Part of the PMR spectrum of trideutero-β-promedol alcohol recorded at 100 MHz in $CDCl_3$ (Sweep width 250 Hz).

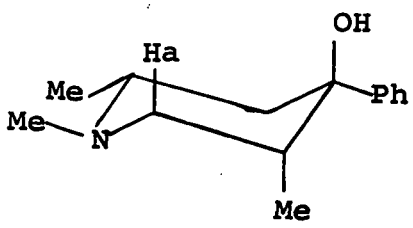


181

Attempts to prove the position of the 6-methylene proton by irradiation (100 MHz field) of the 5-methine proton in the normal alcohol met with little success, because the overlap of all the methylene and methine protons caused an effect in the general area and therefore the 6-methylene proton could not, with certainty, be identified by this method.

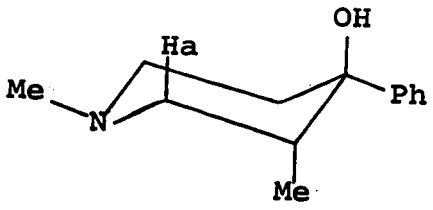
It was anticipated that the resolution difficulties referred to above would be resolved by recording the spectra of the β-alcohol at 220 MHz. When this was done, however, the multiplet around the N-methyl signal remained complex. The lower field 6-methylene and 2-methine signals moved apart, however, and the former appeared as a quartet with J values of 10.5 and 3 Hz. The last coupling must be a vicinal value and its magnitude is consistent with a/e or e/e coupling as must occur if the 5-methyl group is axial (173). A clearly resolved one-proton quartet of similar chemical shift (relative to the multiplet about the N-methyl singlet) and line separations, as those of the 220 MHz quartet mentioned above, is seen in the 100 MHz spectrum of β-prodinol (34) recorded in pyridine. It seems reasonable to assign both signals to

the similarly situated axial protons of the alcohols as shown below.



β-promedol alcohol

173



β-prodine

34

Therefore, in summary, the chemical shift values for β-promedol alcohol base indicate that the molecule has a cis 5-Me/4-Ph and a cis 2-Me/5-Me configuration and has the preferred conformation (173).

α-PROMEDOL ALCOHOL

PMR spectral analysis of the α-promedol alcohol base in $CDCl_3$ at 60 MHz showed a 2-methyl doublet at δ1.18, and a 5-methyl doublet at δ0.75 which collapsed to a singlet in the deuterated alcohol. Also clearly visible was one complete 3-methylene proton quartet centered at δ1.67 giving J gem (14.5 Hz) and J vic (4.25 Hz), and half of the other quartet which gave the second J vic value of 6 Hz. All signals were absent in the spectrum of the deuterated alcohol (Figures XIII and XIV).

If assignments to the γ- and β-isomers are correct, the α- form must be either (182) or (183), again employing the chair conformation of the piperidine ring with the 4-phenyl equatorial.

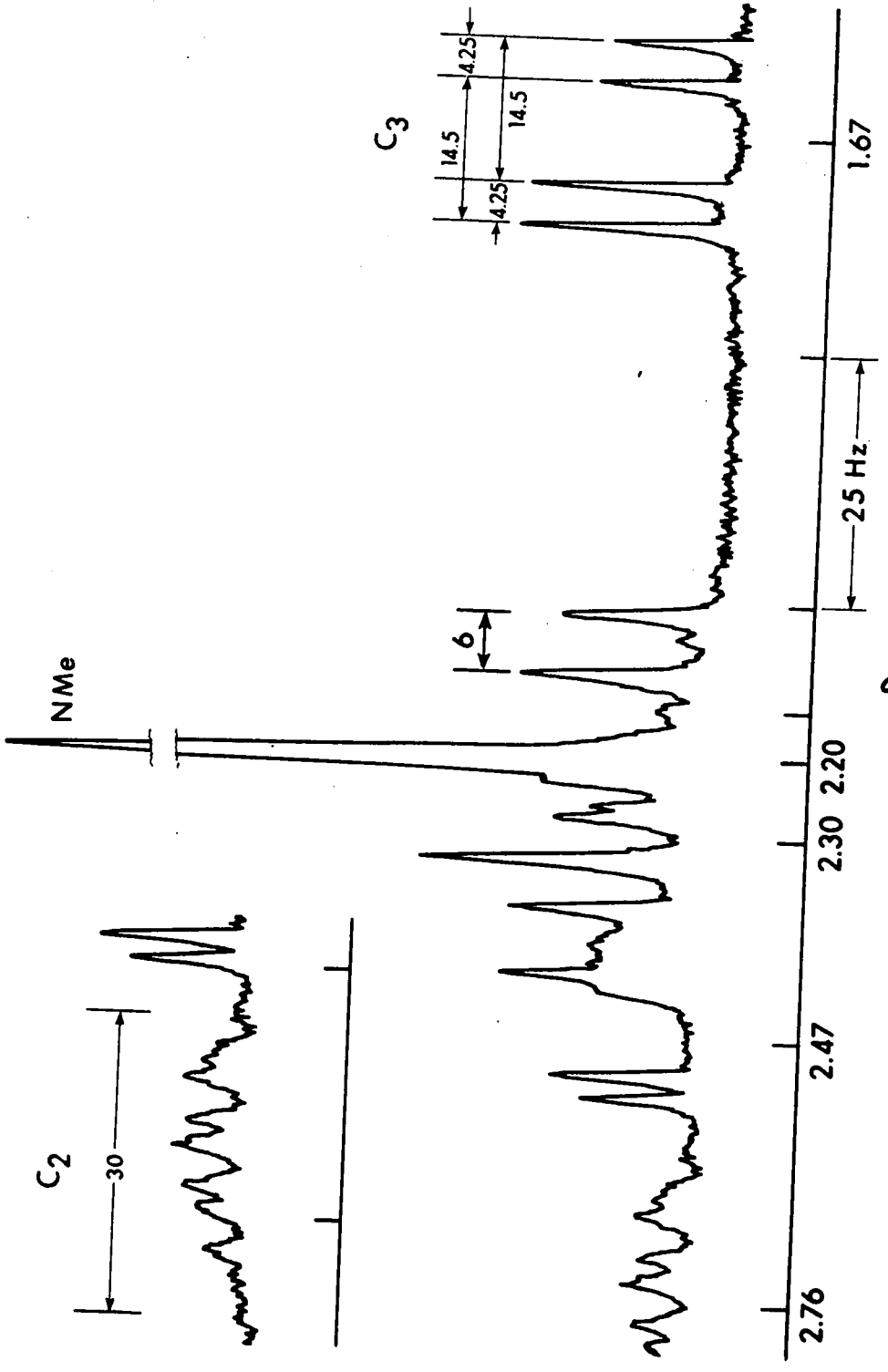


Figure XIII. Part of the PMR spectrum of α-promedol alcohol recorded at 100 MHz in $CDCl_3$ (Sweep width 250 Hz).

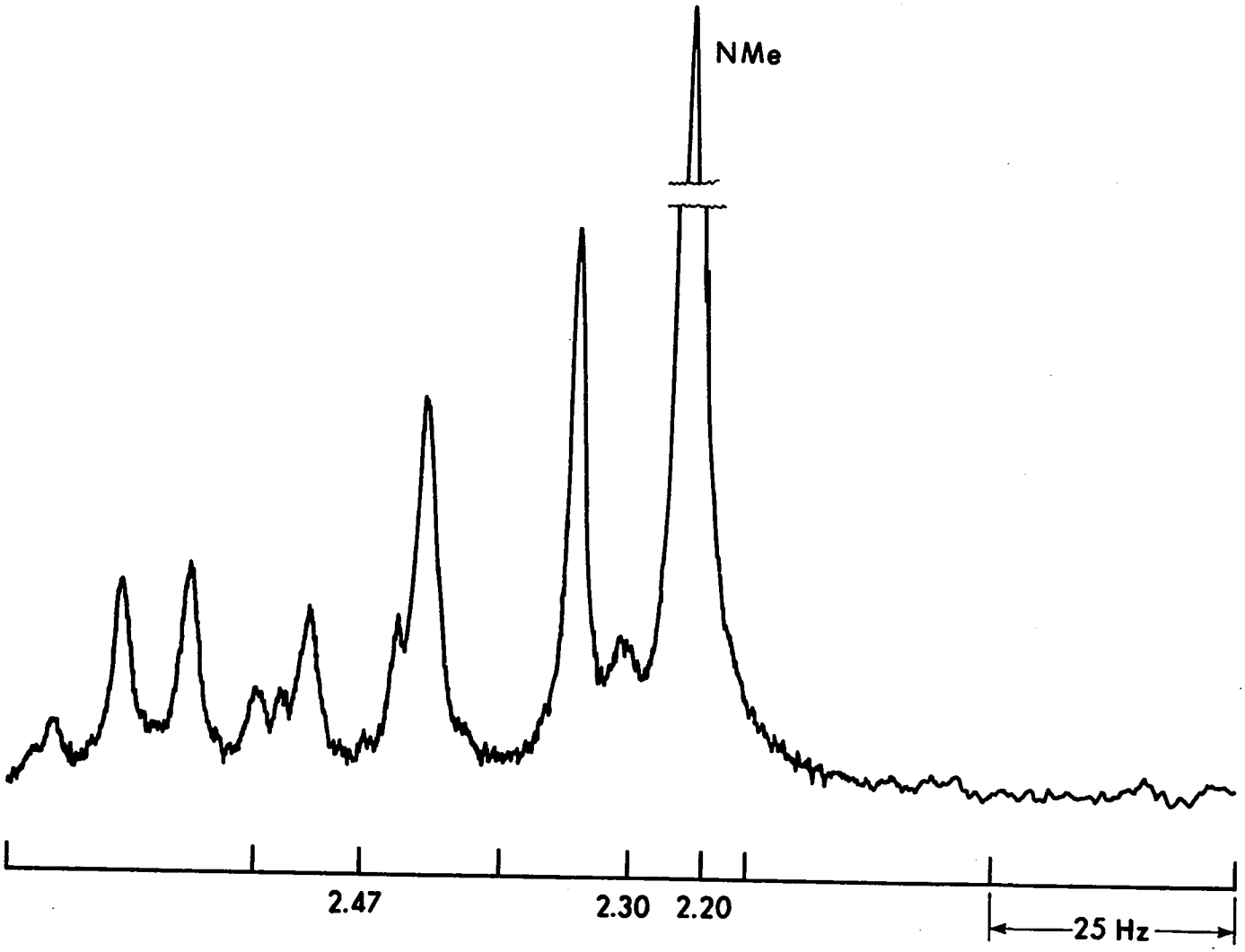
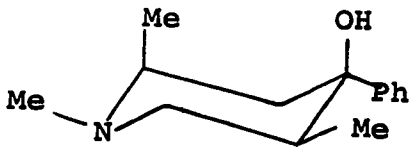
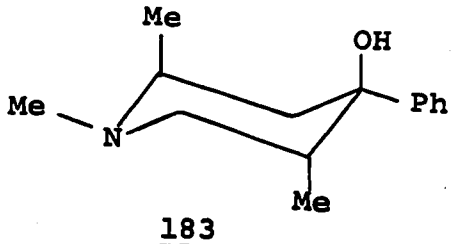


Figure XIV. Part of the PMR spectrum of trideutero α-promedol alcohol recorded at 100 MHz in $CDCl_3$ (Sweep width 250 Hz).



182



183

The small 3-methine proton J vic value of 4.25 Hz agrees with both forms above but the second value of 6 Hz is too large for a gauche coupling, yet too small for a diaxial interaction. Structure (182) is more favoured on thermodynamic grounds but (183) is the form expected from the more abundant trans ketone; that is, it is the product of axial attack by PhLi (see p. 52). Also since the α- and β-5-methyl chemical shift values (Table XVI) are nearly identical, while the same is true for the OH shifts in DMSO-d_6, it seems probable that both isomers have similar geometry about the C4, C5 and C6-half of the molecule.

TABLE XVI. PMR CHARACTERISTICS OF α- AND β-PROMEDOL ALCOHOL BASES IN VARIOUS SOLVENTS[a]

	α-Promedol Alcohol PMR Chemical Shifts			β-Promedol Alcohol PMR Chemical Shifts		
	Pyridine	$CDCl_3$	DMSO-d_6	Pyridine	$CDCl_3$	DMSO-d_6
5-Me[b]	0.78	0.73	0.65	0.96	0.75	0.68
4-OH[c]	-	-	4.75	-	-	4.78

(a) Chemical shift values in δ units measured at a frequency of 60 MHz. (b) Doublet. (c) Singlet.

The 100 MHz PMR spectrum of the deuterated α-isomer shows that all signals upfield from the N-methyl signal (δ2.2) in the spectrum of the normal alcohol are absent. The two doublets that should exist for the two-6-methylene protons in the deuterated alcohol are not clearly resolved but are probably centered near δ2.3 (*J* gem = 11 Hz) and δ2.47. (The higher field line of the low field doublet is broadened because it contains the OH signal determined by integral trace after D_2O addition.)

As is the case of the β-alcohol spectrum a complete and unambiguous analysis of ring proton resonances in the region downfield of the N-methyl signal (100 MHz, in $CDCl_3$) cannot be made because of the overlapping pattern (Figure XIII). However, when the spectrum was run in pyridine-d_6 at 100 MHz, a quartet downfield from the N-methyl could be identified with reasonable confidence. This gave the coupling parameters J gem (11 Hz) and J vic (5.5 Hz). The change of solvent, $CDCl_3$ to pyridine-d_6, does not alter the conformation of the molecule significantly because the clearly defined quartet due to a 3-H proton (upfield of the N-methyl signal) has essentially the same separations in the two solvents.

The 220 MHz spectrum of the α-alcohol did not improve resolution of signals closest to the N-Me signal but it did show a separation of the lowest field quartet from the 2-methine multiplet. The former (which appeared as an apparent narrow doublet in the 100 MHz spectrum) had the coupling

J gem (11 Hz) and J vic (8.5 Hz) at 220 MHz. The 2-methine multiplet could not be resolved but its base width (Δ = 30 Hz) was of the order anticipated from the 3-methylene and 2-methyl J vic values (3 × 6.5 + 4.25 + 6.0 = 29.75 Hz).

Coupling constant data for the methylene protons of α-promedol alcoholare summarized below:

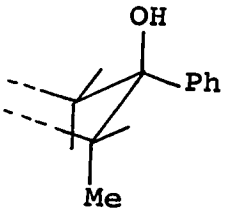
	J gem (Hz)	J vic (Hz)
3-methylene	14.5	4.25, 6.0
6-methylene	11.0	5.5 , 8.5

The values 4.25 and 5.5 Hz fall in the range of Jae coupling and possibly Jee, although they are somewhat large for the latter (Thomas, 1968; Sternhill, 1969). The values 6.0 and 8.5 Hz, however, are typical of neither Jae, Jee nor Jaa couplings as must obtain in a single chair conformation. Instead they indicate that the molecule

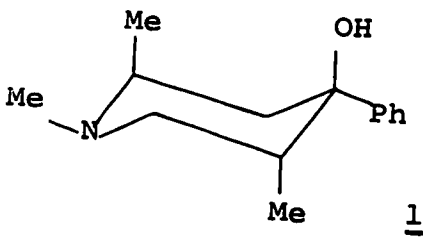
(i) has a preferred flexible conformation, for example a skew boat, or

(ii) displays preference for more than one conformation; these are in rapid equilibrium and J vic couplings observed are time averaged values.

The similar 5-methyl and 4-O<u>H</u> (Table XVI) chemical shifts of the α- and β-isomers is strong evidence that their geometry about C3, C4 and C5 is alike, and is shown in (<u>184</u>).

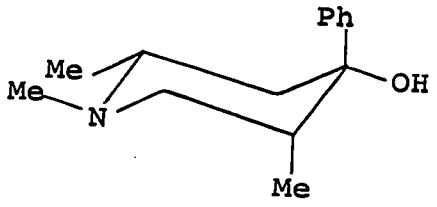


<u>184</u>



<u>183</u>

In the chair conformation corresponding to this arrangement, the α-isomer thus has the structure (183) (an equatorial 2-methyl group has already been assigned the β-isomer). The alternative configuration (one conformer is shown in 185) cannot provide this relationship of Ph, OH and 5-methyl groups.



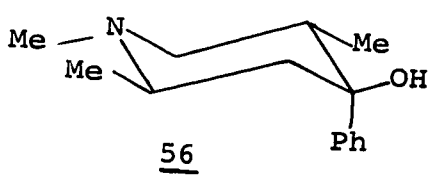
185

(183) cannot be the preferred conformation, however, because it would not be associated with the J vic values of 6 and 8.5 Hz as already explained. A significant population of the inverted chair (56) may well account for the observed J vic values (if these are an average) but the population is probably low because

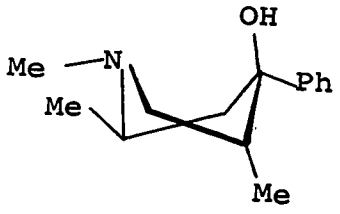
(i) it places the large phenyl group in an axial position (see discussion on conformational free energy values later);

(ii) it places the 5-methyl in an environment that differs considerably from that of the β-5-methyl group.

The flexible boat form (186) remains to be considered and



56



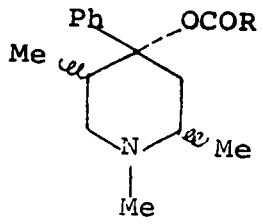
186

is an attractive possibility due to the fact that it lacks axial-axial couplings and it leaves the 5-methyl group in a similar environment to that of the chair (183). There is good reason to believe that flexible forms such as (186) are the principle conformations of the α-alcohol. In themselves they provide dihedral angles between vicinal C-H groups that are compatible with the J vic values observed, while the chair form (183) is destabilized by three axial interactions.

It will be seen later that PMR data upon esters of the α-promedol alcohol and chemical evidence are best interpreted in terms of the α-derivatives having a trans 2-Me/5-Me, cis 5-Me/4-Ph configuration and a preferred skew boat conformation.

ESTERS OF ISOMERIC 1,2,5-TRIMETHYL-4-PHENYL-4-PIPERIDINOL (PROMEDOLS)

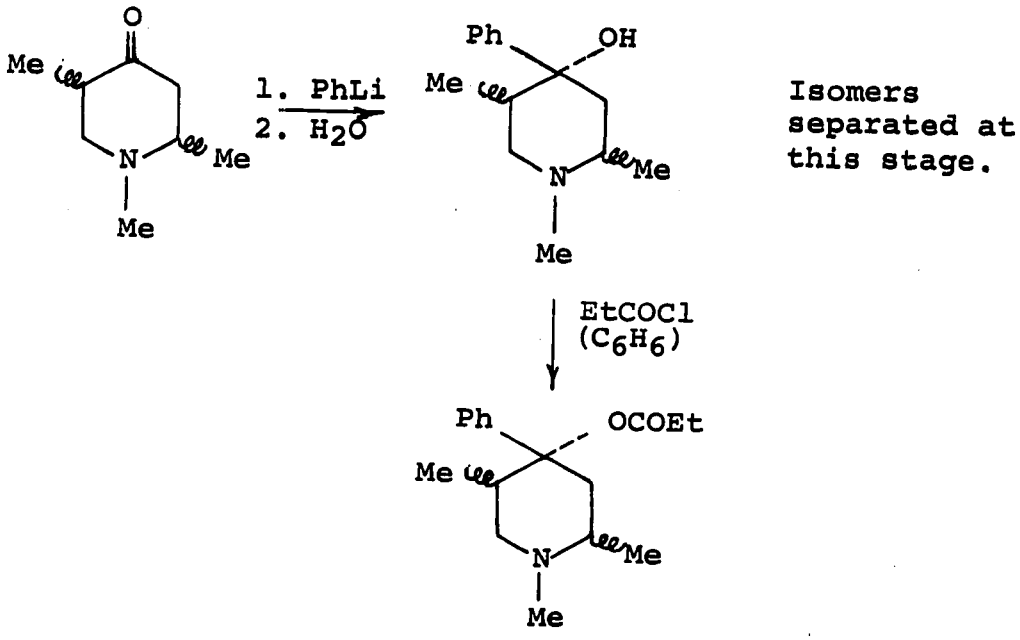
The esters of the promedol alcohols (187), of which the



187

ethyl esters are known as promedol (γ-), isopromedol (β-), alpha promedol (α-) and δ-promedol, were synthesized from the corresponding alcohols and reported in the Russian literature (Nazarov et al., 1956). The normal procedure is to synthesize the

alcohols and then treat the isomers that have been separated with propionyl chloride, or propionic anhydride in pyridine.



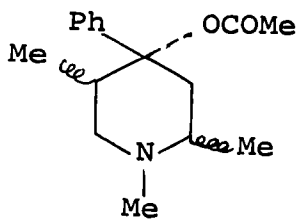
In the synthesis of promedol from γ-promedol alcohol the route used by Nazarov (same ref.) was to react the alcohol with propionyl chloride (in benzene, presumably) or to use propionic anhydride in pyridine. In this work the use of the acyl chloride in benzene gave reasonably good yields of γ-promedol. The β- alcohol was reacted with propionyl chloride in chloroform by the original workers to give 60% yields of isopromedol. Upon repeating this procedure it was found not possible to isolate any of the desired ester. It was found necessary to reflux the alcohol with propionyl chloride in benzene for several hours in order to attain sufficient reaction to allow separation of the β- ester from the unreacted alcohol. Similar reaction with propionic anhydride

in pyridine produced less favorable results and the product was generally more difficult to purify.

The α-ester was more easily prepared in a shorter time using propionyl chloride in refluxing benzene and from which α-promedol was recovered in nearly quantitative yields.

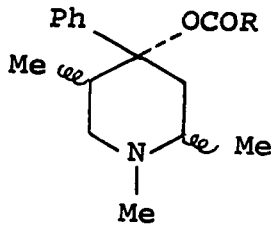
The α-isomer has been found to possess an ambient melting point (p. 120) in both the alcohol and ester series. This was evidently also found to be the case by Prostakov (1962 and refs therein) who noted that α-promedol base and hydrochloride melt at several points but all samples appear to be identical from other evidence. γ-Promedol has also been reported as having two melting points; that is, it melts at 198 - 199°, then solidifies and begins to melt again above 215°. If the product melting at 198 - 199° is purified by several recrystallizations the isomer is found to melt at 221 - 222°. Both products analyze correctly and both hydrolyse to give γ-promedol alcohol (55). This was explained by a change in conformation, although no more detail was provided. In the present investigation, material melting significantly lower (Table XVII) was obtained and recrystallization would not raise the melting point. At no time was the PMR indicative of any conformational change.

In general the methyl esters (188) were more readily



188

TABLE XVII. PHYSICAL CHARACTERISTICS OF ESTERS OF THE ISOMERIC PROMEDOL ALCOHOL HYDROCHLORIDES

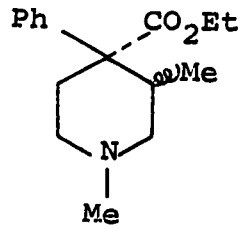


Form	R	M.P. Recorded	M.P. Reported
γ	Et	184-186	198,199, 221-222[a], 222-223[b]
β	Et	180-181	182-183[b]
α	Et	217-218	101-108, 98-102, 102-106, 104-106, 108-112, 132-140, 153-154[a], 227-229b
δ	Et	-	196-197[c]
γ	Me	221-222	222-223
β	Me	181-183	
α	Me	197-198	

Literature cited: (a) Prostakov, 1962; (b) Nazarov, 1956; (c) Shvetsov, 1959.

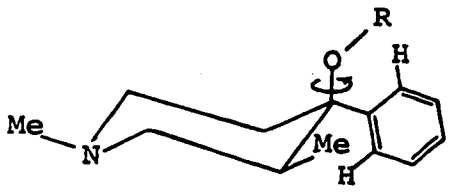
prepared for all three isomers using acetyl chloride in refluxing benzene. The acetate of the γ-isomer was also prepared by Nazarov by a similar procedure but no literature could be found on the β- and α-derivatives.

The PMR signals of the proton groups of the 4-oxygenated functions of reversed esters of pethidine (Casy, 1966, 1968) and other 3-methyl analogues of pethidine (189) (Casy et al., 1969) differ according to whether the α- or β-isomer is

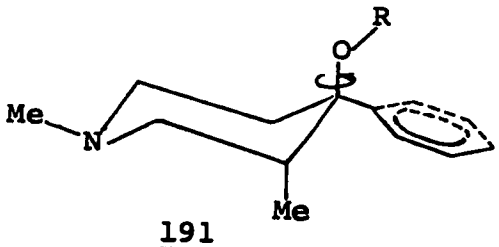


189

examined, signals due to the β- form invariably falling at the higher field position. This difference has been attributed to the differential shielding influence of the 4-phenyl group upon the 4-oxygen function in the two isomeric forms. It has been argued (Casy, 1966) that the preferred orientation of the 4-phenyl group will be in a plane approximately at right angles to that of the piperidine ring when an equatorial 3-methyl group is present, as in (190). In this conformation the 3-methyl/ortho aromatic hydrogen interactions are at a minimum. When the 3-methyl is axial, however, the same orientation is not favoured since it would bring an ortho aromatic hydrogen in close proximity to the axial methyl group, therefore in this case the more nearly



190



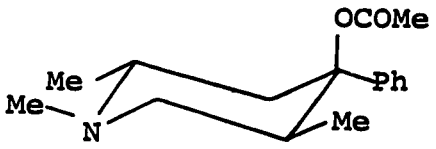
191

co-planar arrangement (191) is felt to be preferred. Support for these arguments of relative phenyl-piperidine ring orientations is provided by X-ray studies of α- and β-prodine (Kartha et al., 1960; Ahmed et al., 1963) although these results have the limitation of referring to the solid state. Turning again to PMR differences between the 4-oxygenated function proton signals of α/β pairs, it may be argued that the higher field values of the β- signals are consistent with the β- derivative having a preferred configuration of the type (191) because the R group will spend some of its time above the plane of the phenyl ring (i.e., will fall within the aromatic shielding zone) if the plane of the 4-C-O bond and aromatic ring are approximately perpendicular.

Differences in the PMR signals of the ester groups of 4-aryl piperidines thus provide additional information about the stereochemistry of the molecules, and the above principles are applied in the following PMR analysis of esters derived from the promedol alcohols.

ACETATES DERIVED FROM THE ISOMERIC PROMEDOL ALCOHOLS

The OCOMe PMR signal of γ-promedol acetate (192) appeared as a singlet for the hydrochloride at δ2.25; and at δ2.17 (base) in $CDCl_3$.

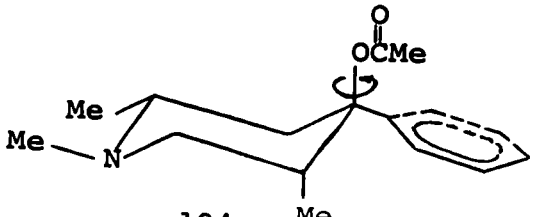


192

193

This was in close agreement with the OCOMe signals of α-prodine acetate (193) at δ2.27 (hydrochloride and base) in $CDCl_3$, and is therefore in accord with configurational assignments already made.

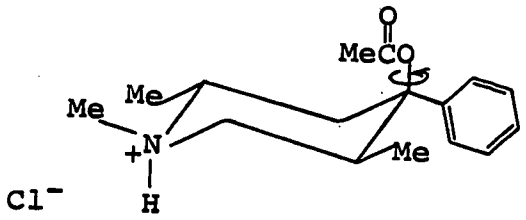
The β-promedol acetate (194) displayed an OCOMe signal in the PMR at δ2.03 for both the base and hydrochloride in $CDCl_3$. The acetate of β-prodinol displayed an OCOMe singlet at δ2.09. The higher field position of the acetate signal indicates that, like β-prodine acetate, the OCOMe spends a considerable portion of its time over the aromatic ring which must therefore be oriented in the same plane as the



194

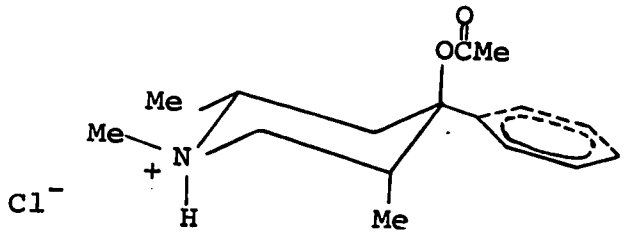
piperidine ring in order to have a shielding influence on the OCOMe group.

PMR evidence of N+H epimers did not appear in the spectrum of γ-promedol acetate hydrochloride (195) as was



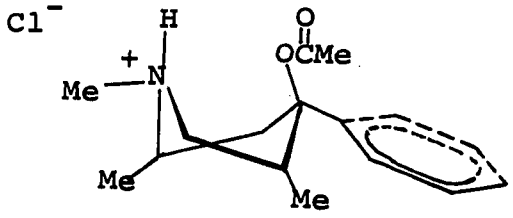
195

expected, since the epimer shown is by far the more stable. However, in the β-promedol acetate spectrum epimeric signals did occur when a drop of trifluoroacetic acid was added to the hydrochloride salt in $CDCl_3$. The 2-methyl group then displayed two doublets at δ1.67 and δ1.45 and the 5-methyl group had doublets at δ0.97 and δ1.04. The N-methyl signal appeared as two singlets at δ7.35 and δ7.39. The OCOMe signal was not duplicated. From relative intensities of the 2- and 5-methyl signals the epimers appear to be equally populated. Using previous arguments based on epimers of β-promedol alcohol, the lower field 5-methyl doublet and higher field 2-methyl doublet were assigned to the axially protonated form (196). This assignment agrees with the



196

axial 3-methyl signal in β-prodine acetate (δ1.01). The other 2- and 5-methyl signals were assigned to the equatorially protonated epimer (197), depicted as a skew boat for reasons previously outlined.

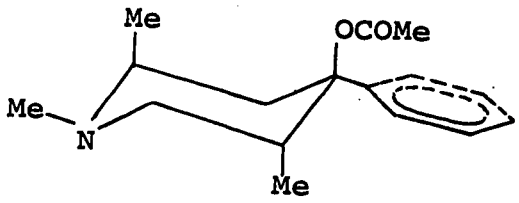


197

The spectrum of β-promedol acetate hydrochloride in D_2O displayed single 2-methyl (δ1.49) and 5-methyl (δ0.80) doublets and evidence of individual epimers only become apparent after the addition of a drop of TFA (cf. spectrum of β-promedol alcohol hydrochloride in D_2O, p. 141). The epimers were not equally populated, however, with the major signals at δ1.51 (2-methyl) and δ0.78 (5-methyl) and the minor at δ1.56 (2-methyl) and δ0.95 (5-methyl). The minor signals were assigned to the chair form (196) and the major to the skew boat (197). Support for these assignments is provided by the similar chemical shifts of the 5-methyl of the major epimer of β-promedol acetate hydrochloride and the 3-methyl in β-prodinol acetate hydrochloride (δ0.67) when the two salts are examined in D_2O, since arguments that β-prodinol ester hydrochlorides adopt skew boat conformations in polar solvents have been advanced in the literature (Casy, 1966).

The α-promedol acetate displays an OCOMe signal at δ1.95

in the base in $CDCl_3$, which is significantly higher than the β- or γ-promedol acetate signals, suggesting that the OCOMe is substantially shielded by the 4-phenyl ring (198).



(or skew boat form)

198

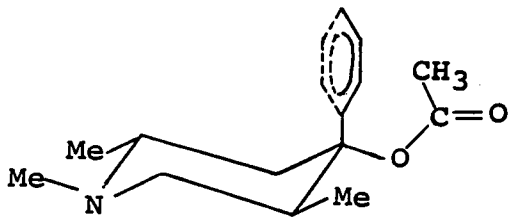
In the hydrochloride, however, the OCOMe signal moved downfield to δ2.23, which is close to the chemical shift of the γ-promedol acetate (δ2.25) signal. This large change, upon protonation, of the acetate signal had not been seen in the other isomers and must indicate a major conformational change. Another unusual feature (providing further evidence in the last respect) is the fact that the 5-methyl signal (δ1.06) in the base is shifted upfield to δ0.75 when the base is protonated. In all other cases the 5-Me shift (base→HCl) is to lower field. This effect is also seen in the α-promedol alcohol itself, shifts being smaller in extent than in the ester (see Table XVIII).

The unusually deshielded condition of the 5-methyl protons of the ester (δ1.06) may be accounted for if the base has a significant population of the axial phenyl conformer (199). In this arrangement the aromatic ring will probably adopt a preferred orientation at right angles (or nearly so) to the mean plane of the piperidine ring so as

TABLE XVIII. 5-METHYL CHEMICAL SHIFT VALUES OF OF α-PROMEDOL ALCOHOL[a]

Solvent	Base[b]	Salt[b]
$CDCl_3$	0.75	0.68 (TFA)[c]
DMSO-d_6	0.65	0.53 (HCl)

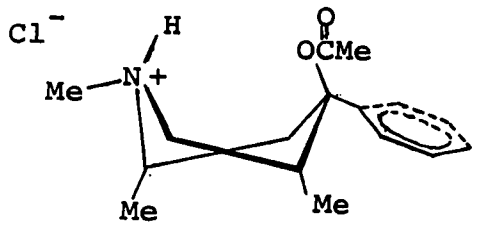
(a) Chemical shifts in δ units from TMS measured at a frequency of 60 MHz. (b) doublet. (c) the hydrochloride was insoluble in $CDCl_3$.



199

to avoid interactions with the 2,6-diaxial protons (Allinger et al., 1962). In this arrangement, the equatorial 5-methyl group is close to the aromatic plane and therefore should be deshielded (Johnson and Bovey, 1958). The same conformation will also lead to shielding of the OCOMe group as it rotates above the plane of the aromatic ring.

The chemical shift data shows that (199) is not favoured after protonation. The preferred form of the hydrochloride on the basis of the chemical shift of OCOMe and its 5-methyl signal (δ0.75) appears to be a skew boat form (200). If the



200

chair form (198) were favoured then the 5-methyl chemical shift should have a much lower field position due to its proximity to the NH function. The conformer (200) might be stabilized by a $\overset{+}{N}H\cdot\cdot OCOMe$ interaction which cannot operate in the base, in fact a repulsion between the lone electron pair and the OCOMe would be within reason.

PROPIONATE ESTERS OF ISOMERIC PROMEDOL ALCOHOLS

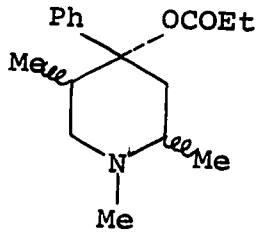
The propionate esters of the individual promedol alcohol isomers were prepared by reaction of the alcohol bases with propionyl chloride in benzene and were isolated as the hydrochloride salts.

The PMR data obtained from the promedols are shown in Table XIX, and will be noted to resemble those of the acetate derivatives, hence similar arguments regarding their stereochemistry will be proposed.

Again the ester signals of γ-promedol hydrochloride signals were found to resemble those of α-prodine hydrochloride (OCH_2Me, δ2.58; OCH_2Me, δ1.22), both observed in $CDCl_3$ (Casy 1968), hence the structural similarity pointed out for the acetates also holds for the propionates and the conformation of γ-promedol base (and hydrochloride) are substantiated as being (201a) and (201b) respectively.

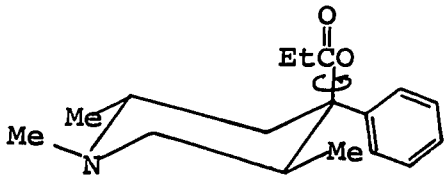
Signals for the β-promedol (isopromedol) isomer are duplicated in the hydrochloride (although the ester signals are not), and the ester signals were found to resemble those of β-prodine hydrochloride in $CDCl_3$ (OCH_2Me, δ2.39; OCH_2 Me,

TABLE XIX. PMR DATA ON ISOMERIC PROMEDOLS IN $CDCl_3$

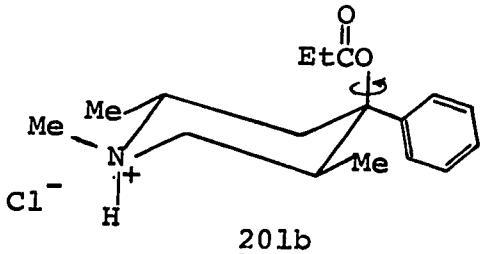


Isomer	Form	PMR Signals[a] N-Me	OCH_2Me[e]	OCH_2Me[f]	2-Me[d]	5-Me[d]
γ	HCl	2.85[d]	2.58	1.23	1.57	0.73
γ	Base	2.32	2.47	1.22	1.07	0.67
β	HCl	b	2.34	1.08	1.65, 1.55[g]	0.97[g,c]
β	Base	c	2.34	1.08	1.32	0.87
α	HCl	c	c	1.25	1.42	0.77
α	Base	c	c	1.06	1.13	1.05

(a) Chemical shifts in δ units from TMS measured at a frequency of 60 MHz. (b) Epimer formation made definite assignment impossible. (c) Could not be assigned due to signal overlap with other signals. (d) Centre of doublet. (e) Centre of quartet. (f) Centre of triplet. (g) Epimer formation.

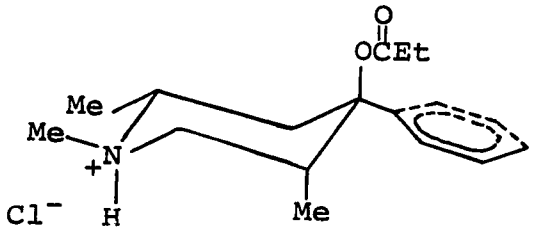


201a

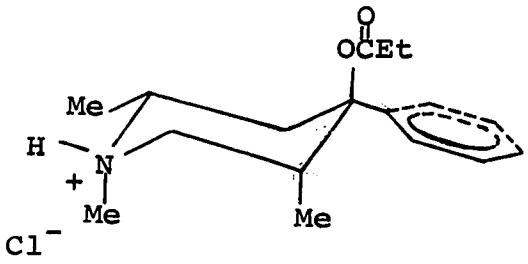


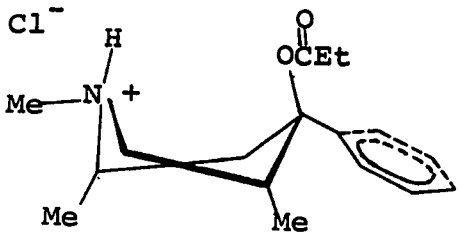
201b

δ1.08). These data are consistent then with β-promedol hydrochloride having the structures (202) and (203).



202

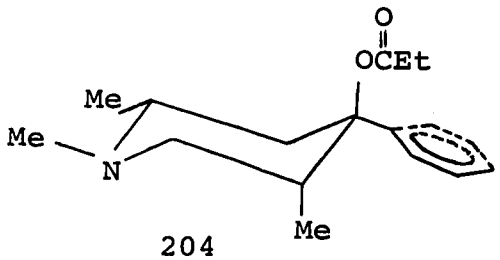




203

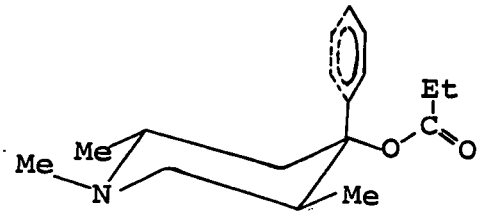
In the base, in $CDCl_3$, the propionate signals were displayed at δ2.34 (OCH_2Me) and δ1.08 (OCH_2Me) as compared to δ2.32 and δ1.08 for the same signals for the β-prodine base. The 5-methyl signal of the β-promedol base (δ0.87) was close to the 3-methyl signal (δ0.82) of the β-prodine base, both in $CDCl_3$. The chair form (204) is thus substantiated as being the anticipated structure.

α-Promedol hydrochloride displayed its 5-methyl signal at higher field than that of the base, thus indicating a

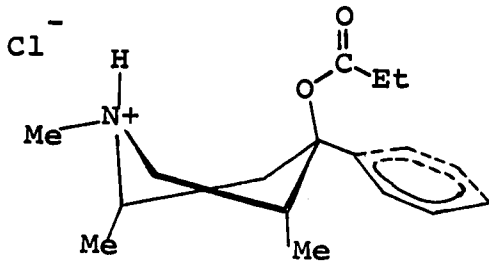


204

conformational change after removal of the N-proton as was the case of α-promedol alcohol and its acetyloxy ester. The deshielded position of the 5-methyl signal again indicates that the 4-phenyl group may be oriented axially in the base. Thus the α-promedol base and hydrochloride are assigned the preferred conformations (205) and (206), which are identical to those arrived at in the acetate derivatives.



205



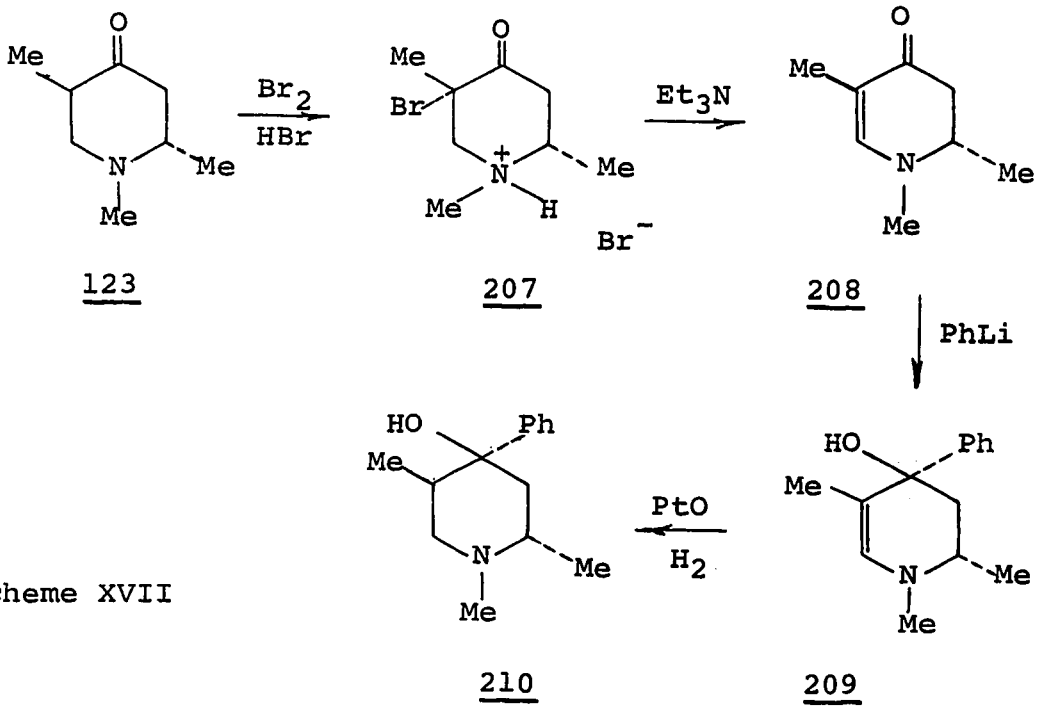
206

X-RAY CRYSTALLOGRAPHY

Data concerning the stereochemistry of the promedol alcohols in the solid state by x-ray crystallography was not yet available at the time of writing this manuscript. However, personal communication with Dr. W.H. DeCamp (National Research Council, Ottawa), who is investigating this problem from material supplied from this laboratory, indicates that the answer will be shortly available.

STEREOSPECIFIC SYNTHESIS OF ALPHA PROMEDOL ALCOHOL

In the synthesis of isomeric promedol alcohols it is possible to isolate only small quantities of the α-isomer. Nazarov and Shvetsov (1959) prepared the α-alcohol by a synthesis outlined in scheme XVII, which they claimed to be stereospecific.



123 207 208

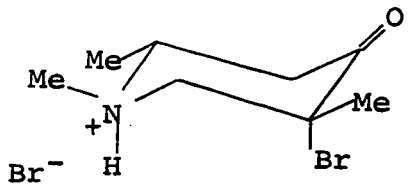
210 209

Scheme XVII

Unfortunately, stereochemical proof of the intermediate structures (207) to (210) was not given, apart from the elemental analysis in one case and U.V. and physical data for the others. With a view to investigating the method and establishing the structure and stereochemistry of the intermediates (and final product), this work was repeated.

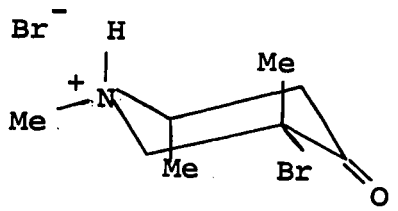
STEP 1. BROMINATION OF THE KETONE:

1,2,5-Trimethyl-4-piperidone (123) was brominated using bromine and 48% hydrobromic acid to yield a crystalline hydrobromide salt (211) which had a melting point of 145 - 145.5° (reported by Nazarov, 143 - 144°). The PMR spectrum in D_2O displayed a prominent 2-methyl doublet at δ1.43 and a 5-methyl singlet at δ1.82, as well as an N-methyl singlet at δ2.95. The fact that the 5-methyl signal is a singlet supports the proposal that the bromine has entered the 5-position only. The next questions therefore was one of configuration of the 5-bromo product (211/212) or (213/214).

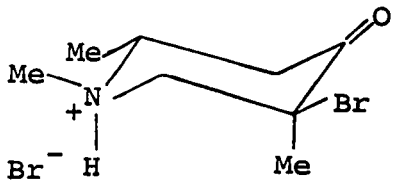


211

trans 2,5-dimethyl

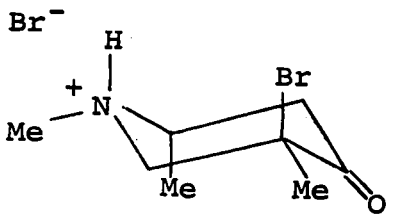


212



213

cis 2,5-dimethyl



214

The starting ketone (1,2,5-trimethyl-4-piperidone) has been shown to consist of a cis and trans mixture (see p. 121) but with the trans isomer as the major component.

Infrared evidence was employed to indicate the configuration around C4 - C5. The carbonyl stretching frequency of the non-brominated ketone hydrobromide was found to be little changed after bromination (see below).

INFRARED SPECTRAL DATA FOR HYDROBROMIDE SALTS

	IR Absorption	
	Nujol	$CHCl_3$ (2%)
Non-brominated ketone (HBr)	1730 cm^{-1}	1735 cm^{-1}
Brominated ketone (HBr)	1735 cm^{-1}	1740 cm^{-1}

The spectral data indicate that the 5-bromo substituent is axial, for if the bromine was equatorial it would be near the oxygen function of the C=O group and the former's negative field will repel the non-bonding electrons of the oxygen atom, thereby causing the carbonyl group to absorb energy at a higher frequency. This principle is well established in the literature (Silverstein and Bassler, 1968). The shift is normally in the order of 45 cm^{-1}, while the above results show a shift of only 5 cm^{-1} which may be attributed to the effect of an axial, but not an equatorial bromine. Hence the configurations (212) or (213) cannot be present; rather, the arrangement consisting of an axial bromine must be the case. This leaves structures (211) and (214) as more likely from the IR evidence, and of these the latter is less probable since it has two axial groups.

The 3-methylene PMR signals in D_2O may be fairly confidently assigned because they form an isolated multiplet between δ2.1 and δ3.0 (see Figure XVI).

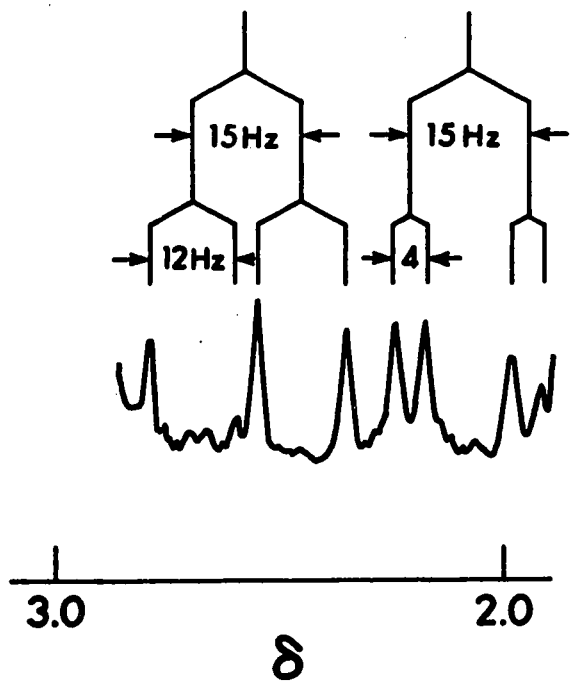


Figure XV. Part of the PMR spectrum of 1,2,5-trimethyl-5-bromo-4-piperidone hydrobromide recorded at 60 MHz in D_2O. (Sweep width 500 Hz)

This yields the values J gem (15 Hz) and J vic (12 and 4 Hz), which verify the equatorial orientation of the 2-methyl group, since large (12 Hz) and small (4 Hz) coupling value would be expected for a Jaa and Jae arrangement of the 3-methylene proton; hence the probable configuration of the bromoketone is (211).

We were not entirely satisfied with this conclusion, however, because the PMR spectrum of the bromoketone salt—although displaying prominent signals consistent with the above arguments—possessed numerous minor lines that did not diminish in the spectra of recrystallized material. These minor signals became better resolved in the 100 MHz spectra in D_2O. In the C-methyl resonance region a major and a minor methyl singlet and four methyl doublets (one major) could be identified (see Figure XVI).

In addition, at least two N-methyl signals were present, a major singlet at δ3.52 and a minor one at δ3.62. These anomalous signals could be due to a stereoisomeric form of the bromoketone, which co-crystallizes with the major form. Alternatively the signals could be the result of the ketone existing in D_2O as a mixture of free (C=O) and hydrated (strictly DO$\times$OD) species. The last probability must be seriously considered because it is known that the 4-piperidone salts of the type (215) exist in D_2O as a mixture of the free ketone and and 4-4-diol species (216) in approximately equal proportions (Hassan and Casy, 1969 and 1970), as detected by duplication of the methyl signal adjacent to the C-4 centre

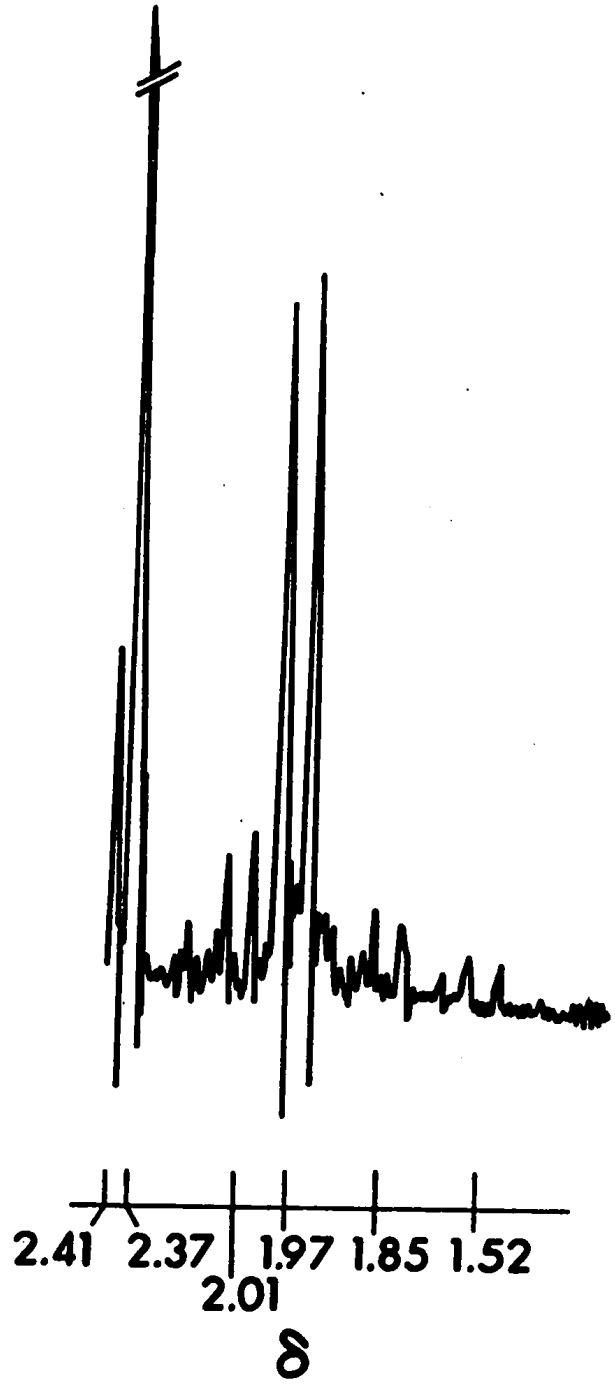
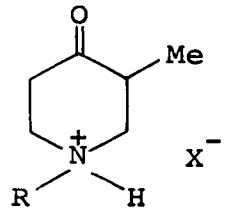
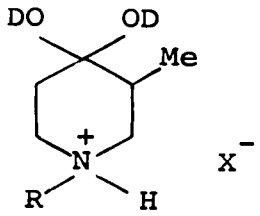


Figure XVI. Part of the PMR spectrum of 1,2,5-trimethyl-5-bromo-4-piperidone recorded at 100 MHz in D_2O (Sweep width 1000 Hz).



215



216

and of the N-R signal. In addition α- ring protons were moved upfield compared with those of the free ketone and appeared near δ2.2.

In the course of this work it was found that 1,2,5-trimethyl-4-piperidones formed the same sort of equilibrium mixture when the salts of the free ketone were examined in D_2O. Details of the spectrum of <u>trans</u> 1,2,5-trimethyl-4-piperidone in D_2O are given below; unfortunately the <u>cis</u> isomer could not be isolated in a pure state (Table XX).

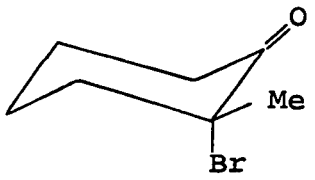
Returning now to the spectrum of the bromoketone hydrobromide in D_2O, this displays a major 2-methyl doublet at δ1.43 and a minor 2-methyl doublet at δ1.50. The major signal was thought to correspond to the 2-methyl of the dideuteroxy form (δ1.38), while the minor signal was felt to be related to the free ketone form (δ1.47), of the parent ketone. Admittedly these are not identical but they are of the correct order, the free species being generally lower field. To compare the two 5-methyl signals of the parent and the bromoketone spectra, however, it is first necessary to compensate for the deshielding influence of the geminal bromine atom. This can be done from the following data of

TABLE XX. PMR CHARACTERISTICS OF TRANS 1,2,5-TRIMETHYL-4-PIPERIDONE SALTS IN D_2O

Salt	Ratio, Free/ Di-deuteroxy	Signal	Chemical Shifts[a] Free ketone	Di-deuteroxy
HCl	50/50	2-Me[b]	1.47	1.38
		5-Me[b]	1.07	0.98
		N-Me[c]	3.02	2.88
		α-ring protons	within 2.7 - 4.0 band	2.1
HBr	50/50	2-Me[b]	1.47	1.38
		5-Me[b]	1.07	0.98
		N-Me[c]	3.02	2.88
		α-ring protons	within 2.7 - 4.0 band	2.1

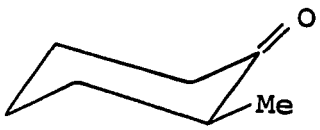
(a) Chemical shifts in δ units from internal DSS, measured at a frequency of 60 MHz.
(b) Centre of doublet. (c) Singlet.

Garbisch (1965), who found that when an axial bromine was introduced into a cyclohexanone ring (217) the methyl group came to resonance at 0.82 ppm further downfield than the unsubstituted ketone (218).



δ Me 1.80

217

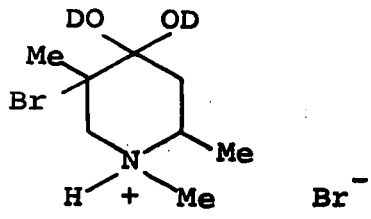


δ 0.98

218

The chemical shift of the 5-methyl group in the bromo-4-piperidone (211) corrected for the geminal shielding of the bromine (and assuming that geminal shielding obtained in CCl_4 is valid in D_2O) is δ1.83 - 0.82 = 1.01. This value is close to the 5-methyl dideuteroxy form value of δ0.98 and somewhat different from the 5-methyl chemical shift of the free ketone in the spectrum of the parent 4-piperidone at δ1.07.

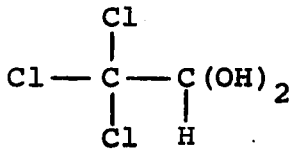
On these grounds the minor signals are attributed to the N-methyl and 5-methyl groups of the free ketone and the major ones to the 4,4-dideuteroxy form (219).



219

The values obtained are not exactly the same as the non-brominated form of the free and dideuteroxy ketones but are of the correct order.

The spectrum of the hydrobromide salt in DMSO-d_6, to which only the free ketone may contribute, showed a singlet for the N-methyl and 5-methyl resonance lines, also signals attributed to the 3-methylene (α-) protons in the spectrum in D_2O were absent in the DMSO-d_6 spectrum. In the spectrum of 1,2,5-trimethyl-4-piperidone salts in D_2O the relative intensities of signals due to free and dideuterated forms are approximately equal; in the spectrum of the bromo-analogue, however, the 4-4-dideuteroxy signals are distinctly more intense than all others. These results indicate that the carbonyl group of the bromoketone is more extensively deuterated (hydrated) than the carbonyl of the original 4-piperidone. This is not unexpected in view of the known power of the α-halogen substituent in activating the C=O group towards nucleophiles (Noller, 1965). A good example of this is the stability of the hydrate of chloral (220).

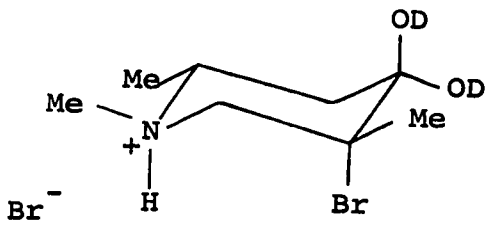


220

The preceding arguments only account for two sets of signals in the spectrum of the bromoketone (it will be recalled that four methyl doublets were present in the 100 MHz spectra,

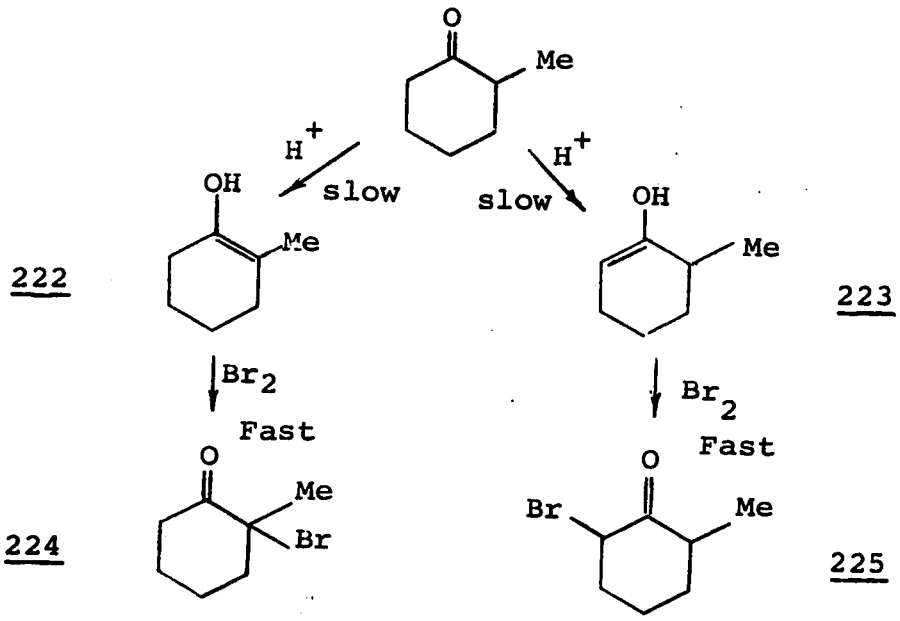
Figure XVI), and it is probable that additional spectral complexities are due to the existence of epimeric conjugate acid forms of the 4,4-dideuteroxy and free ketone species. To test this the bromoketone (HBr) was examined in D_2O at high temperature, with the result that the high field minor doublets remained; however, noticeably affected were the signals due to the α- protons of the dideuteroxy form, and as well, the N-methyl signals. This was thought to indicate that epimers were not the cause of the "extra" C-methyl signals (they may be due to the cis bromoketone which crystallizes with the trans form) and that the dideuteroxy form is not favoured at high temperature, instead the free bromoketone (211) is most probably the sole species present.

In summary, we have established that the product of brominating 1,2,5-trimethyl-4-piperidone is the 5-bromo derivative and no significant amount of the 3-bromo ketone could be detected by PMR analysis. The configuration and preferred conformation of the 1,2,5-trimethyl-5-bromo-4-piperidone hydrobromide is (211), but in D_2O the salt exists largely as the 1,2,5-trimethyl-5-bromo-4,4-dideuteroxypiperidine hydrobromide (221).



221

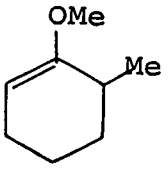
The rationale for the bromine entering the 5- position of 1,2,5-trimethyl-4-piperidone follows from an investigation of Garbisch (1965) who proposed that the important feature governing the direction of bromine attack upon substituted cyclohexanones is the relative stabilities of the intermediate enols (Scheme XVIII).



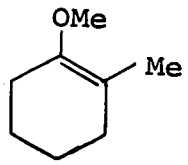
Scheme XVIII

Compound (222) has a more highly substituted double bond, hence it is more stable and will be formed more rapidly. Therefore in aqueous hydrobromic acid more of (222) is formed than (223). In methanol, Garbisch (same ref.) found that the intermediate methyl ethers (226) and (227) may tend to stabilize the alkene forms, and a significant formation of (226) was found

to occur prior to bromination; therefore the 2- and 6-bromo products will likely result.



226



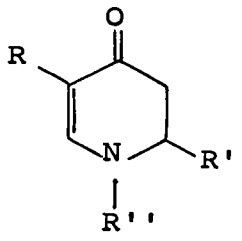
227

The bromination of 1,2,5-trimethyl-4-piperidone was repeated using methanol as a solvent with the idea that at least some of the 3-bromo derivative may be produced due to the aforementioned enol ethers stabilizing the intermediates formed. In two separate trials the total product displayed a complex PMR with evidence of a major 5-bromo product plus unreacted starting ketone, and as well, due to signal complexity, what was tentatively identified as 1,2,5-trimethyl-3-bromo-4-piperidone. Unfortunately, the latter compound could never be isolated in a pure state, hence the assignment is a possibility only, and remains to be proven.

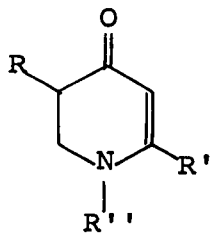
STEP 2. DEHYDROBROMINATION OF 1,2,5-TRIMETHYL-5-BROMO-4-PIPERIDONE:

The second step in the stereospecific synthesis involved the dehydrobromination of the 5-bromo ketone (211), previously prepared, to give an alkene (228). This was supported in the original literature only by ultra-violet evidence, a boiling point for the base, and a melting point for a picrate derivative, but no analysis.

The original workers (Nazarov and Shvetsov, 1959) used triethylamine to effect the dehydrobromination by refluxing the mixture for 90 minutes and then filtering off the triethylamine hydrobromide formed, and recovering the alkene product (208) as an ether soluble base. When this step was repeated, difficulty was encountered in dissolving the bromoketone (211) in the quantity of base used by the original workers. Therefore a large excess of the triethylamine as well as prolonged reflux was required to effect solution and subsequent dehydrobromination. The resulting product was distilled (b.p. 100 - 104°/1 mm., reported 100 - 101°/1 mm.); its elemental analysis indicated that the desired alkene had indeed been isolated. The UV spectrum of the product, however, differed somewhat from the literature (λmax 336 mμ., log ε 4.052; reported λmax 308 mμ., log ε 3.444). Compounds of the type (228) and (229) are known in the literature; however, the basic difference in absorption between an α or β substituent

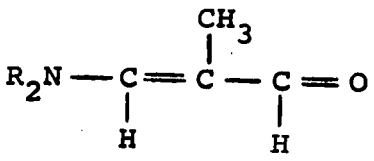


228



229

is generally thought to be 2 mμ. Scott (1964) gives the basic absorption of compounds of the type (230), which is certainly part of the cyclic structure shown in (228) or (229), as being in the neighborhood of 320 mμ. This figure is larger



230

than that obtained by the Russian workers and less than the present result. It is not feasible that a cyclic system of the type (228) would alter the U.V. absorption of the basic chromophore.

Another point that could account, at least partially, for the difference is the fact that the Russian authors did not quote a solvent system for the ultra violet spectrum. Since ethanol is known not to affect the basic absorption of unsaturated ketones it was the solvent employed in this spectral analysis; however, solvents like hexane are known to reduce the absorption wavelength of ketones of this type significantly and it would be therefore reasonable to assume that this type of solvent could have been used by the original workers.

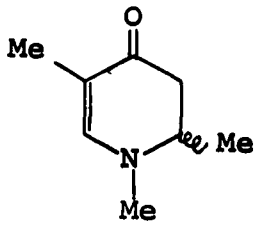
The IR spectrum showed a carbonyl absorption at 1710 cm^{-1} and a broad band at 1600 cm^{-1}, characteristic of α,β-unsaturated ketones.

PMR spectral analysis was carried out and this gave the following chemical shifts, determined in CCl_4:

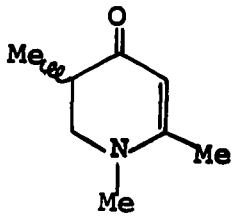
5-methyl singlet	δ1.66
2-methyl doublet	δ1.21
6-proton singlet	δ6.77

3-methylene quartets δ2.18, 2.66 (J vic 6, 7.5 Hz; J gem 16 Hz)

The two alkenes possible are (207) and (231); the form (231)



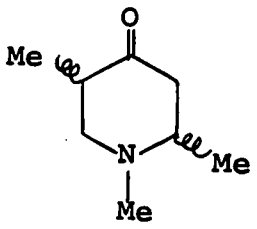
207



231

can be produced by isomerization from (207) (the latter being most likely because of the bromoketone structure), can be differentiated by the preceding spectral data.

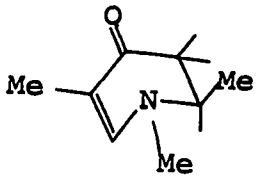
If structure (207) is correct then the 2-methyl doublet (δ1.21) would be expected to be similar to that of the normal ketone (123); and in fact this was found to be the case, for



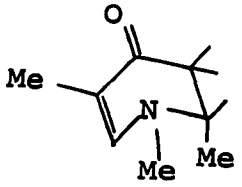
123

the 2-methyl doublet of the latter ketone comes to resonance at δ1.22. On the other hand, if structure (231) was correct then its 5-methyl doublet (δ1.21) should agree with the 5-methyl doublet (δ0.92) of the normal ketone (122). Obviously, this is not the case and structure (231) is therefore ruled out as a possibility.

The preferred conformation of the α,β-unsaturated ketone is best represented by the half chair (232) with a pseudo equatorial 2-methyl group, than the form (233), with a pseudo axial 2-methyl substituent. The unusually large value of

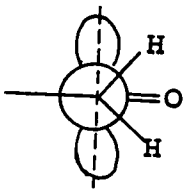


232



233

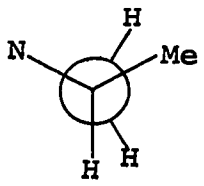
J gem of the 3-methylene signal has already been noted and it gives a clue to the relative orientation of the O=C-CH_2- feature. In this, the two 3-methylene protons must lie on the same side of the p-orbital of the carbonyl function as in (234) since this arrangement leads to a numerical enhance-



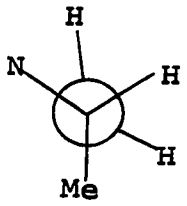
234

ment of the geminal value (Barfield and Grant, 1963; Cookson et al., 1966) and is consistent with the J gem value (16 Hz) observed for the 3-methylene protons. (This result is further proof for the CH_2 being adjacent to the C=O group.) In models made incorporating the arrangement (234), dihedral angles respecting the 3-CH_2 and 2-CH protons of approximately 150° and 30° are seen for (232) as are shown in the Newman

projection (235). Two values close to 60° for (233) are shown in the Newman projection (236). The latter values



235



236

would lead to small J vic values on the basis of the Karplus relationship, whereas the former would give values near 6 - 7 Hz. Only structure (232) is consistent, therefore, with the J vic values observed (6 and 7.5 Hz).

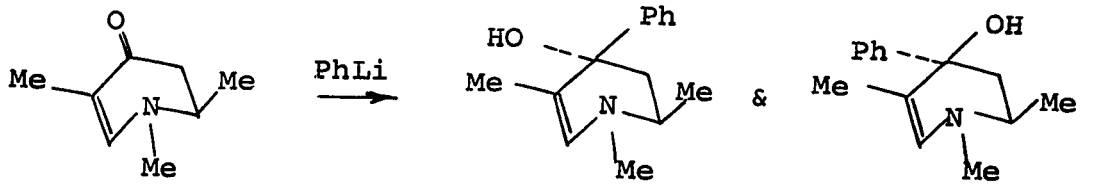
STEP 3. TREATMENT OF 2,3-DIHYDRO-1,2,5-TRIMETHYL-4-PYRIDONE WITH PHENYLLITHIUM:

When the α,β-unsaturated ketone whose structure has been confirmed as being (232) was treated with phenyllithium by the original workers there was isolated 1,2,5-trimethyl-1,2,3,4-tetrahydro-4-phenyl-4-pyridinol (209). A melting point as well as microanalysis was the only proof of structure offered; no infrared evidence was noted and as well no stereochemical analysis was given.

When this work was repeated, it was not possible to isolate a solid free base as reported, nor could we obtain a crystalline hydrochloride salt. The IR spectrum of the crude free base (film) did show a broad OH band at 3360 cm^{-1} and as well two bands at 745 and 690 cm^{-1}, indicative of both an alcohol function and a monosubstituted benzene ring. The

spectrum showed no significant absorption at 1710 cm^{-1} characteristic of the ketone starting material.

The α,β-unsaturated ketone (232) should form two possible isomers depending on the direction of Ph attack (237) and (238).



cis 2-Me/4-Ph trans 2-Me/4-Ph

232 237 238

The PMR spectrum of the total product (base) in CCl_4 showed 2-methyl doublets at δ1.13 (major) and δ1.11 (minor); and 5-methyl singlets at δ1.55 (major) and δ1.45 (minor). The phenyl group showed a broad complex multiplet between δ7.0 and 7.5. The 2-methine proton displayed a broad multiplet centered at δ7.38, and the C6-vinylic proton singlet appeared at δ6.64. Basically the spectrum was identical to the starting ketone with one exception (other than the absorption due to the phenyl ring and slight shifts in signal position); the singlet observed for the 5-methyl, and doublet for the 2-methyl groups, were now duplicated, with the ratio approximately 2:9, as determined by relative intensities. The isomeric nature of this product will be discussed later.

STEP 4. HYDROGENATION OF 1,2,5-TRIMETHYL-4-PHENYL-1,2,3,4-TETRAHYDROPYRIDIN-4-OL

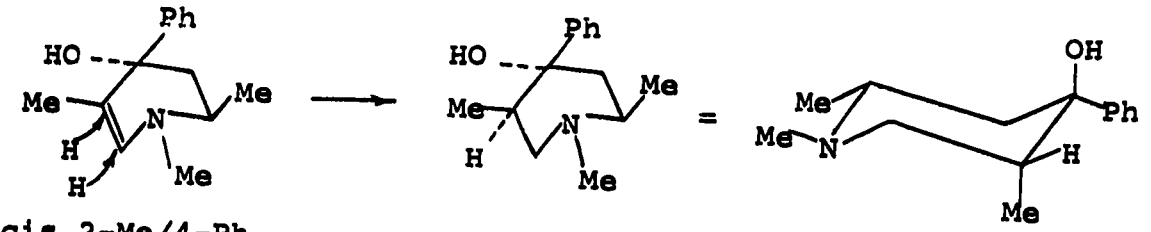
The original workers reduced the alkene double bond with platinum oxide under hydrogen to give α-promedol alcohol as the base (evidence offered were m.p. and mixed m.p. with an authentic sample) and an additional crop of crystals from the mother liquors remaining (isolated as the hydrochloride) which was also said to be the α-isomer but whose melting point (233 - 235°) agreed with β-promedol alcohol hydrochloride (m.p. 233 - 235°).

When the hydrogenation was repeated, no reduction was found to occur using Adam's catalyst under hydrogen (IR showed identical spectrum to the starting material). Therefore the platinum catalyst was removed and palladium charcoal (10%) substituted in its place. After stirring under hydrogen for a week the product was examined by PMR. The spectrum still displayed the C-6- vinylic proton at δ6.64, while the C-methyl region (δ0 - 2)was extremely complex and it was impossible to assign even a single signal. Evidently considerable isomerization and/or decomposition had occurred during the lengthy reduction, and a pure crystalline product could not be isolated.

In view of the fact that the structure and probably conformation of the intermediate α,β-unsaturated ketone (232) has been established, in this repetition of the Russian work, a prediction of the stereochemistry of the reaction products derived from the ketone may be justified in order to see if these arguments corroborate the stereochemistry already assigned.

Returning to the unsatured t-alcohols (237) and (238), the trans form (238) is likely to preponderate because it is formed by addition of Ph to the less hindered side of the ketone (232) molecule, and also interaction between 4-phenyl and 2-methyl are negligible whereas they are significant in the cis form (237) especially in the inverted form. Therefore the major 2-methyl doublets (δ1.13) and 5-methyl singlet (δ1.55) are tentatively assigned to the structure (238).

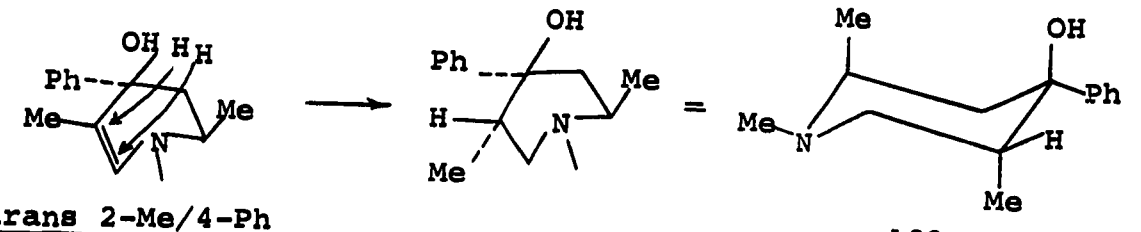
Subsequent hydrogenation of the mixture of unsaturated t-alcohols can give rise to four possible products. However, if it is assumed that hydrogen addition occurs in the cis manner and from the less hindered side of the molecule (that is, the side away from the 4-phenyl ring), only two products may be considered (Scheme XIX).



cis 2-Me/4-Ph

237

173



trans 2-Me/4-Ph

238

183

Scheme XIX

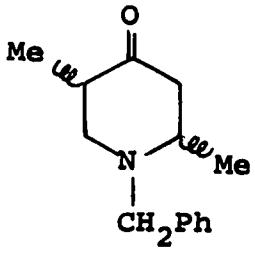
Thus the product of reduction of the minor cis 2-Me/4-Ph isomer will be the cis 2-Me/4-Ph promedol alcohol, which has been shown previously to be the β-isomer (173). Similarly, the major isomer (238) will yield the trans 2-Me/4-Ph alcohol which has been assigned the α-promedol alcohol (183).

These results are in keeping with the Russian workers, Nazarov and Shvetsov, who found that the α-promedol alcohol was the major isomer isolated while the only other form isolated corresponded, presumably, to the β-promedol alcohol isomer.

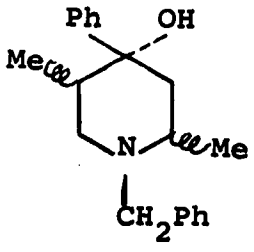
The synthesis was not repeated at this point since the α-promedol alcohol became available by fractional cyrstallization of a normal synthesis of the isomeric promedol.

N-BENZYL-2,5-DIMETHYL-4-PHENYL-4-PIPERIDINOL

The N-benzyl-2,5-dimethyl-4-piperidone (126) previously prepared by the exchange reaction (see p. 92) was subjected to phenyllithium reaction with the hope of separating the resulting isomeric alcohols (239). It was mentioned earlier that the configuration of the 2-methyl group can be determined

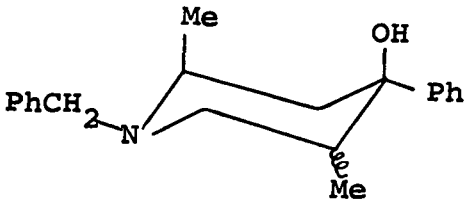


126

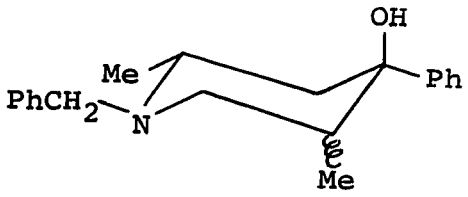


239

by observing the nature of the benzylic methylene proton signal. A singlet has been observed when the 2-methyl group is axial as in (240) and an AB quartet displayed when the 2-methyl group is equatorial (241). The PMR spectrum of the

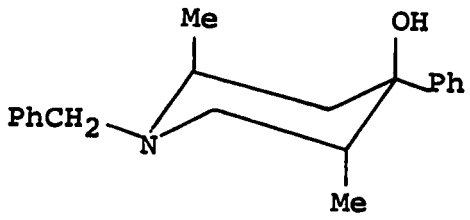


240



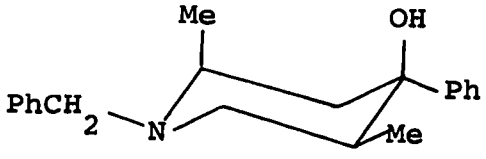
241

total crude base showed that both configurations of (240) and (241) existed in the alcohol product. It was therefore hoped that separation of this isomer would produce one form with the 2-methyl group axial. This could only be the α-form (242), drawn in the chair conformation with the 4-phenyl



242

equatorial, or the δ- form (243), again shown in the chair

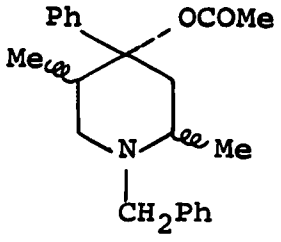


243

form with the 4-phenyl equatorial. If the quartet of form (242) remained in a significant amount it would allow some estimation of the stability of the two diaxial 2,5-methyl groups.

By subsequent debenzylation and then N-methylation of the above alcohol we expected to confirm the stereochemistry of the α-promedol alcohol.

Unfortunately, separation of these isomers could not be accomplished by any of several methods tried, that is, column chromatography, fractional crystallization of the bases or hydrochlorides, or conversion of the total mixture to an acetyloxy derivative (244), and then fractional crystallization of the salt. Therefore this synthetic route had to be abandoned.

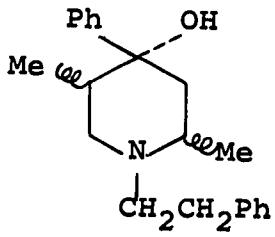


244

N-PHENETHYL-2,5-DIMETHYL-4-PHENYL-4-PIPERIDINOL AND DERIVATIVES

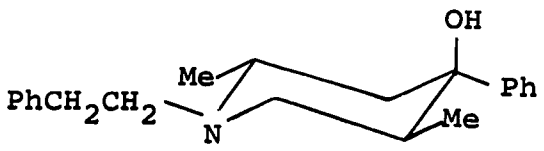
The N-phenethyl-2,5-dimethyl-4-piperidone (129) produced previously by the exchange reaction (see p. 93) was treated with phenyllithium and a portion (1/3) poured onto ice and acetic acid. The solid which separated was suspended in water and basified and then extracted with chloroform to yield

N-phenethyl-2,5-dimethyl-4-phenyl-4-piperidinol (245).



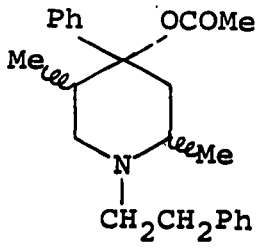
245

This product was examined as the total crude hydrochloride salt whose PMR spectrum displayed only two doublets for the 2- and 5-methyl groups at δ1.48 and δ0.67 while the free base also showed only two doublets at δ1.02 and δ0.64. These values are very close to the γ-promedol alcohol 2- and 5-methyl doublets at δ1.45 and δ0.65 (HCl) and δ1.09 and δ0.62 (base). Since the trans 2,5-dimethyl has been shown to be the major isomer, and the similarity of chemical shift values of the two analogues is nearly identical, the N-phenethyl analogue most likely has a trans 2,5-dimethyl, cis 5-Me/4-Ph configuration and a preferred conformation as shown in (246). This was of course expected in light of the lone trans 2,5-dimethyl-N-phenethyl-4-piperidone isomer obtained from the exchange reaction previously.



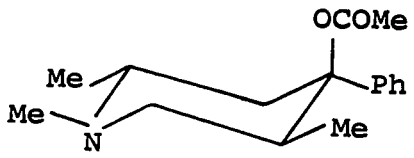
246

To half of the reaction mixture remaining was added acetic anhydride, which subsequently yielded N-phenethyl-2,5-dimethyl-4-phenyl-4-acetyloxypiperidine (247).



247

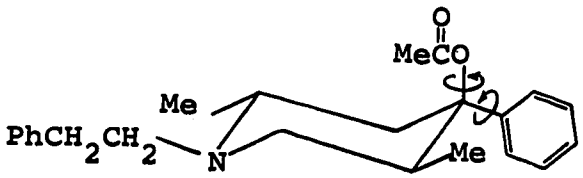
PMR analysis of the total crude product (as the hydrochloride) showed only two doublets for the 2- and 5-methyl groups at δ1.58 and δ0.74 respectively. The signals for the base appeared at δ1.16 for the 2-methyl group and δ0.68 for the 5-methyl group. The OCOMe signal appeared at δ2.29 (HCl) and δ2.18 (base). All values were obtained in $CDCl_3$. These signal positions are quite similar to those of the γ-1,2,5-trimethyl-4-phenyl-4-acetyloxy piperidine, of known stereochemistry (248), whose 2-methyl group appears at δ1.57



248

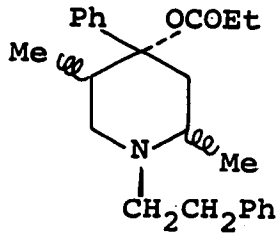
(HCl) and δ1.13 (base) and 5-methyl group at δ0.72 (HCl) and δ0.67 (base). The γ-OCOMe signal is shown at δ2.27 (HCl) and δ2.18 (base). The similarity of all these signal positions

would indicate that the N-phenethyl analogue must have a similar stereochemistry. As was shown previously, the low field signal position of the OCOMe group tends to indicate that it is not preferentially over the shielding zone of the aromatic ring, which, from the simplicity of the aromatic signal at δ3.30, indicates that the phenyl ring also lacks a definite conformational preference. The configuration and possible preferred conformation are therefore shown in (248).



248

To the remaining lithium complex propionic anhydride was slowly added to yield N-phenethyl-2,5-dimethyl-4-propionyloxypiperidine (249).



249

PMR analysis of the total hydrochloride again showed that only one isomer existed. The 2-methyl group signals appeared at δ1.59 (HCl) and δ1.17 (base), while the 5-methyl group doublets came to resonance at δ0.77 (HCl) and δ0.71

(base). The $OCOCH_2Me$ signal quartet appeared at δ2.57 (HCl) while the signal of the base could not be discerned from the piperidine ring protons. The triplet due to the $OCOCH_2Me$ protons appeared at δ1.22 in both the base and hydrochloride.

These signals are similar to both the acetyloxy ester (244) and to those of the γ-promedol (200), therefore the same arguments applied earlier also will be valid in the present situation. The N-phenethyl-2,5-dimethyl-4-propionyloxypiperidine is therefore most probably the trans 2,5-dimethyl, trans 5-methyl/4-phenyl isomer which is again shown in the chair conformation with the phenyl group equatorial (250).

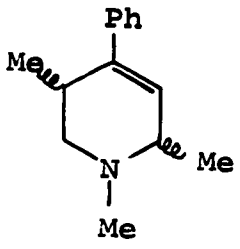
250

The other trans isomer could not be isolated from the mother liquors remaining; in fact, no evidence was obtained that pointed to its even being formed in the reaction.

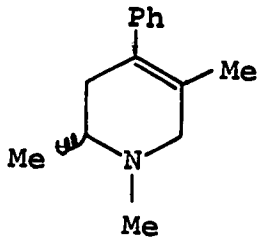
CHEMICAL EVIDENCE CONCERNING THE STEREOCHEMISTRY OF THE PROMEDOL DERIVATIVES

Chemical data, that has been employed in the prodine alcohols as evidence for stereochemistry, was also used in the case of the promedol alcohols in the hope that principles found earlier would confirm the proposed conformational relationships that exist between the prodine and promedol alcohols.

The differing behaviour of α- and β-prodine alcohols toward thionyl chloride has already been described (see p. 111) In the reaction with thionyl chloride, under reflux, the γ-promedol alcohol was found to undergo dehydration yielding a mixture of the trisubstituted (251) and tetrasubstituted (252) alkenes (isolated as the HCl salts) in almost equal



251



252

proportions as seen by the PMR spectrum. The IR spectrum showed dehydration was essentially complete. The PMR of the total free base in $CDCl_3$ showed the tetrasubstituted (252) 3-methyl group as a broad singlet at δ1.55, while the 5-methyl doublet at δ1.07 of the trisubstituted alkene (251) overlaps with the 6-methyl doublet of the tetrasubstituted isomer (these derivatives being named as isomers of the parent

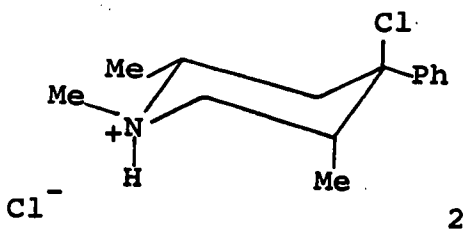
1,2,5,6-tetrahydropyridine). The vinylic proton of (251) appears as a poorly resolved triplet at δ5.53.

Reaction with thionyl chloride at room temperature produced only a small amount of alkene mixture while the main product proved to be unreacted γ-alcohol.

Elimination of water induced by HCl/HOAc under the same conditions as employed in the case of the prodine alcohols produced the same result with γ-promedol alcohol as refluxing with thionyl chloride; that is, complete dehydration yielding the same mixture of alkenes. These experiments seem to confirm that the 5-methyl group has the same conformation as the 3-methyl group of α-prodinol (in both cases two trans diaxial pathways for dehydration exist).

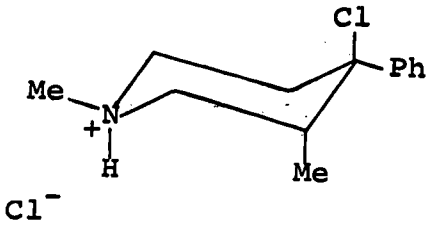
When β-promedol alcohol was treated with thionyl chloride under mild refluxing conditions it also dehydrated (IR evidence showed no OH remaining), but in this case only the trisubstituted alkene (251) was formed, as shown by the complete absence of any vinylic methyl signal.

This product was not in keeping with the results obtained from similar treatment of β-prodinol (34) where it was shown that having the 3-methyl group axial to the axial 4-hydroxyl group enabled the formation of a 4-chloroderivative (164). It was assumed that the 4-chloro compound (253) was first

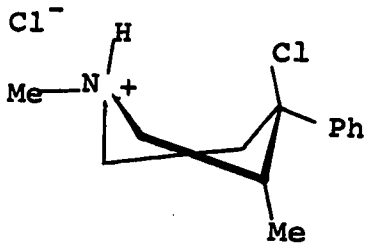


253

formed (as in the case of β-prodinol), since the additional 2-methyl group of β-promedol should not interfere with its formation. However, the stability of the latter must be less than that of β-prodinol (possibly because conformational isomers of (157), for example a skew boat (254), which will



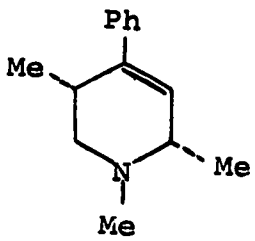
157



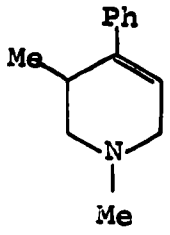
254

relieve non bonded interaction of the axial 4-chloro and 3-methyl groups, are not liable to arise in the case of the promedol analogues because they place the 2-methyl group in a less favourable orientation).

The configuration (253) allows only one trans diaxial pathway for elimination, hence isolation of the alkene (255) as a sole dehydration product is consistent with the configurational assignments. Acid catalysed dehydration of β-prodinol (34) under mild conditions similarly yields only the corresponding trisubstituted (140) alkene (Casy et al., 1967).



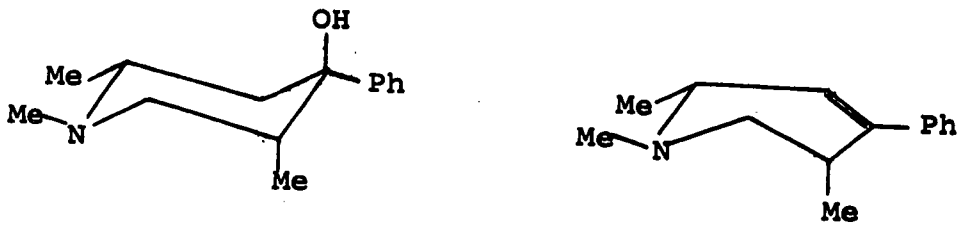
255



140

The remote possibility of (252) being the initial dehydration product, followed by its conversion to the trisubstituted (255) form is disposed of by the fact that equilibration of the trisubstituted form (255) with HCl - HOAc acids yields a mixture that contains a substantial amount (30%—as determined from integral trace) of the tetrasubstituted isomer, as seen by the appearance of a broad singlet in the spectrum of the base for the tertiary methyl group at δ1.57. In the 3-methyl analogues, the tetrasubstituted alkenes are distinctly more stable forms (Casy et al., 1967). Thus any equilibration process must yield a mixture of isomers and the alkene (255) must therefore be the initial product of the reaction. Attempts at isolating the chloro derivative (253) intermediate by reaction with thionyl chloride at room temperature proved fruitless for the main product of such reactions was the unreacted alcohol and a small proportion of the trisubstituted alkene (IR and PMR evidence).

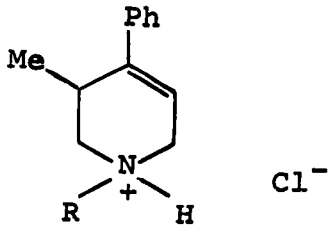
The structure of the alkene obtained from the β-isomer should have the stereochemistry shown in (256) if the configuration and conformation arrived at earlier are correct. The PMR spectrum of the alkene hydrochloride gives clear evidence of epimer formation with duplicate N-methyl, 2-methyl and



256

5-methyl doublets. These signal pairs merged to form broad ill-resolved bands when the temperature was raised (not controlled) or when D_2O was added (both changes speed up the N^+-H proton exchange rate).

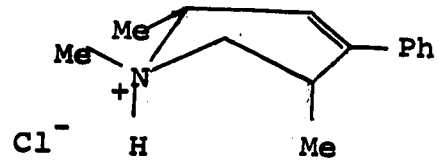
Epimers also arise in the case of the salts of the tetrahydropyridines (257) and have been investigated in



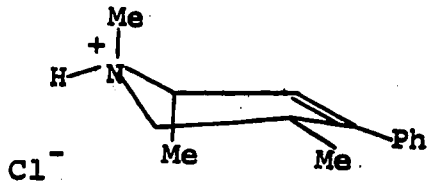
257

detail by Casy and coworkers (1965). Therefore the epimeric possibilities of the alkene derived from the β-promedol alcohol are shown below.

Epimer I
trans 1,5-diMe

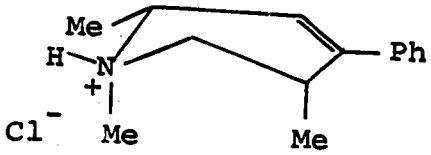


258

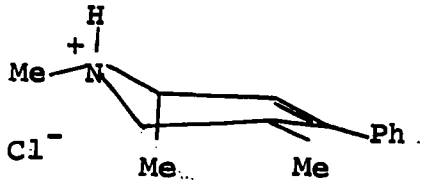


259

Epimer II
cis 1,5-diMe



260



261

In epimer I (trans 1,5-dimethyl) the conformer (258) has an axial methyl group that interferes less with the styrene chromophore than is the case in (259) or (261), where the chromophore is disturbed and the phenyl ring will have to rotate out of coplanarity with the double bond. Also in conformation (259), two axial methyl groups exist, hence conformer (258) is clearly the more favoured. UV evidence is in agreement: λmax 242 mμ, log ε 3.92; with that found by Casy and Iorio (1966) for compounds of type (254): λmax 238, log ε 4.06, for the hydrochlorides in ethanol, and indicates effective conjugation of C=C-Ph system.

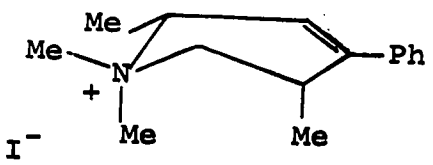
In epimer II (cis 1,5-dimethyl) the conformer (260) will be destabilized by the large 1,3-diaxial methyl interaction, while in structure (261) only one axial 2-methyl group exists, hence the conformer (261) is deduced to be the more favoured member of the pair.

Assignments of the 5-methyl PMR signals to the two epimers were thought likely to agree with those made earlier for epimers of type (257). The signal at δ1.12 (J=5.5 Hz) was low field due to the nearness of the deshielding NH^+ group. This, however, does not coincide too closely with the 3-methyl signal (δ1.30, J=7.5 Hz) in the trans epimer of (257) analogous to (258). This difference (0.13 ppm) may reflect the existence of a significant population of the trans conformer (259) in which the gauche N-Me/2-Me interaction of (258) is relieved.

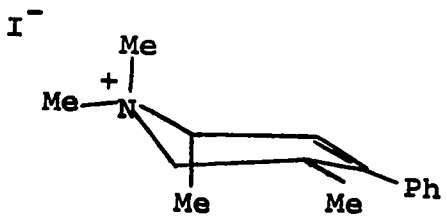
In the cis epimer (261) the 5-methyl group is further

from the N^+H and will be less deshielded, therefore the signal at δ0.93 (J=7 Hz) was assigned to the 5-methyl group. The 5-methyl group in the epimer of (257) analogous to (261) appears at δ0.93 (J=7.5 Hz), hence both assignments agree and (261) is probably the second epimer.

Formation of the methiodides of the total dehydration product derived from β-promedol alcohol may result in two possible salts (262) and (263) which correspond with (258)

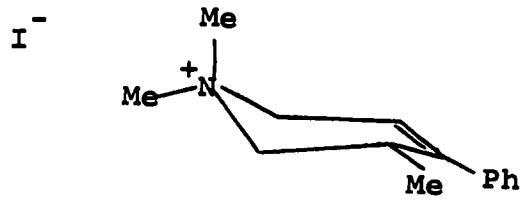


262



263

and (261). Structure (262) is unlikely due to 1,5-diaxial interaction, but the methiodide (263) is quite feasible. PMR analysis of the total reaction mixture showed only one product formed, with a 5-methyl signal at δ1.03 (J=6.0 Hz), which compares closely with the corresponding signal of the methiodide of the mono C-methyl (δ1.03, J=6.0 Hz) analogue (264), all observed in DMSO-d_6 (Table XIX). Interestingly



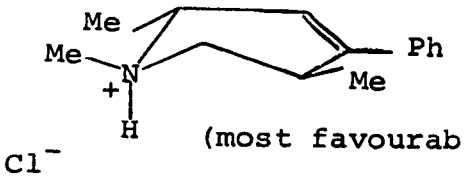
264

the two N-methyl signals are quite widely separated in (263) coming to resonance at δ3.24 and δ3.64, while those of the analogue (264) appear at δ3.74 and δ3.55.

This result reflects the shielding influence of an axial 2-methyl group upon the adjacent N-methyl substituents, the equatorial group being shielded but the axial group being deshielded (see p. 261). On these grounds the lower field N-methyl signal is assigned to the axial group.

Returning to the elimination product of the γ-promedol alcohol, one of the anticipated structures is (265) which would lead to the conjugate acids (266) and (267), both of which are shown in their most probably conformations; however, (266) should be the major form. If epimers arose,

265



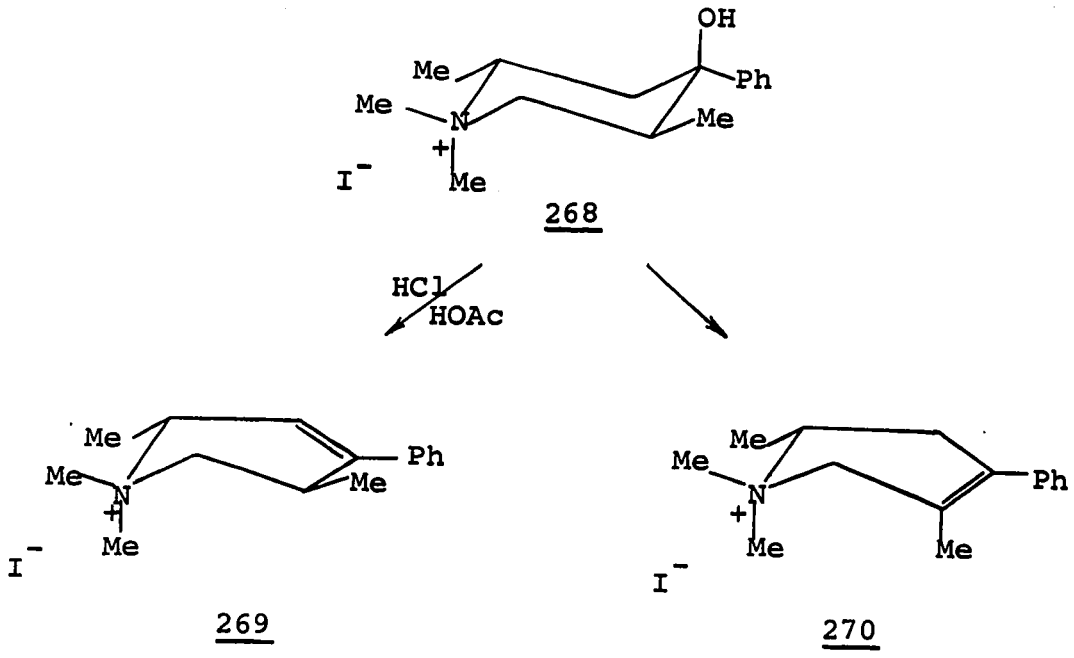
(most favourable)

266

267

therefore, distinct N-methyl and 2-methyl but similar 5-methyl PMR signals were to be anticipated. The PMR results obtained, however, did not come up to these expectations, and in fact the γ-trisubstituted alkene base (which was not obtained pure but as a mixture enriched in the trisubstituted

form) had PMR characteristics very similar to those of the β-promedol alcohol dehydration product. We therefore concluded that the γ-alcohol gives an initial alkene mixture which equilibrates to form a substantial amount of the trisubstituted alkene identical with that obtained from the β-isomer. This occurs possibly because it allows the formation of the epimer which has a maximum conjugation of the styrene chromophore. Isomerization may only occur via the tetrasubstituted alkene (252) and the fact that it was present in the dehydration mixture from γ-promedol alcohol shows that such a pathway is indeed feasible.



It was thought that if the γ-alcohol methiodide (268) was dehydrated with acid there would be no incentive to produce the isomer with the axial 5-methyl group (262) by equili-

bration from (270), and the trisubstituted alkene (269) should consist of a structure directly related to the γ-alcohol. The mixture of alkenes that resulted after this reaction (IR evidence showed dehydration essentially complete) was fractionally crystallized. A pure sample of the trisubstituted alkene was not obtained but rather a mixture enriched in this alkene which gave a spectrum that corresponded closely with that of the β-quaternary alkene salt. Thus equilibration must have occurred again, as was found in the dehydration of the γ-alcohol, and this can only occur via the tetrasubstituted alkene (270).

The N-methyl region of the trisubstituted alkene (enriched mixture) displayed singlets at δ3.24 and δ3.64, which correspond to the β-trisubstituted alkene methiodide (263) described earlier. The signal at δ3.64 was most likely due to the axial N-methyl group since this will be deshielded by the axial 2-methyl group. As well, a signal at δ3.34 was assigned to the tetrasubstituted portion (270) of the mixture, this signal being due to the equatorial N-methyl group, for the signal at δ3.64 was thought to be due to the axial N-methyl group of both the tri- and tetrasubstituted alkenes.

Subsequent formation of the methiodide of the trisubstituted alkene derived from dehydration of γ-promedol alcohol had PMR spectral characteristics identical to that of the β-trisubstituted alkene methiodide and also to those of the trisubstituted alkene derived from dehydration of

the methiodide salt of γ-promedol alcohol (Table XXI).

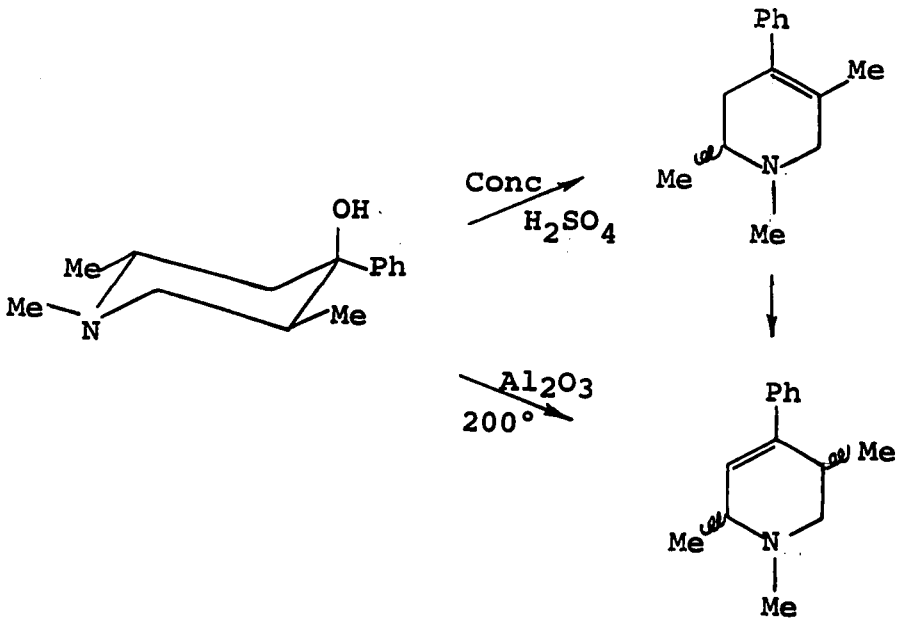
TABLE XXI. PMR CHEMICAL SHIFT VALUES OF METHIODIDE ALKENES DERIVED FROM γ- AND β-PROMEDOL IN DMSO-d_6 [a]

Substituent	γ-Promedol Alkene MeI	β-Promedol Alkene MeI
N-Me[b]	3.24	3.24
N-Me[b]	3.62	3.64
5-Me[c]	1.03	1.03
2-Me[c]	1.56	1.56

(a) Chemical shifts in δ units from TMS measured at a frequency of 60 MHz. (b) Singlet. (c) Doublet.

In summary, it has been shown that the γ-promedol alcohol dehydrated readily with either thionyl chloride or acid treatment to give both a trisubstituted and tetrasubstituted alkene mixture. The trisubstituted alkene has been shown to be identical to the same alkene derived from β-promedol alcohol. This could only be the case if equilibration had occurred via the tetrasubstituted alkene (252).

Prostakov et al. (1965) dehydrated γ-promedol alcohol by two alternate routes as shown in Scheme XX. Unfortunately no proof for the structural assignments was given. They did find, however, that the tetrasubstituted alkene could be equilibrated to the trisubstituted form which is in agreement with our findings with the alkene derived from β-promedol alcohol.



Since these routes, if they were in fact stereospecific, would offer easy access to both alkenes the procedure was repeated. After refluxing γ-promedol alcohol with concentrated sulphuric acid for five hours (during which time the reaction mixture turned black) the product obtained (isolated as the free base) displayed a PMR that was unresolvable in the C-methyl region. It was concluded, therefore, that an extensive amount of decomposition had occurred, and, as well, the presence of a vinylic proton signal at δ5.53 indicated the procedure not to be a stereospecific route to the tetrasubstituted alkene, hence the reaction was not investigated further.

It should be mentioned that no dehydration experiments were carried out on the α-promedol alcohol isomer because of the small supply available.

HYDROGENATION OF THE ALKENES DERIVED FROM γ-PROMEDOL

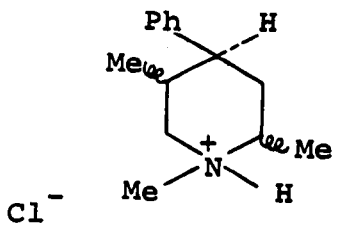
The total dehydration product derived from γ-promedol alcohol was catalytically reduced as the hydrochloride salt and the PMR spectrum of the product recorded. The spectrum lacked a vinylic signal, hence reduction was complete. It displayed three doublets in the 5-methyl region and three in the 2-methyl region, plus a pair of HN-Me doublets (Table XXII).

TABLE XXII. PMR CHARACTERISTICS OF ISOMERIC 1,2,5-TRIMETHYL-4-PHENYLPIPERIDINE HYDROCHLORIDES IN $CDCl_3$[a]

N-Me[b]	2-Me[b]	5-Me[b]
2.90	1.45	0.74
2.85	1.53	1.08
	1.69	1.11

(a) Chemical shifts in δ units from TMS measured at a frequency of 60 MHz. (b) Doublet.

The 2- and 5-methyl doublets had intensities (moving downfield) of 1:2:6. Thus at least two hydrocarbons of type (271) are present.



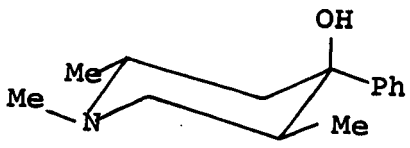
271

Fractional crystallization of the mixture yielded a pure hydrochloride whose spectrum displayed a single 2-methyl and 5-methyl signal at positions corresponding to the major component of the hydrocarbon mixture. The chemical shift values of the free base of this isomer for the 2- and 5-methyl doublets were δ1.18 and δ0.80. These values represent a significant shift of the 5-methyl signal (0.31 ppm) which has been used previously as being indicative of an axial 5-methyl orientation. Thus this hydrocarbon analogue may be due to an α- or β-promedol type isomer in which the 5-methyl is axial.

Since the other hydrocarbon isomer(s) could not be separated, a definite comparison could not be made to confirm whether the isomer on hand was, in fact, of the α- or β-type. Therefore, it was felt that Raney nickel hydrogenolysis of the individual isomeric alcohols may provide a stereospecific route to the 4-H analogues, and thus allow positive identification of the above isomer.

The γ-promedol alcohol (56) when treated under reflux with Raney nickel failed to give any trace of the reduction product. This was of course anticipated in light of the previous experience with α-prodine alcohol (33), in which

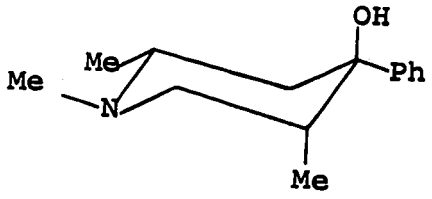
33



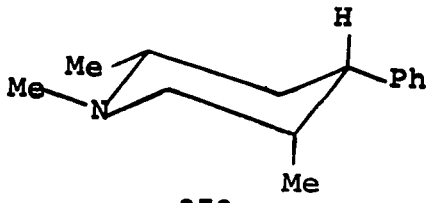
56

the equatorial 3-methyl group was shown to interfere with hydrogenation by this method.

Raney nickel hydrogenation of β-promedol alcohol (173) was found to give a product whose IR spectrum indicated that the 4-OH group had been fully reduced. This sample should have the structure (272) if earlier assignments to the β-alcohol are correct.



173



272

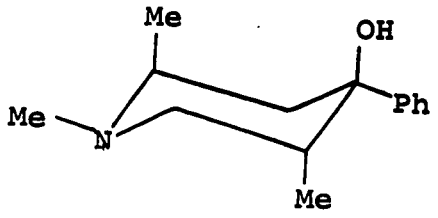
The PMR spectrum of the free base in $CDCl_3$ displayed single 2- and 5-methyl doublets at δ1.01 and δ0.73 and as well a singlet for the N-methyl group at δ2.24. The positions of these signals were found to correspond to some of those in the spectrum of the free base of the total reduction product of the alkene derived from γ-promedol alcohol but were not the same as those of the lone isomer isolated from this latter mixture.

The hydrochloride salt (in $CDCl_3$) of the reduction product obtained from the β-alcohol displayed a poorly resolved spectrum consisting of a multiplet centered at δ2.87 for the N-methyl group, and a pair of overlapping doublets centered at approximately δ1.50 for the 2-methyl group, while two badly deformed doublets appeared at δ1.13 and δ0.80 due

to 5-methyl group. These signals (since the spectrum of the base displayed only sharp signals indicative of a single isomer) were thought to be due to the presence of protonated epimers of the β-hydrocarbon analogue. Signals very close to these were observed in the total hydrochloride of the reduction product of the alkene derived from γ-alcohol.

It was concluded therefore that the latter product must contain the hydrocarbon analogue identical to that derived by hydrogenolysis of β-promedol alcohol and as well another reduction product (already isolated in a pure state), which is apparently not of the β-isomer type.

Thus the last isomer to be reduced was α-promedol alcohol (183) which is depicted in the chair form with the



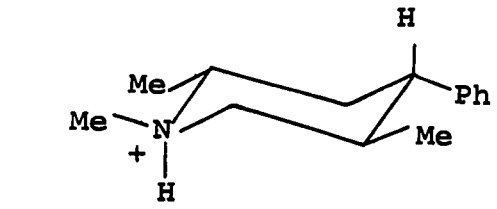
183

4-phenyl equatorial. When this isomer was reacted with Raney nickel in refluxing ethanol, complete reduction occurred as shown by the absence of an OH band in the IR spectrum.

The PMR spectrum of the hydrochloride salt of the reduction product in DMSO-d_6 (this salt was insoluble in $CDCl_3$) displayed 2- and 5-methyl group doublets at δ1.37 and δ0.65 respectively. These signals were shifted to δ1.04 and δ0.60 when the base was liberated. The small chemical shift

difference of the 5-methyl group between the salt and base was not expected since from past experience the 5-methyl group which has been axial has always exhibited a large shift when the proton was removed from the basic centre. Also, the signal due to the 5-methyl group displayed evidence of virtual coupling—a situation that has been associated with an equatorial orientation of this function.

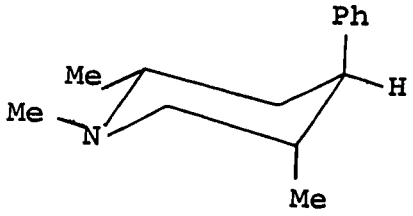
This led to the conclusion that the reduction product derived from α-promedol alcohol had not maintained the parent compound's stereochemistry, but instead must have isomerized to a γ- type configuration (273), since in an



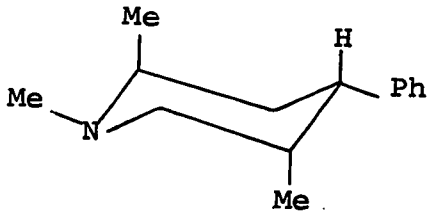
273

isomer of this type the 5-methyl group should exhibit a small shift upon protonation of the basic centre, and as well, would exhibit virtual coupling.

Therefore the identity of the isomer derived from dehydration and subsequent reduction of γ-promedol alcohol can not be of the γ- or β- type configuration since these two forms have been identified and are different from this isomer. This then leaves the δ- form (274), which is of somewhat unlikely conformation, and the α- form (275). The latter configuration is most probable since the 5-methyl

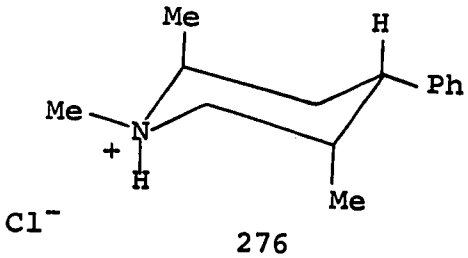


274

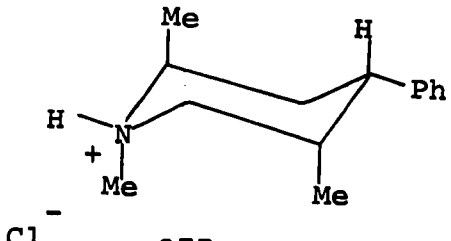


275

group in this conformation will show a significant shift when the basic centre is protonated; however, in this type of structure epimers (276) and (277) were expected. The



276

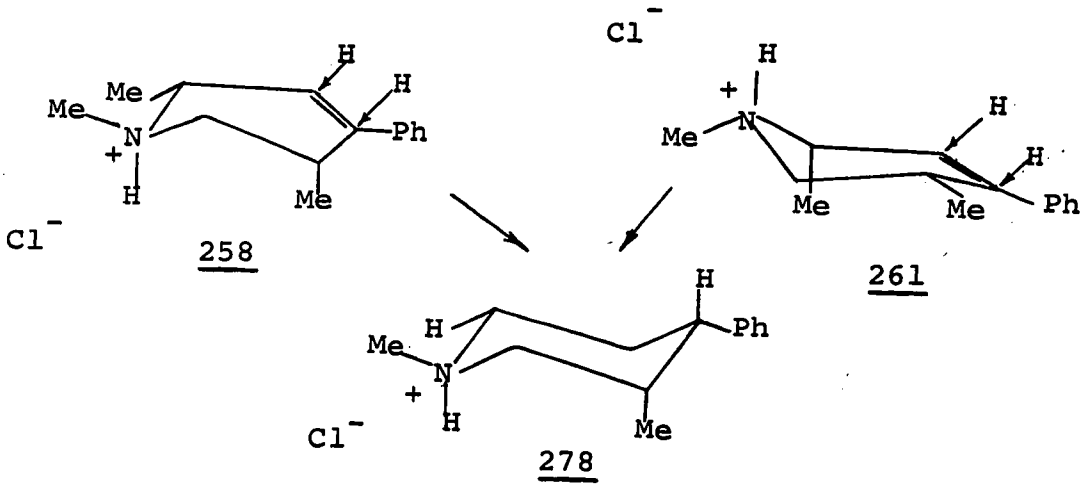


277

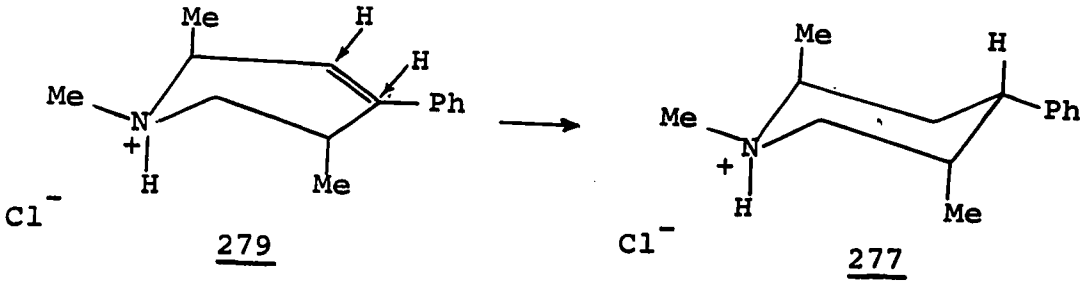
epimer (277) should be significantly different so as to appear as a distinct set of signals in the PMR spectrum, especially if it forms a skew boat conformation. Since this apparently is not the case here it may be postulated that, unlike the alcohol analogues, the α- type isomer does not form a skew boat conformation when the 4-OH or 4-OCOR groups are absent. Thus the hydrocarbon analogue is assigned the structure (276).

The question that arises is, then, can the α- and β- type hydrocarbon analogues arise from the γ-alkene product, assuming cis addition of hydrogen from the least hindered

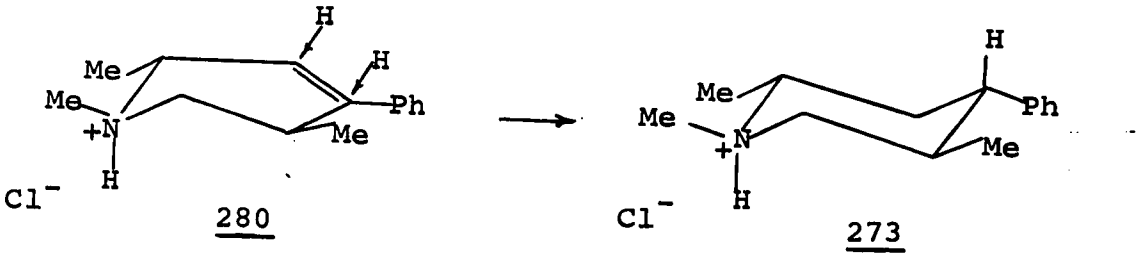
side of the alkene. It has already been shown that evidence points to the fact that a good deal of β-alkene is present in the total mixture of alkenes obtained, and this will yield the β-hydrocarbon analogue (278) from either epimer (258) or (261).



The α-hydrocarbon analogue (277) can only be produced from the alkene that has the structure (279); the latter



alkene would be preferred over the type (280) since this

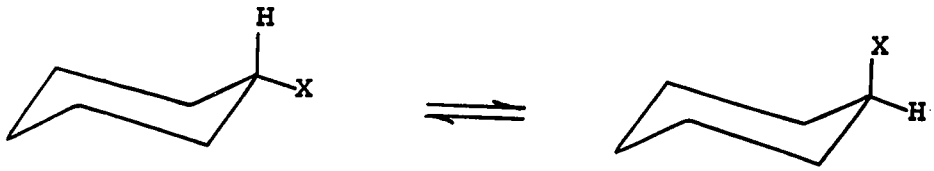


has a less stable styrene chromophore effect (see earlier) and will give rise to the γ- type hydrocarbon analogue. Evidence for the α-alkene was not immediately apparent in the alkene mixture, but this could be due to difficulty in detecting this isomer in a complex mixture.

In summary, it has been shown that at least three 4-H analogues of the α-, β-, and γ-type stereochemistry have been produced. The probable structure of two of these has been postulated and the origin of each shown to be the result of both stereospecific and non-stereospecific reduction of the corresponding alcohols. As well, the third isomer isolated from a mixture has been tentatively shown to arise via the appropriate alkene intermediate.

CONFORMATIONAL FREE ENERGY CONSIDERATIONS

Estimation of the conformer populations of substituted six-membered alicyclic molecules may be made if the free energy difference between likely conformers is known (usually only the two chair forms are considered). Take the case of a monosubstituted cyclohexane $C_6H_{11}X$ (281) in which equatorial X and axial X chair conformers will be in equilibrium. Chair-chair interconversion readily occurs because the



281

energy requirements of this change is low, but at any given instant in time the population of the more stable (here the equatorial conformer) will exceed the population of the axial conformer.

This equilibrium is expressed by the equation:

$$K = \frac{[E]}{[A]}$$

where K = the conformational equilibrium constant

[E] = concentration of the equatorial conformer

[A] = concentration of the axial conformer.

The greater the free energy difference between e-X and a-X forms, the smaller will be [A] and the greater the K value.

The free energy difference ($-\Delta G^{\circ}_{X}$) and K are related by the expression:

$$-\Delta G^{\circ}_{x} = RT \ln K$$

where x refers to the substituent in question

R = gas constant

T = absolute temperature.

$-\Delta G^{\circ}_{x}$ (also known as the "A" value) is often simply called the "conformational energy". If K or $-\Delta G^{\circ}_{x}$ are known, the percentage of the more stable conformer may be calculated. Thus a K value of unity ($-\Delta G^{\circ}_{x} = 0$) is indicative of an absence of conformational preference, while K = 1.5 corresponds with 60% and K = 4.0 corresponds with 80% of the more stable conformer (Eliel, 1962).

Various techniques have been employed for the measurement of K (and hence $-\Delta G^{\circ}_{x}$) values, including PMR procedures (Thomas, 1970). Conformational free energy data upon a large number of substituents has been compiled (Eliel, 1965), from which the conformational preferences of polysubstituted 6-membered alicyclic derivatives may be calculated. The validity of the conclusions will be defined:

(i) on the accuracy of the individual $-\Delta G^{\circ}_{x}$ values (in many cases considerable variation in the experimental values is observed);

(ii) the assumptions of the summation of $-\Delta G^{\circ}_{x}$ values.

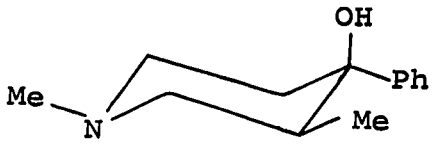
For example, α- and β-prodinol alcohols possess reasonable $-\Delta G^{\circ}_{x}$ values (Garbish and Patterson, 1963; Eliel, 1965) as shown below.

Group	$-\Delta G^{\circ}_{x}$
Ph	2.8 (average of 2, 2.6, 3.1, 3.6)

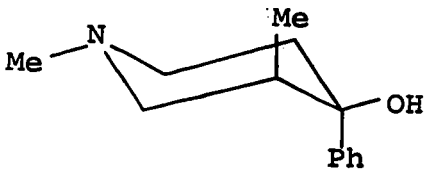
Me 1.7 (PMR procedures)

OH 0.7 (PMR procedures in non polar solvents)

For α-prodinol, the free energy of the axial 4-phenyl chair (282) conformer (see later) will exceed that of the equatorial 4-phenyl (33) chair by: 2.8 (Ph) + 1.7 (Me) - 0.7 (OH) = 3.8 kcal/mole (the value of the 4-hydroxyl is



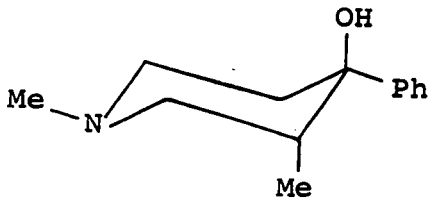
33



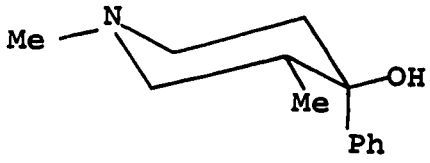
282

deducted since it is equatorial). This is a large difference and means that the population of the equatorial 4-phenyl conformer will be almost 100%.

For β-prodinol, the equatorial 4-phenyl conformer (34) has two axial substituents, hence the free energy difference between the two forms should be less. This will be: 2.8 (Ph) - 1.7 (Me) - 0.7 (OH) = 0.4 kcal/mole (two deductions are



34



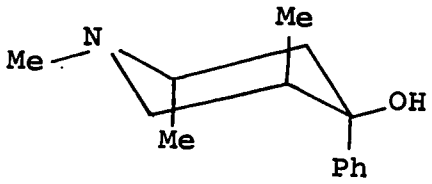
283

made in this case for the equatorial 4-hydroxyl and 3-methyl groups). This value indicates that there is now a significant

population of the axial 4-phenyl form (30 - 35%).

The same energy calculations can now be applied to the promedol alcohols. The γ-isomer (58) has 3 fully equatorial substituents and therefore will populate the form shown to essentially 100%. The conformer (284) is of very high energy.

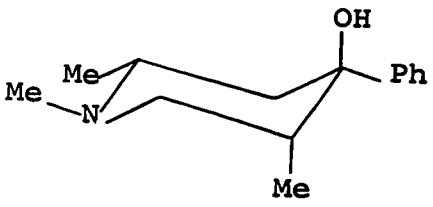
58



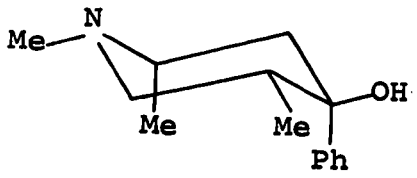
(unlikely conformation)

284

β-Promedol alcohol (173) will have $-\Delta G^{\circ}_{x}$ values of: 2.8 (Ph) + 1.7 (2-Me) - 1.7 (5-Me) - 0.7 (OH) = 2.1 kcal/mole. Therefore the population of conformer (173) is between 95 and 98%.



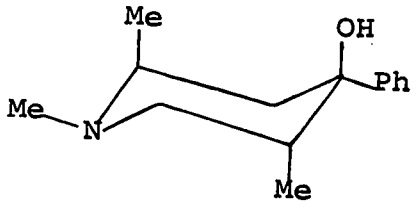
173



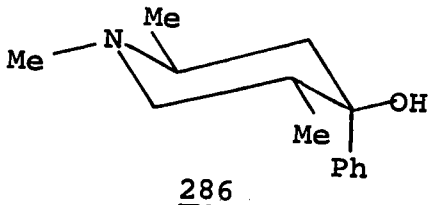
285

For α-promedol alcohol (183) the $-\Delta G^{\circ}_{x}$ value will consist of: 2.8 (Ph) - 1.7 (2-Me) - 1.7 (5-Me) - 0.7 (OH) = -1.3 kcal/mole. The negative sign indicates that (286) is in fact the less energetic form and has a population of about 60 - 65%.

This calculation does not take into account the



183



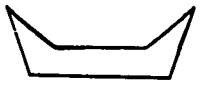
286

destabilizing 1,3 interaction of the axial 2-methyl and 4-hydroxyl groups in (183), of unknown $-\Delta G^{\circ}_{x}$ value. Conformational free energy arguments therefore predict that the axial 4-phenyl conformer (286) will be the more highly populated form.

As already discussed, however (p. 156), PMR data upon the α-promedol alcohol are not in agreement with this conclusion and point to a skew boat (not allowed for in the above) as the preferred form.

The free energy differences between isomers believed to exist exclusively in chair and boat forms amount to 4 - 6 kcal/mole. These experimental values fall toward the lower end of the theoretical range of 5.28 - 8 kcal/mole (Robinson and Theobald, 1967) and are probably relevant to twist or skew boat conformations (287) rather than the

287



288

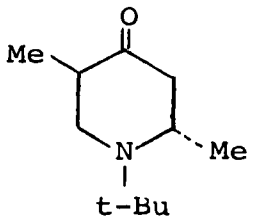
classical boat (288) itself. In the former flexible forms,

both 1,4 non-bonded interactions (flagpole - bowsprit) and eclipsed ethane type interactions of a true boat are partially relieved. The energy difference is thus of an order where it might well be outweighed by the energy of interactions between bulky substituents and in such cases, populations of flexible forms may become significant. The existence of preferred flexible conformations in cyclohexane derivatives in which chair forms are destabilized by non-bonded interactions of the 1,3-diaxial type (R/R') or (R''/H) where R'' is a very bulky group, are well documented (Robinson and Theobald, 1967). Piperidine derivatives have received less attention* but it is to be noted that the flagpole-bowsprit interaction in flexible forms of piperidine bases may be reduced because it involves a nitrogen lone pair and hydrogen rather than two hydrogen substituents. There is even evidence that a 1,4 interaction of this type can constitute a factor stabilizing the flexible form.

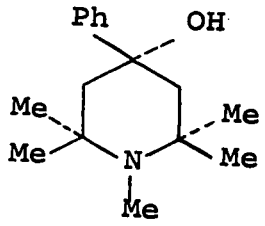
Thus the compound (289) displays intramolecular hydrogen bonding, a fact explained by its having a preferred skew-boat

---

*PMR analysis of trans N-t-butyl-2,3-dimethyl-4-piperidone (291) shows it to exist in a preferred skew boat conformation whereby the N-t-bu/2-Me interactions are minimized (Hassan and Casy, 1970).

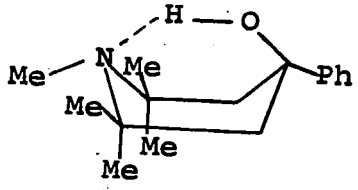


291



289

conformation (290).



290

Other 1,4 interactions, for example $\overset{+}{N}H$--OH, $\overset{+}{N}H$--O=CO, might also influence conformational preference in 4-piperidones and their derivatives.

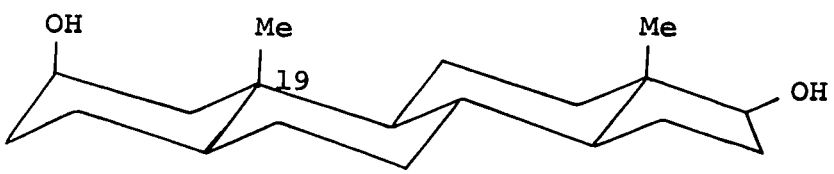
SOLVENT EFFECTS UPON THE PMR SIGNALS OF ISOMERIC 4-PHENYL-4-PIPERIDINOLS

1. USE OF PYRIDINE:

Pyridine serves as an alternative to benzene as an aromatic solvent capable of inducing changes in chemical shifts relative to values obtained in $CDCl_3$ and CCl_4. More recently it has found application in the study of polar molecules containing an OH function to which pyridine will hydrogen bond (Demarco et al., 1968). In many alcohols unexpectedly large solvent shifts ($\Delta = \delta CDCl_3 - \delta C_5D_5N$) are observed for protons and proton groups oriented in certain ways towards the hydroxyl group, and their magnitudes provide useful stereochemical information. The relationships of interest to the present work are as follows:

(i) 1,3-Diaxial deshielding

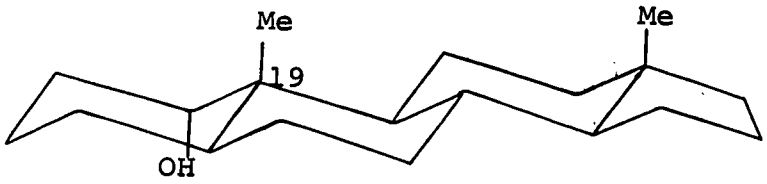
Single protons or methyl groups occupying positions 1,3-diaxial to OH experiencing effects of the order of 0.2 - 0.4 ppm in C_5D_5N relative to $CDCl_3$. For example the following polycyclic system (292) exhibits a downfield shift of the C-19 methyl group protons of 0.3 ppm in $C_5D_5N_N$ as compared to the chemical shift in $CDCl_3$ (this effect will be used later in the 1,2-dimethyl-4-phenyl-4-piperidinols (300), see p. 243).



292

(ii) Vicinal deshielding

Protons and methyl groups vicinally situated to an OH function are deshielded, and in extents dependent on the dihedral angle between the proton (or methyl group) and the OH function. Only small values are observed when the angle is large, for example in compound (293), but large shifts occur when ϕ is close to 60°, as in (294).

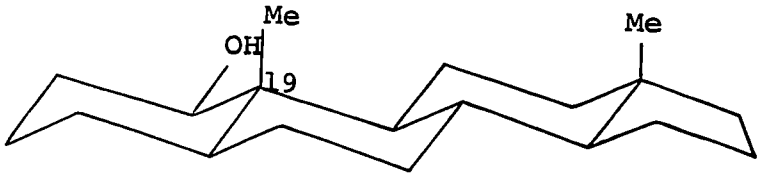


293

C_{19}-Me

Δ = -0.03 ppm

ϕ = 180°



294

C_{19}-Me

Δ = -0.22 ppm

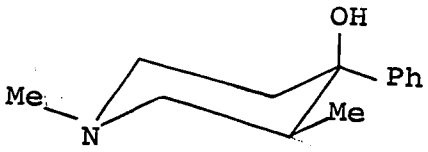
ϕ = 60°

Thus pyridine shifts seen in the spectra of isomeric alcohols may provide stereochemical information, and for this reason the spectra of isomeric prodinols and promedol alcohols as well as some 1,2-dimethyl-4-phenyl-4-piperidinols were recorded in this solvent in the hopes that chemical shift data of such value would result.

PRODINE ALCOHOLS:

Results for the prodinols are shown below. Note that significant shifts are seen for the 3-methyl signals but not

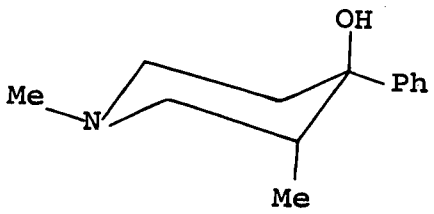
for the N-methyl, a result which emphasizes the specificity of the effect.



α-prodinol

3-Me Δ = -0.17 ppm

N-Me Δ = 0

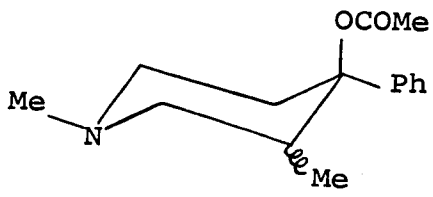


β-prodinol

3-Me Δ = -0.17 ppm

N-Me Δ = 0

The shift seen for the α-3-methyl signal was as anticipated in view of the 60° dihedral angle relationship between 4-OH and 3-Me. The fact that the β-3-methyl signal shows an identical shift was unexpected however, since the hydroxyl is further removed the the 3-Me in this isomer (ϕ = 180). Evidence that both shifts are a result of a solute-solvent complex formed through a hydrogen bonding interaction involving the 4-OH is provided by the fact that the 3-methyl Δ values are negligible in the isomeric esters (295).

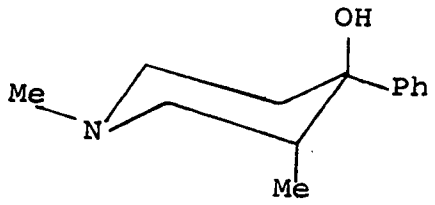


295

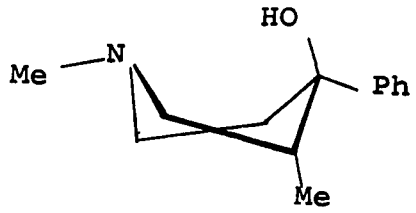
α-3-Me Δ = 0 ppm

β-3-Me Δ = -0.01 ppm

The shift for β-prodinol may be accounted for by assuming that pyridine induces a conformational change from (34) to an arrangement (296) in which the 3-methyl is closer to the

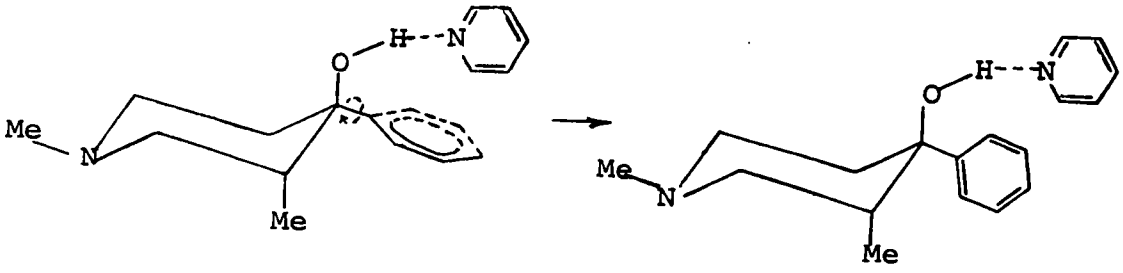


34



296

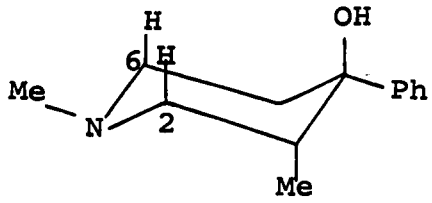
$OH-C_5D_5N$ feature. This possibility is discounted, however, by data upon the isomeric promedol alcohols (see later). An alternative explanation is that association between the hydroxyl group and pyridine in the β-alcohol modifies the preferred orientation of the 4-phenyl group with respect to the piperidine ring. This change then makes the shielding influence of the 4-phenyl ring upon the axial 3-methyl group different than its effect in solvents such as $CDCl_3$ and CCl_4.



β-prodinol

A feature of both the 60 and 100 MHz spectra of β-prodinol in pyridine was the clear emergence of a one-proton doublet of doublets (J=11 and 3.25 Hz) downfield of the ring

proton complex about the N-methyl signal. This signal was assigned with reasonable confidence to the axial 2-methylene proton which will be 1,3-diaxial to the OH-C_5D_5N feature (297) and hence strongly deshielded (2-Ha should be lower field than 6-Ha because it is trans diaxial to a methyl group—Booth, 1966).



297

PROMEDOL ALCOHOLS:

Pyridine induced solvent shifts were also employed in the isomeric promedol alcohols in the hopes that the relative configuration and conformation could be verified as previously having been correctly assigned.

The γ-promedol alcohol (56) from principles already outlined should experience a relatively large shift for the

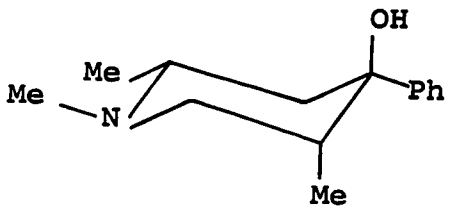
56

5-methyl group, for the relative configuration of this group is identical to that of α-prodinol (33). Data obtained show that a significant shift was observed for the 5-methyl group in pyridine when compared with its position in chloroform (0.16 ppm). This figure is therefore in close agreement with the shift (0.17 ppm) seen for the α-prodinol and serves to confirm stereochemical similarity about this point.

The 2-methyl group was not found to be deshielded at all. This is expected in view of the equatorial arrangement of the group and the distance therefore involved in the C_5D_5N-OH feature.

The N-methyl group was not seen to change resonance position hence no association can be involved at the basic centre.

Pyridine shifts of the β-promedol alcohol (173) confirm



173

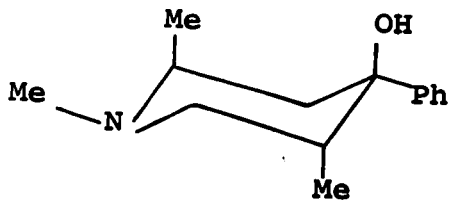
earlier stereochemical assignments. There was observed no significant shift of the 2-methyl group (0.03 ppm), which was expected since this group has been shown earlier to be equatorial and hence should not be affected by the C_5D_5N-OH association.

Like γ-promedol, the 5-methyl group of β-promedol was

significantly shifted down field (0.21 ppm). This was unexpected in view of the 180° angle between the 4-hydroxyl and 5-methyl groups but is in agreement with the same shift in β-prodinol discussed earlier.

The N-methyl signal of β-promedol alcohol did not experience a shift in pyridine which is in line with previous findings.

The 2-methyl group of α-promedol alcohol was found to be shifted 0.13 ppm when pyridine was substituted for chloroform as a solvent. This suggests that some contribution from the 1,5-diaxial methyl group arrangement (183) must exist.



183

However, this value is too small to be consistent with such a form being the major contributor.

The 5-methyl shift of the α-isomer (0.21 ppm) is of the same order as that experienced for the γ- and β-isomeric alcohols. Again the N-methyl signal did not change position.

The unexpected shifts for the α- and β-promedol alcohol 5-methyl signals may be thought as being due to a conformational change. If this is true, however, the parameters of ring proton signals should differ in $CDCl_3$ and C_5D_5N since any conformational change will alter the coupling constants

for the piperidine ring protons.

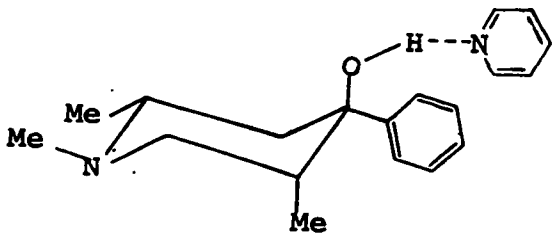
With the β-prodinol (34) form the axial 2-methylene proton was clearly visible and was used as proof of conformational stability.

From the 60 and 100 MHz spectrum of the α- and β-promedol alcohols one of the 3-methylene protons could be identified. (This was identified earlier from the work on the α-trideuterated alcohols, see p. 184.)

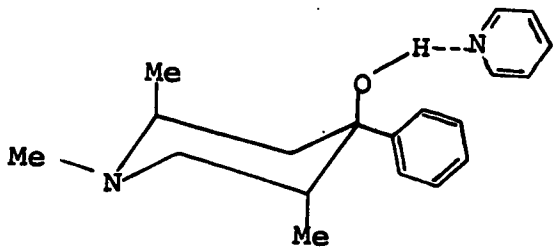
The spectrum of the β-isomer displayed a clear doublet of doublets at δ1.72 in $CDCl_3$ which was shifted to δ2.05 in pyridine. (This shift of 0.23 ppm is of the correct magnitude and the result of vicinal deshielding experienced by protons oriented at 60° to hydroxyl functions.) In both solvents the coupling constants (J gem 13.5 Hz, J vic 9.5 Hz) were identical therefore no conformational change has occurred.

The same 3-methylene proton signal was visible in the spectrum of α-promedol alcohol. In $CDCl_3$ it appeared at δ1.69 and in pyridine at δ2.05. The coupling values (J gem 14 Hz, J vic 4 Hz) remained the same in both solvents.

These results are strong evidence that the preferred conformation of the α- and β-promedol alcohols is the same in the two solvents. We concluded therefore that the shifts seen are the result of changes in the preferred orientation of the 4-phenyl ring with respect to the piperidine ring, which effects 4-Ph/3-Me shielding:



β-promedol alcohol



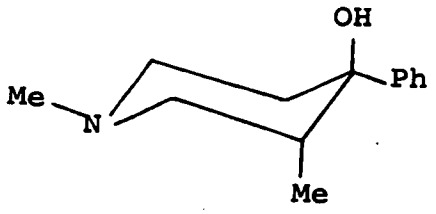
α-promedol alcohol

USE OF BENZENE

PRODINOL AND PROMEDOL ALCOHOLS:

When the PMR spectra of α- and β-prodinol (33) and (34) were recorded in benzene it was noted that the 3-methyl

33



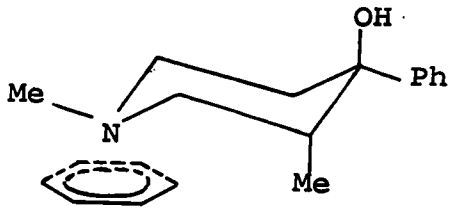
34

signal was unaffected in the α-isomer but was deshielded by 0.07 ppm for the β- form. The N-methyl signals in both isomers were shifted upfield by 0.18 ppm.

Association of the benzene solvent with the hydroxyl function is unlikely and would not adequately explain the

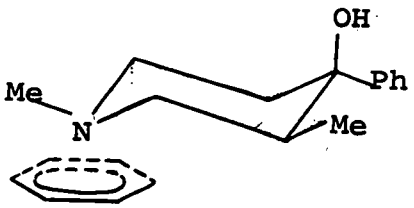
significant shift of the β- form but the complete lack of shift of the α-alcohol 3-methyl groups. Further, in both isomers the N-methyl function is shielded.

A possible explanation was thought to be that the benzene ring may associate with the nitrogen lone pair. If the aromatic ring is below the nitrogen in both forms (298) and (299) then the N-methyl group will fall within the



β-prodinol

298



α-prodinol

299

ring's diamagnetic shielding zone and will be expected to come to resonance at higher field than was the case in chloroform. With the β-isomer (298) the axial 3-methyl group is approximately at the edge of the aromatic ring and hence would be expected to be deshielded to some extent. This does not occur, however, with the α- form (299) since the equatorial 3-methyl is further removed and away from the benzene ring.

The results for the isomeric promedol alcohols are tabulated in Table XXIII.

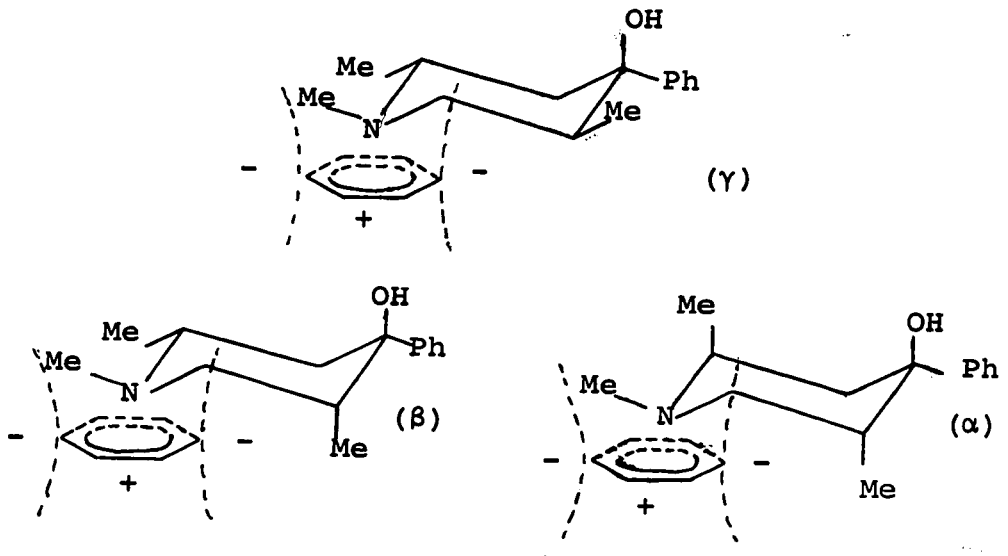
From the preceding table the N-methyl signals are seen to experience a significant upfield shift in the neighborhood of 0.16 to 0.20 ppm. It will also be noted that the 2-methyl signal is shifted upfield relative to its position in $CDCl_3$ but to a lesser degree. Therefore it was assumed

TABLE XXIII. PMR CHEMICAL SHIFT DATA FOR ISOMERIC PROMEDOL ALCOHOLS[a]

Isomer	Chemical shifts observed in $CDCl_3$			Chemical shifts observed in C_6H_6		
	N-Me[c]	2-Me[b]	5-Me[b]	N-Me[c]	2-Me[b]	5-Me[b]
α	2.32	1.18	0.74	2.15	1.06	0.78
β	2.31	1.13	0.75	2.09	1.02	0.74
γ	2.32	1.08	0.62	2.18	1.02	0.65

(a) Chemical shifts in δ units from TMS (internal) measured at a frequency of 60 MHz.
(b) Doublet. (c) Singlet.

that in all three isomers the aromatic ring is once more oriented below the nitrogen lone pair, an arrangement that will shield the N-methyl group and to some extent the 2-methyl group but the latter will be affected much less since it is further away.



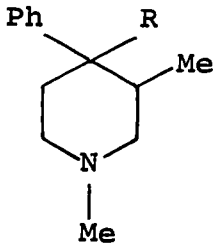
The shift of the 5-methyl group in all three isomers is small. It was expected that a shift similar to that observed in the case of β-prodinol would also be evident with the β-promedol alcohol and to some extent for the α-promedol alcohol's contribution from the diaxial 2,5-dimethyl conformation.

Japanese workers (Yonewaza et al., 1968) obtained evidence that there is a repulsive interaction between benzene solvent molecules and the nitrogen lone pair (attraction has been assumed in the above models). The difference may be due to the fact that the Japanese investigators used sp^2 type nitrogen compounds (imines, aziridines and oximes), not sp^3 as in the present work.

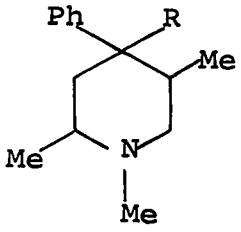
Further studies of this type of compound are required before definite conclusions may be drawn.

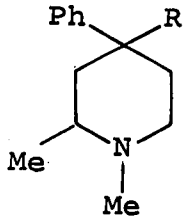
1,2-DIMETHYL-4-PHENYL-4-PIPERIDINOLS:

The prodine and promedol analogues discussed up to this point have both possessed a substituent on an α-position of the piperidine ring. Therefore, in order to complete the data on the mediation of analgesia, a "hybrid" was planned in an attempt to show the contribution of a 2-methyl substituent. To this end the preparation of t-alcohols derived from 1,2-dimethyl-4-piperidone (90) was undertaken and evidence sought relating to the stereochemistry of the products and their derivatives. The preparation of the precursor ketone has already been discussed (p. 79).



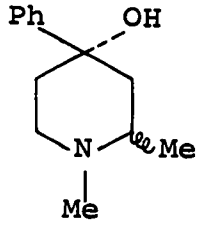
Prodines





Promedols

Only one reference (Mistryukov, 1967) to the preparation and possible stereochemistry of 1,2-dimethyl-4-phenyl-4-piperidinol (300) was found in the literature. These workers were able to isolate two isomers but data on the configuration



300

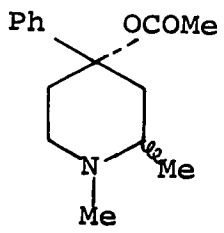
and preferred conformation were not given. Chromatography on alumina showed that the β-isomer (Rf 0.23) was eluted first followed by the α- form (Rf 0.53). Physical data on the isomers isolated were restricted to a suitable micro-analysis and a melting point for the bases; major form (α) 122-123°, minor form (β) m.p. 111-112°.

In the present work, the total base isolated from phenyl-lithium treatment of the 1,2-dimethyl-4-piperidone (90) had a PMR spectrum (in CCl_4) that displayed evidence of two isomers. The two 2-methyl doublets were present in a

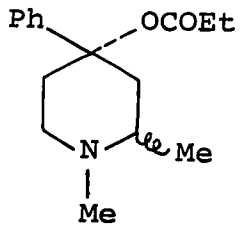
proportion slightly favouring one isomer (which later proved to be the α-isomer) by a ratio of 11:9 as determined by relative intensities. The chemical shifts of these two methyl groups differed by a very small amount; having values of δ0.97 and δ0.95; while the N-methyl signals were significantly separated at δ2.07 and δ1.97. The latter two signals are therefore used later as an indication of isomeric purity since the small difference between the 2-methyl groups of each isomer would preclude the use of these signals as an effective indication of isomeric composition.

One of the isomers isolated, which had a melting point corresponding to that of the β-isomer isolated by the Russian workers, was obtained by fractional crystallization of the total base from petroleum ether. The other isomer was subsequently isolated by column chromatography of the mother liquors remaining after partial exhaustion of the β-form, on a small column filled with Woelm neutral (activity I) alumina and eluted with chloroform. The initial eluate contained a small amount of the unreacted ketone, followed by a mixture of α- and β-isomers and finally pure α-1,2-dimethyl-4-phenyl-4-piperidinol of m.p. 109-110°. Since we now had a sample of the pure α-isomer base, this was used as a seed crystal in subsequent fractional crystallizations after isolation of the α-isomer.

Acetyloxy (301) and propionyloxy (302) esters were prepared from the individual isomers by the action of acetyl



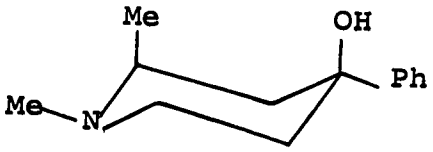
301



302

chloride or propionyl chloride on the samples of pure α- or β-1,2-dimethyl-4-phenyl-4-piperidinols and were isolated as the hydrochloride salts from benzene.

PMR analysis of the pure alcohol bases and their salts was hoped to give a ready solution to the configuration of each isomer. It was thought that the most probable conformation of the piperidine ring would be the chair form with the 4-phenyl group equatorial. This would then lead to two orientations of the 2-methyl group (303) and (304).



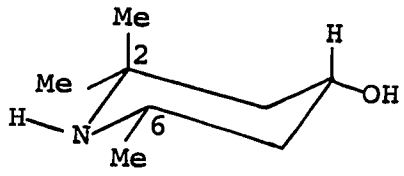
303

304

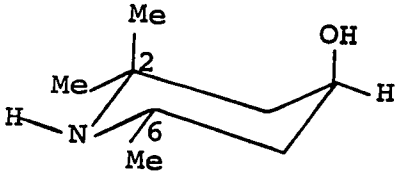
In one form (303) the 2-methyl group is axial and it was anticipated that the deshielding influence of the axial 4-hydroxyl group would allow easy identification of this form, since such 1,3- diaxial deshielding influences are well documented in the literature (Shoolery and Rogers, 1958;

Kawazoe, 1962; Tori and Komeno, 1964; and Carr and Huitric, 1964).

The effects of the hydroxyl upon an axial 3-methyl group was verified for piperidinol derivatives in the present work from data on isomeric 2,2,6-trimethyl-4-piperidinols (305) and (306). (Kindly supplied by Drs. F. Perks and P.J. Russell, School of Pharmacy, Portsmouth, England.)



305



306

The two isomers were differentiated by the C-4-proton signal; in (305) it is broad (two axial couplings are involved) while in (306) it is narrow (no axial coupling).

The PMR spectrum of (306) in $CDCl_3$ showed one of the methyl signals distinctly lower field than the other two. Their assignments were made as follows:

equatorial	6-methyl (doublet)	δ1.07
equatorial	2-methyl (singlet)	δ1.09
axial	2-methyl (singlet)	δ1.35

Thus the axial 2-methyl group is deshielded to the extent of 0.3 ppm relative to the equatorial group.

PMR data obtained from the isomeric 1,2-dimethyl-4-phenyl-4-piperidinols are shown in Table XIV.

It will be noticed that no appreciable difference exists

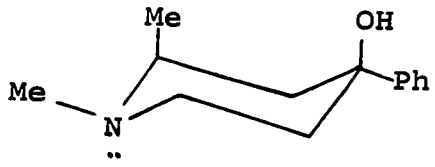
TABLE XXIV. PMR CHEMICAL SHIFT DATA OF ISOMERIC 1,2-DIMETHYL-4-PHENYL-4-PIPERIDINOLS[a]

Isomer	Chemical Shifts Observed in: $CDCl_3$ 2-Me[b]	$CDCl_3$ N-Me[c]	$DMSO-d_6$ 2-Me[b]	$DMSO-d_6$ N-Me[c]	Pyridine 2-Me[b]	Pyridine N-Me[c]
α-	1.08	2.14	1.08	2.17	1.12	2.15
β-	1.07	2.30	1.05	2.32	1.08	2.30

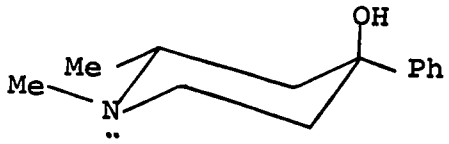
N.B. Notations used here have the same meaning as those in Table XXIII.

for the chemical shifts of the 2-methyl group between the isomers. Possible reasons for this lack of chemical shift difference are as follows:

(i) The deshielding influence of the 4-hydroxyl is offset by shielding due to the N-methyl and axial lone pair.



2-Me trans diaxial to lone pair cis to N-Me

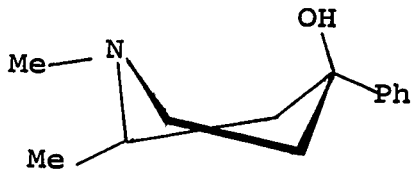


2-Me cis to lone pair trans to N-Me

There is evidence that a lone pair of electrons on a nitrogen significantly shields protons to which it bears a trans diaxial relationship (Hamlow et al., 1964) and also that the shielding interaction between cis N-methyl/α-C-methyl groups in piperidine is greater than that

between trans groups as obtained in the equatorial 2-methyl isomer (Hassan and Casy, 1970).

(ii) If the preferred conformation of (303) is not as depicted but a flexible skew boat form (307) then the



307

2-methyl group will have a pseudo-equatorial orientation and will display a chemical shift very similar to the other isomer where the piperidine ring retains the chair form and the 2-methyl group is equatorial.

Evidence that the trans 2-Me/4-Ph isomer (303) does prefer the skew boat conformation is provided by PMR studies in pyridine. Demarco et al. (1969) have shown that single protons or methyl groups occupying positions 1,3-diaxial to an hydroxyl function experience deshielding effects of the order of 0.2 to 0.4 ppm in pyridine relative to $CDCl_3$. The expected shift was seen in the axial 2-methyl signal of the isomeric 2,2,6-trimethyl-4-piperidinol (306) with an axial hydroxyl group, while in the equatorial hydroxyl isomer (305) none of the three methyl signals were significantly affected by the same solvent change. In the spectra of the α- and β-isomer of 1,2-dimethyl-4-phenyl-4-piperidinol, however, the 2-methyl signals had virtually the same resonance

position in pyridine as they did in $CDCl_3$. The α-isomer had 2-methyl group signals at δ1.08 ($CDCl_3$) and δ1.12 (pyridine) while the β-form displayed the same group at δ1.07 ($CDCl_3$) and δ1.08 (pyridine). This was anticipated in the chair form of (304) but not for the chair form of (303).

The PMR spectrum of the hydrochloride and methiodide salts exhibits a clear difference between the signal positions of the two isomers (Table XXV).

TABLE XXV. CHEMICAL SHIFTS FOR SALTS OF 1,2-DIMETHYL-4-PHENYL-4-PIPERIDINOLS IN DMSO-d_6[a]

Form	PMR Chemical Shifts 2-Me[b]	N-Me	OH[c]
α-HCl	1.45	2.67[b]	5.46
β-HCl	1.33	2.75[b]	5.46
α-MeI	1.46	3.22, 3.14[c]	3.69
β-MeI	1.30	3.20, 3.02[c]	3.80

N.B. Notations used here have the same meaning as those in Table XXIII.

In the spectrum of the α-isomer hydrochloride and methiodide the 2-methyl signal is at lower field in both cases than the corresponding β-isomer. It is possible therefore that when the lone pair of electrons is no longer free they are not available for shielding the axial 2-methyl group, hence the deshielding effect of the axial 4-hydroxyl function is

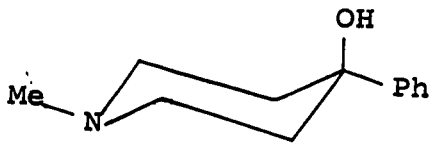
evident.

Attention is now turned to other PMR differences between the isomeric 1,2-dimethyl-4-phenyl-4-piperidinols and their derivaties, that may be of value in stereochemical assignments.

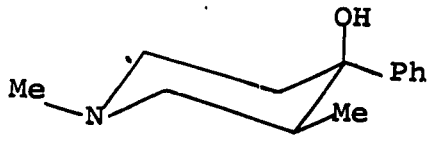
N-METHYL SIGNALS:

The data in Table XXIV shows that the α-N-methyl signal is higher field in all three solvent systems ($CDCl_3$, DMSO-d_6, pyridine). The consistently higher position of the α-N-methyl will also be seen in the esters (Table XXVIII, p. 266). This was expected since the N-methyl group should be more shielded in (303), where a cis N-Me/2-Me arrangement exists, than in (304) where the N-Me/2-Me groups are trans.

There is, however, a significant upfield shift of the N-methyl group of the α-isomer as compared to N-methyl-4-phenyl-4-piperidinol (159) (N-Me: δ2.27), and also as compared to the N-methyl signal of α-1,3-dimethyl-4-phenyl-4-piperidinol (33) (N-Me: δ2.32). However,if (303) adopts the skew boat form (307) preferentially then it might not exhibit a



159



33

significant difference because the N-Me/2-Me relationship is similar to the trans form as in (304).

The fact that the α- and β-N-methyl signals differ to the same degree in pyridine as they do in $CDCl_3$ and DMSO-d_6 (Table XXIV) is good evidence that high populations of skew boat forms of the trans 2-Me/4-Ph-4-piperidinol exists in all three solvents. This fact has already been established for one of the isomeric alcohols in pyridine from the lack of a pyridine induced 2-methyl downfield shift.

With this conclusion in mind, then, it must be admitted that a firm interpreation of α-/β-N-methyl chemical shift differences in terms of configurational assignments is not possible.

EPIMER FORMATION IN 1,2-DIMETHYL-4-PHENYL-4-PIPERIDINOLS:

Epimeric conjugate acids have been shown previously to arise as a result of the two possible modes of protonation of the basic centre in the piperidine ring, and the stereochemical values of cases where epimer formation is restricted to one number of an isomeric series has already been illustrated for the promedol derivatives. This situation also occurs in the present isomeric series, epimers being restricted to α-derivatives. The α-1,2-dimethyl-4-phenyl-4-piperidinol hydrochloride in DMSO-d_6 displayed a 2-methyl signal as a broad doublet. When a small amount of trifluoroacetic acid was added (the same technique was sometimes found necessary with β-promedol alcohol hydrochloride) a clear pair

of overlapping doublets were seen of approximately equal intensity at δ1.5 and δ1.41. The hydrchloride salt was insoluble in $CDCl_3$; however, when the base plus TFA was run in $CDCl_3$ the spectrum displays an apparent triplet (two overlapping doublets) at δ1.5 and δ1.41.

Variable temperature trials on the α-isomer in DMSO-d_6 showed that the two overlapping doublets coalesced at 100° to give a single doublet at δ1.46, midway between the epimeric signals obtained at normal operating frequency (see Figure XVII).

Spectra of the β-1,2-dimethyl-4-phenyl-4-piperidinol hydrochloride gave no evidence of the separate existence of epimeric conjugate acids. Consideration of the energy requirements of the two isomers will show that one epimeric form is expected to have far lower energy than the other and hence only a single protonated species should be detected; this is the one following axial protonation.

If the epimer formed following equatorial protonation relieves non-bonded interaction obtained in the product of axial approach, then a significant population of the two forms is liable to be seen. In the present examples, the α-epimers have similar energies as seen by the almost equal intensities of the pair of 2-methyl signals. If the α-isomer is (303) then the two epimers will be (308) and (309). Epimer (309) may arise because it avoids the gauche N-methyl/2-methyl interaction of (308) and/or because a conformational change to a skew boat (310) relieves the 2,4-diaxial 2-Me/

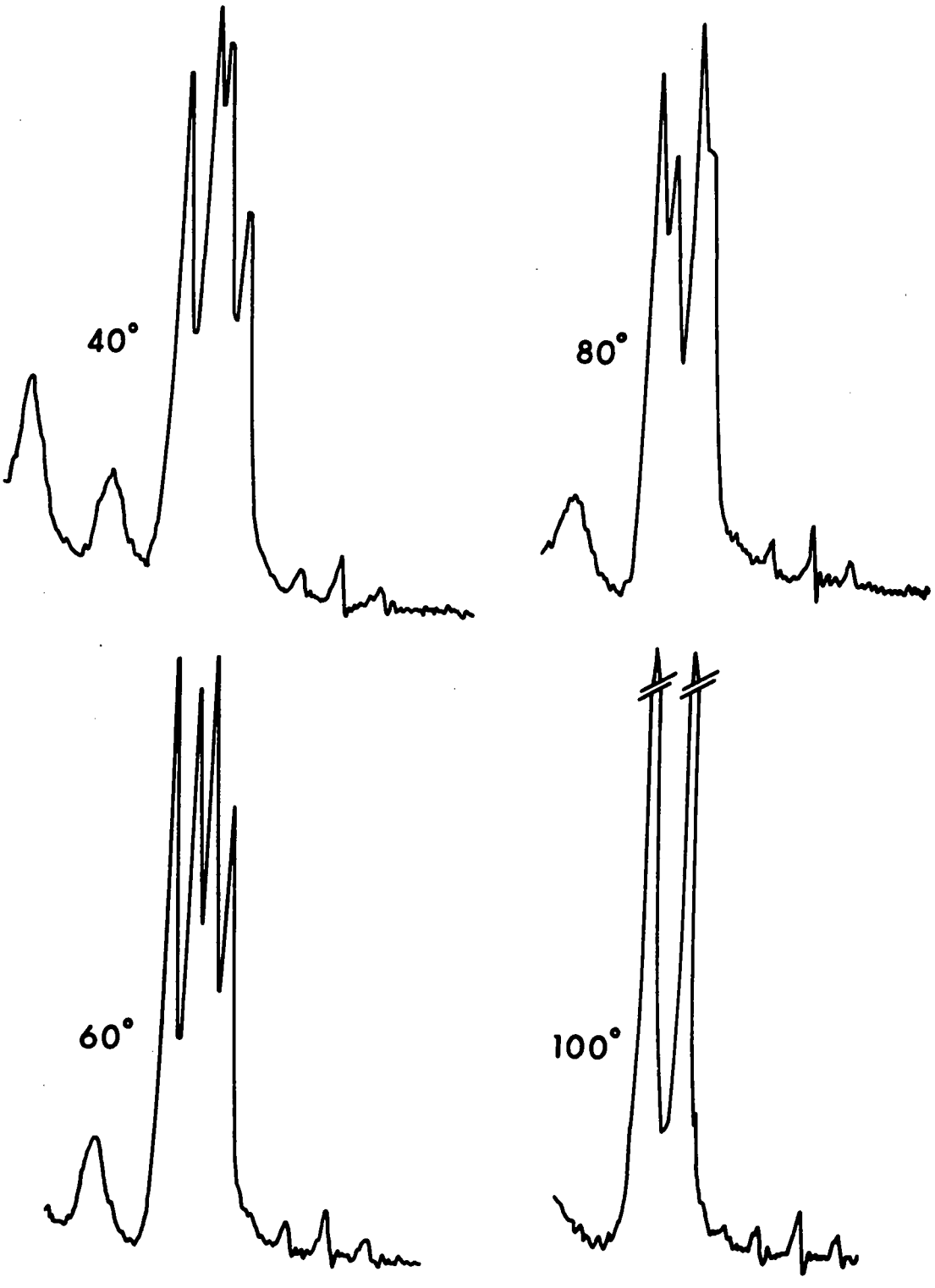
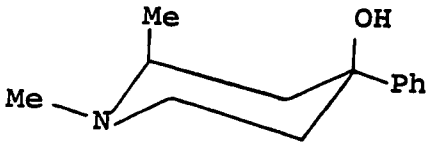
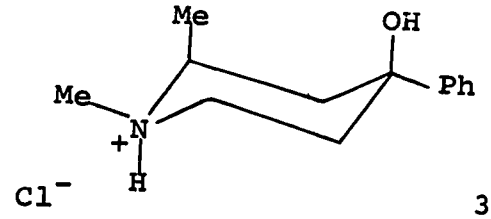


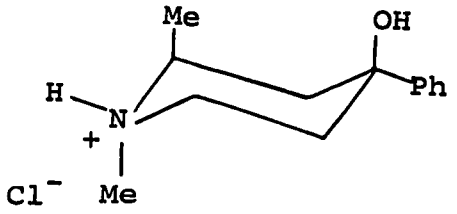
Figure XVII. Part of the PMR spectrum of α-1,2-dimethyl-4-phenyl-4-piperidinol hydrochloride showing the effects of variable temperature on the 2-methyl group signal. Recorded at 500 sweep width in DMSO-d_6 (60 MHz).



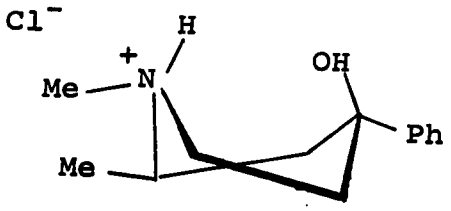
303



308



309

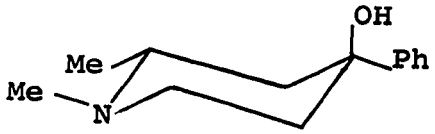


310

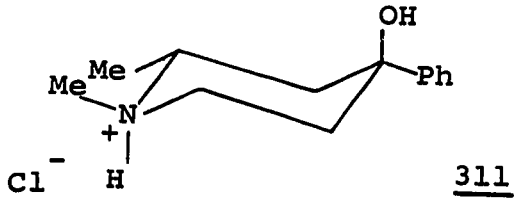
4-OH interaction as well. This change is less probable in (308) because it would place the N-methyl in a pseudoaxial position whereas in (309) the change is aided by the axial N-methyl group attaining a pseudoequatorial orientation.

If the β-isomer is (304), then the two epimers will be (311) and (312).

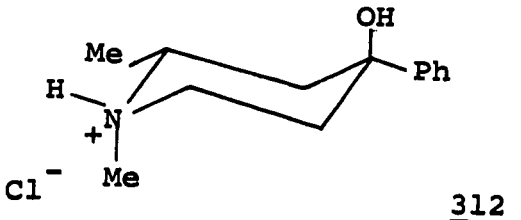
The population of (312) is unlikely to be high because its formation does not relieve the gauche N-methyl/2-methyl interaction of (311) while any conformational change it may undergoe will place the 2-methyl group in a less favourable orientation.



304

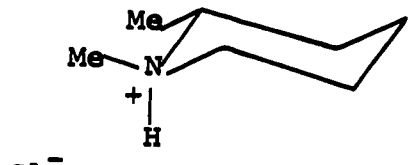


311

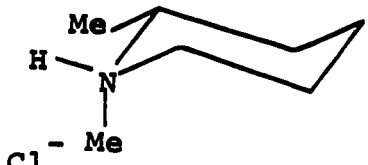


312

Epimer hydrochlorides (in D_2O) are seen in 1,2-dimethylpiperidine (which is a comparable equatorial 2-methyl example) but the population of the major form (314) from axial protonation far exceeds the product of equatorial protonation (313) (see Figure XVIII).



313



314

On these grounds, comparable populations of epimers, as observed in the case of the α-isomer, are only anticipated if these derivatives have a trans 2-methyl/4-phenyl configuration as in (303).

The signal at δ1.41 is likely due to the epimeric form skew boat (310) since this position is similar to the β-form

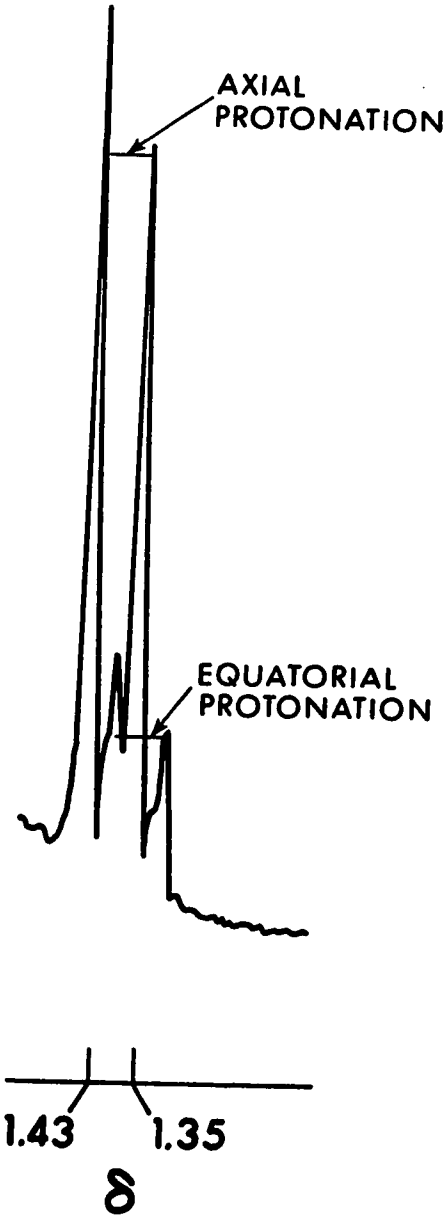


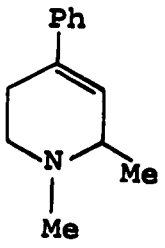
Figure XVIII. Part of the PMR spectrum of 1,2-dimethylpiperidine hydrochloride showing the 2-methyl region and the effect of protonated epimers. Recorded in D_2O at 500 sweep width (60 MHz).

2-methyl group (311) found at δ1.41 (for the basis in $CDCl_3$ protonated with TFA). Both forms are expected to be similar, for the pseudoequatorial position of the 2-methyl in (310) is in a similar environment to that of the equatorial 2-methyl in (311); while the 2-methyl group (δ1.50) in the epimeric form (308) is expected to be lower due to deshielding by the 4-hydroxyl group.

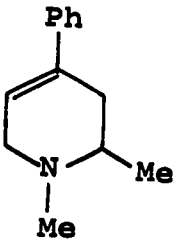
DEHYDRATION OF 1,2-DIMETHYL-4-PHENYL-4-PIPERIDINOL

Thus far the ring protons of the α- and β-1,2-dimethyl-4-phenyl-4-piperidinols have seemingly been forgotten. However, this was not the case, rather, it was found that these signals gave very complex spectra and thus could not be resolved. Examination of the β-isomer using both 100 MHz and 220 MHz instruments provided no improvement in resolution over that observed at 60 MHz and hence other methods employing techniques already explained had to be investigated.

Elimination of water from the α-1,2-dimethyl-4-phenyl-4-piperidinol (303) with a refluxing mixture of acetic and hydrochloric acids resulted in two alkenes (315) and (316),



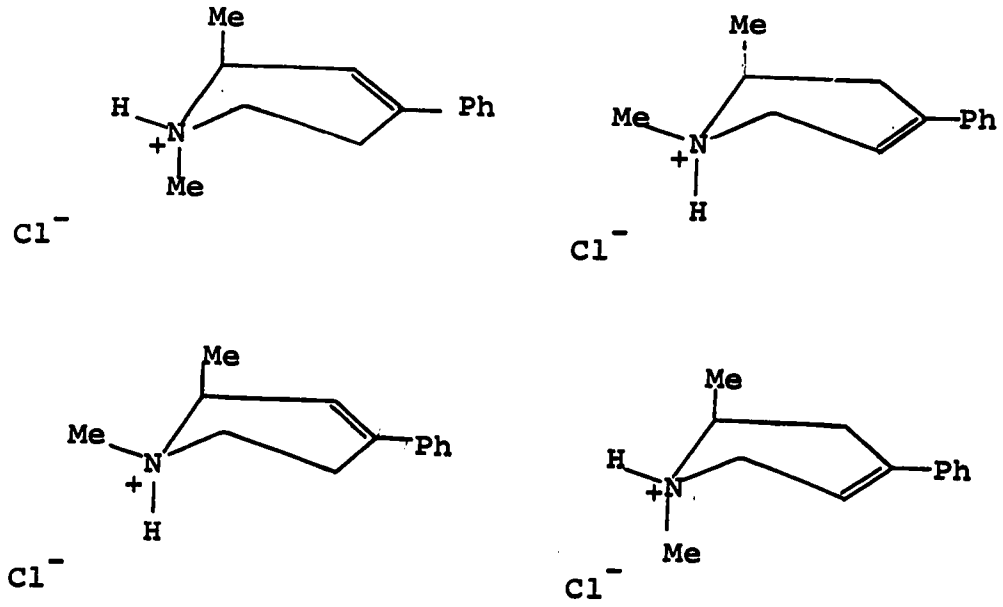
315



316

as indicated by the presence of two vinylic signals (multiplets) in the base in $CDCl_3$ at δ5.92 and δ6.05, and two doublets of equal proportions for the two methyl groups at δ1.17 and δ1.22.

The hydrochloride salt displayed a complex multiplet in the 2-methyl region. Attempts to separate the two isomers were not successful and it appeared that the two alkenes co-crystallize, for successive crystal crops had the same PMR spectra and identical melting points. The multiplet signal observed in the hydrochloride mixture in $CDCl_3$ was thought to be likely due to epimer formation. The possibilities are shown below:

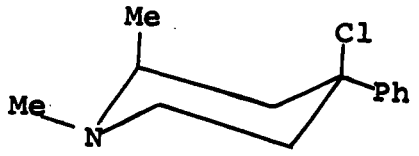


The alkenes shown above can flip without putting the phenyl group axial, hence the same product would be expected from both the α- and β-alcohols (thus the β-alcohol, which

was in short supply, was not dehydrated). Addition of D_2O to the hydrochloride sample in $CDCl_3$ caused the multiplet due to the epimeric forms of the two alkenes to collapse to a broad poorly resolved pair of doublets at δ1.55 and δ1.62. As well the complex N-methyl multiplet centered at δ2.85 collapsed to a broad signal which could not be resolved.

REACTION WITH THIONYL CHLORIDE

By stirring the α-alcohol with thionyl chloride at room temperature, no reaction was observed and the alcohol was recovered. However, when the temperature was raised to 60° for 12 hours, complete elimination of water occurred and no chloro derivative (317) could be isolated. The mixture of alkenes so obtained had a PMR spectrum identical to that of

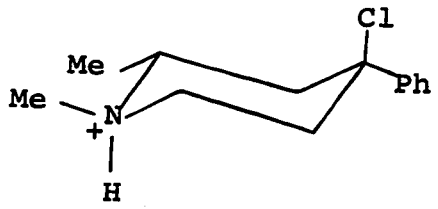


317

the alkenes obtained from acid dehydration of the α-alcohol. The crystalline hydrochloride had a m.p. and mixed m.p. which was also identical to that of the alkenes derived from the acid treatment. The alkene mixture could not be separated by fractional crystallization and it appeared that again the two forms co-crystallize.

Similar treatment of the β-alcohol (4 hours reflux)

resulted in partial elimination of water, and the IR spectrum showed that a substantial amount of alcohol yet remained. Subsequently treatment with thionyl chloride at room temperature for 12 hours yielded β-1,2-dimethyl-4-phenyl-4-chloropiperidine (318) as the sole product isolated as the hydrochloride salt.

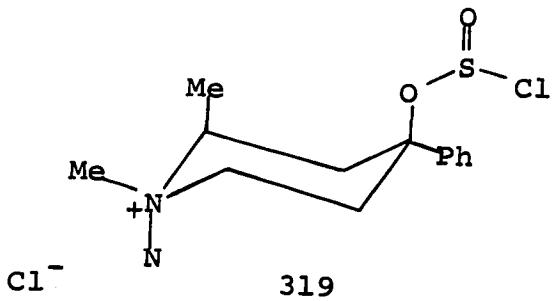


318

The PMR spectrum of this β-4-chloro derivative displayed a 2-methyl doublet at δ1.57 (HCl) and δ1.23 (base) in $CDCl_3$. This is a significant downfield shift from the β-alcohol (δ1.37, HCl; δ1.08, base), but presumably represents the increased electronegativity of the 4-chloro over the 4-hydroxyl group rather than a conformational change. Signal positions of the 2-methyl group for this 4-chloro derivative were not present in the spectrum of the β- product after refluxing treatment with thionyl chloride (see earlier), hence none was formed and the earlier product contained mainly alkene plus some unreacted alcohol.

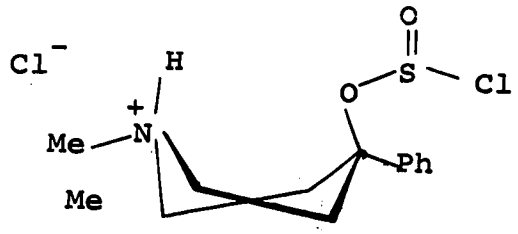
The question of the more ready dehydration of the α-isomer by thionyl chloride treatment at 60° and the fact that the β-isomer forms a chloro derivative while the α- is unreactive when room temperature conditions are employed

can be settled by a consideration of their relative configurations. If the α-isomer has a significant population of the chair form then a chloro sulfite (319) will be



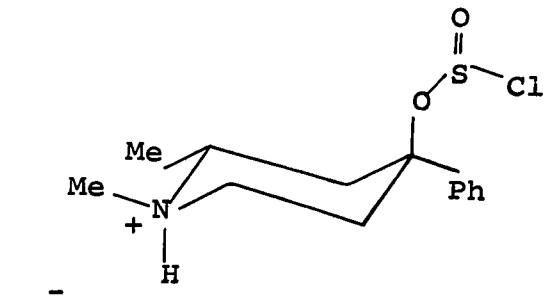
319

sterically hindered by the axial 2-methyl group and elimination rather than substitution will preferentially occur, yielding the two alkenes (314) and (315). If the intermediate chlorosulfite is formed and the piperidine ring adopts the skew boat conformation (which has been shown to probably represent the α-isomer) then the OSOCl and N-methyl groups are close enough to make this intermediate (320) highly unstable and therefore elimination is again likely to occur.



320

The β-alcohol isomer, on the other hand, has been shown to adopt the chair conformation and as such should offer no hindrance to the formation of the intermediate chlorosulfite (321). Therefore the 4-chloro derivative is anticipated



321

in high yields. These differences in reactivity of the isomeric alcohols towards thionyl chloride therefore corroborate the configurational assignments already made to them.

RANEY NICKEL HYDROGENOLYSIS

PMR evidence discussed so far substantially supports a trans 2-Me/4-Ph assignment to the α-derivative in the series and a cis 2-Me/4-Ph configuration to the β-form. Unequivocal interpretations have been hindered, however, by the findings that the trans isomers prefer non-chair conformations. The latter must result in order that the diaxial 2-methyl and 4-hydroxyl interaction be avoided. It was therefore felt that if the 4-hydroxyl could be replaced by hydrogen in a stereospecific manner, clear proof of stereochemistry might be derived from the PMR characteristics of the resultant hydrocarbons. Hydrogenolysis by Raney nickel was again tried as a means of obtaining these compounds.

The β-alcohol (304) was reduced with Raney nickel in refluxing ethanol over a four hour period to give 1,2-dimethyl-4-phenylpiperidine (322) in good yields. IR evidence showed

304 322

that no significant amount of the starting alcohol remained.

PMR analysis of the hydrochloride in $CDCl_3$ showed a single 2-methyl doublet at δ1.57 and a doublet for the N-methyl group at δ2.84. The base displayed the 2-methyl doublet at δ1.17 and the N-methyl singlet at δ2.35. Since all the signals were clean, that is, no extraneous signals appeared which would have been indicative of isomerization, the reduction was assumed to proceed with retention of configuration.

The β-isomer methiodide in DMSO-d_6 displayed a single 2-methyl doublet at δ1.32 and two N-methyl signals at δ3.18 and δ3.03.

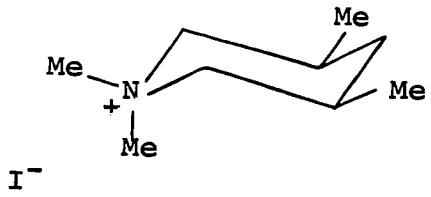
The α-isomer (303) was found considerably more difficult to reduce and thus reflux time was extended to 8 hours. The product displayed no OH peak in the IR spectrum; however, the PMR indicated that some isomerization had occurred. The hydrochloride salt was obtained with considerable difficulty and the PMR signals in $CDCl_3$ for the 2-methyl group appeared at δ1.47 (major) and as well a smaller signal appeared at δ1.57 which was thought to be due to the β-isomer present

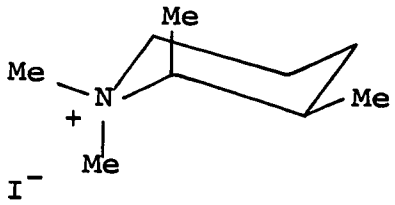
as a result of isomerization. The N-methyl region displayed a major doublet at δ2.75 and minor signals near δ2.84 which correspond to the β-isomer hydrochloride. The 2-methyl signal of the free base appeared as a single doublet at δ1.19, however, the signal was broad and could possibly contain a small contribution from the 2-methyl signal of the β-form (δ1.17). The N-methyl region gave clear evidence of two singlets at δ2.47 (major) and also δ2.36 which would be due to the presence of the β-form.

It was thought possible that epimer formation in the hydrochloride rather than isomerization could be the cause of the extra signals. This is disposed of by the fact that the α-methiodide salt also displayed signals of low intensity which corresponded to the β-isomer methiodide. PMR signals in DMSO-d_6 in the 2-methyl region appeared at δ1.53 (due to α-form) and δ1.32 (due to β-isomer) while in the N-methyl region the α-form displayed two major N-methyl signals at δ3.34 and δ3.10 while the smaller signals at δ3.18 and δ3.03 correspond to those of the β-form.

The shielding influences of axial and equatorial 2-methyl groups upon the axial and equatorial N-methyl protons of N,N-dimethylpiperidinium salts in the chair conformation have been fairly clearly established (Tsuda and Kawazoe, 1967; Hassan and Casy, 1970). In polar solvents, an equatorial 2-methyl has little effect upon an equatorial N-methyl but shields an axial N-methyl, while an axial 2-methyl shields an equatorial N-methyl but deshields an axial N-methyl.

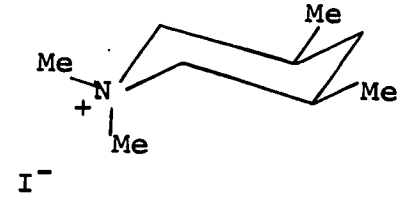
Shifts to be expected in solvent DMSO-d_6 are given below; included are the reference compounds of essentially "frozen" conformation from which their data are derived. The assignments of axial and equatorial N-methyl signals are based upon spectral comparisons of the normal methiodides with quaternary salts formed using CD_3I and the assumption of a preferred axial approach of quaternizing agent (Kawazoe and Tsuda, 1967). Data presented below are from spectra in DMSO-d_6 and are reported in δ units.

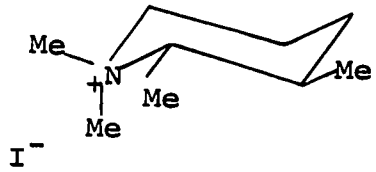




axial 2-Me causes:

e N-Me	3.15	3.07	0.08 ppm shielding
a N-Me	3.10	3.32	0.22 ppm deshielding

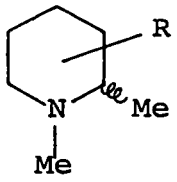




equatorial 2-Me causes:

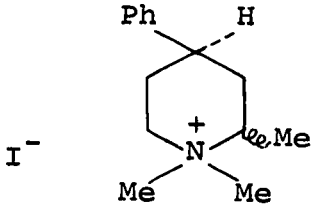
e N-Me	3.15	3.15	no effect
a N-Me	3.10	2.94	0.16 ppm shielding

Thus in isomeric pairs of the type (323) the chemical shifts and relative separation of axial and equatorial N-methyl

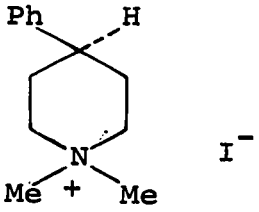


323

signals in the spectra of corresponding methiodides should provide good evidence of conformation because an axial 2-methyl group will cause the two N-methyl signals to diverge more than will an equatorial group. This approach is only valid, however, if the derivatives in question have preferred chair conformations. As the pair of isomers represented by (324) may reasonably be expected to fulfil this requirement, the method may be applied to provide evidence of



324



325

their stereochemistry. The reference compound in this case is (325) whose N-Me signals coincide in DMSO-d_6 at δ3.19. Calculated and observed N-methyl values following insertion of an axial or equatorial 2-methyl substituent are given in Table XXVI.

TABLE XXVI. CALCULATED AND OBSERVED N-METHYL CHEMICAL SHIFT VALUES AS A RESULT OF AN EQUATORIAL AND AXIAL 2-METHYL SUBSTITUENT[d]

Values observed when no 2-methyl substituent is present		Calculated from Shielding Data (p. 261)	Observed
N-Me		Equatorial 2-methyl[b]	Equatorial 2-methyl[b]
equatorial	3.19	3.19 (no effect)	3.19
axial	3.19	3.19-0.16 = 3.03[a]	3.04
		Axial 2-methyl[c]	Axial 2-methyl[c]
equatorial	3.19	3.19-0.08 = 3.11	3.10
axial	3.19	3.19+0.22 = 3.41	3.34

(a) Deduct shielding influence. (b) Data for β-quaternary salt. (c) Data for α-quaternary salt. (d) δ units observed in DMSO-d_6.

The close agreement between observed and calculated values confirm that the α-quaternary salt has an axial 2-methyl substituent while the β-salt has an equatorial 2-methyl group. Even if the order of agreement seen is fortuitous, the fact that the α-N-methyl signals show the greater degree of separation (Δ = α-, 0.23; β-, 0.15 ppm) is, in itself, good evidence for the same assignments. The relative chemical shifts of the 2-methyl groups in the isomeric quaternary salts (α-, δ1.53; β-, δ1.32) are also consistent because the α- signal is anticipated to be lower field as it is reasonable to expect a mutual deshielding interaction between the axial

2-methyl and axial N-methyl groups.

Chemical shifts of N-methyl and 2-methyl groups in spectra of the β-alcohol and β-ester methiodides (see later) are close to those of the β-hydrocarbon and all three derivatives are therefore considered to have preferred chair conformations. In the case of the α-alcohol and α-ester salts, however, the same agreement is not seen (2-Me is higher field while separation of the N-Me signals is much less), as would be expected if these derivatives adopt preferred skew boat conformations in which the trans diaxial orientation of 2-Me/N-Me is lost (Table XXVII).

From the data in Table XXVII, it will be noted that the 4-phenyl signal is complex in the two forms considered to be in the skew boat conformation while in all other forms it is relatively simple. Just why the signal is more complex in these skew boat forms is not readily explained but does serve to differentiate chairs and non-chairs empirically.

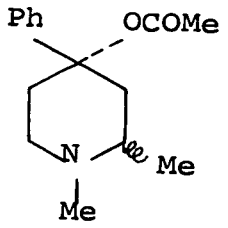
TABLE XXVII. PMR CHEMICAL SHIFT DATA ON METHIODIDES OF ISOMERIC 1,2-DIMETHYL-4-PHENYL-PIPERIDINE ALCOHOL AND ITS DERIVATIVES, IN DMSO-d_6 [a]

Isomer	Group	Ester	Alcohol	4-H
α	N-Me[b]	3.14, 3.10	3.22, 3.14	3.34, 3.10
α	OCOMe[b]	1.92	-	-
α	2-Me[c]	1.39	1.46	1.53
α	4-Ph	complex	complex	simple
β	N-Me[b]	3.27, 3.15	3.23, 3.05	3.18, 3.03
β	OCOMe[b]	2.12	-	-
β	2-Me[c]	1.31	1.30	1.32
β	4-Ph	simple	simple	simple

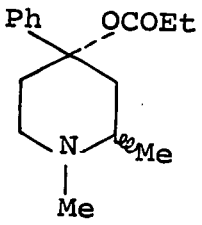
(a) Chemical shifts in δ units from TMS measured at a frequency of 60 MHz. (b) Singlet. (c) Doublet.

PMR CHARACTERISTICS OF ESTERS OF 1,2-DIMETHYL-4-PHENYL-4-PIPERIDINOL

In both the acetyloxy (301) and propionyloxy (302) derivatives the α-isomer resonance signals for the ester functions are distinctly higher field than those of the corresponding β-signals.



301



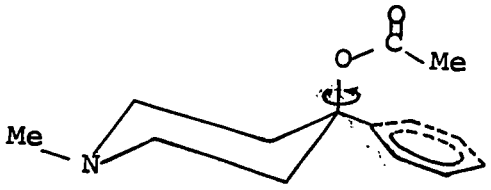
302

TABLE XXVIII. ESTER GROUP PMR CHEMICAL SHIFT VALUES OF α- AND β-1,2-DIMETHYL-4-PHENYL-4-ACETYLOXY AND PROPIONYLOXY PIPERIDINES IN $CDCl_3$[a]

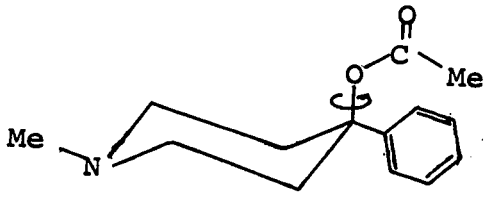
Isomer	Group	PMR Chemical Shifts Base	HCl
α	-OCOMe[b]	1.87	2.07, 1.90 (major)[e]
β	-OCOMe[b]	2.07	2.12
α	$-OCOCH_2Me$[c]	2.05	2.20, 2.17 (major)[e]
β	$-OCOCH_2Me$[c]	2.42	2.42
α	$-OCOCH_2Me$[d]	1.00	1.08, 0.97 (major)[e]
β	$-OCOCH_2Me$[d]	1.12	1.10

(a) Chemical shifts in δ units from TMS measured at a frequency of 60 MHz. (b) Singlet. (c) Centre of quartet. (d) Centre of triplet. (e) Epimer formation observed.

To interpret these differences we must first consider the shielding influences acting upon the axial 4-ester group in the N-methyl-4-phenyl-4-acetyloxy piperidine analogues. As the acetyloxy group rotates about the C4-O bond it will receive a shielding contribution when it passes over the aromatic ring due to the latter's ring current, provided the aromatic group has the orientation shown (326). If the aromatic ring is oriented as in (327), however, the OCOMe

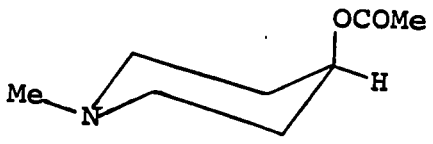


326



327

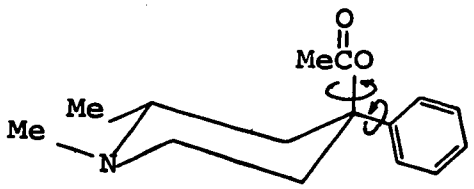
group will be deshielded in its passage about the C4-O bond. The higher the population of conformer of type (326) the greater will be the upfield shift of the OCOMe PMR signal. To check the net shielding of the acetyloxy group of (326) its PMR signal was compared with that of an analogue lacking the 4-phenyl ring (328) (Casy and Jeffery, 1970). In



328

compounds of type (326 - 327) the PMR displayed singlets for the acetyloxy group at δ2.04 (base) and δ2.10 (HCl), whereas with compound (328) the acetyloxy signal was at δ2.09 (base) and δ2.14 (HCl), all values being obtained in $CDCl_3$. Therefore, there exists a small shielding effect by the phenyl ring on the acetyloxy group in compound (326) and the phenyl ring probably has a slight preference for the orientation in which it is roughly parallel to the piperidine ring. (Preference for this type of conformation must be much less than is the case for β-prodine, see p. 39.)

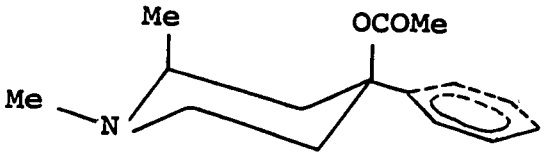
An equatorial 2-methyl group should not alter the population of this conformer, hence the β-isomer of 1,2-dimethyl-4-phenyl-4-acetyloxypiperidine (329) had OCOMe values very close to those of (328) and was therefore assigned the conformation shown, in agreement with previous assignments.



329

Further, the lack of a pronounced conformational preference of the phenyl group in the β-isomer ester was supported by its PMR signal being a fairly narrow singlet.

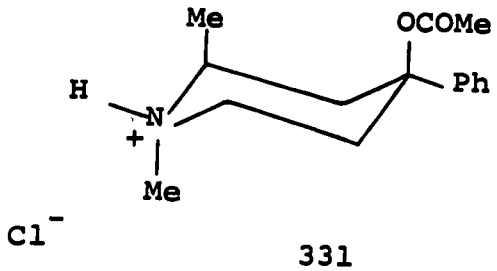
When the 2-methyl group is axial as in (330), a significant population of the conformers in which the OCOMe is directed over the aromatic ring and away from the sterically



330

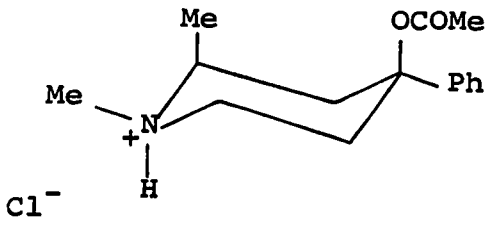
hindering 2-methyl group should arise. This may cause the 4-phenyl ring to adopt a preferred conformation parallel to the piperidine ring, thereby allowing the acetyloxy group to fall over the shielding zone of the phenyl ring. In accord with this the α-ester function had the higher field ester signal (Table XXVIII). The aromatic signal was more complex in both the base and hydrochloride in $CDCl_3$ which was evidence that this group has some conformational preference.

Epimeric conjugate acids were again observed in the α-acetyloxy compounds but not in the corresponding β-isomers. In this case, however, one form preponderated. The minor epimer was probably the result of equatorial protonation (331).



331

If this form adopts a skew boat conformation (as argued in the case of the corresponding epimer of the α-alcohol), the 2-methyl group will move away from OCOMe and no longer impede its passage over the piperidine ring. It is significant, therefore, that the OCOMe resonance of the minor epimer had a chemical shift close to that of the β-isomer (Table XXVIII). As well, the N-methyl and 2-methyl groups will be oriented pseudoequatorially, a condition that offers increased stability. The major isomer was then the result of axial protonation (332) and since there is less incentive for this



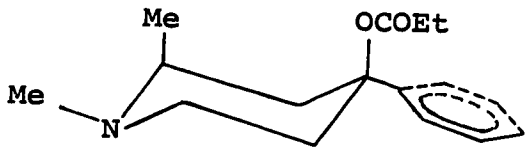
332

epimer to adopt a skew boat, because the N-methyl group is equatorial, the OCOMe group will be preferentially over the plane of the aromatic ring and hence will be significantly higher field.

The 2-methyl group PMR signal of the minor α-epimer (doublet at δ1.56) was found to have a chemical shift value very close to that of the β-2-methyl group (doublet at δ1.55). This was anticipated in view of the similar environment that the α-2-methyl group in a pseudoequatorial orientation will have to the β-2-methyl group in an equatorial position.

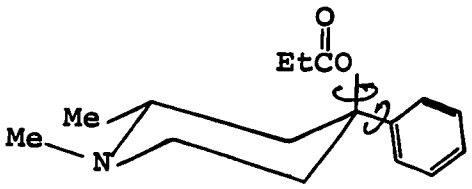
Similar arguments can be applied to the propionates of

α- and β-1,2-dimethyl-4-phenyl-4-piperidinol. In the case of the α-isomer, both the quartet and triplet of the ethyl ester were higher field than the corresponding signals of the propionate, in the base in $CDCl_3$. Therefore, the preferred conformation of the α-isomer appears to be (333).



333

The β-propionyloxy derivative lacks the steric interaction between the 2-Me and 4-OCOEt features and therefore its ester group protons came to resonance at lower field since they do not spend a proportionally large amount of time over the phenyl ring (which lacks a conformational preference as evidenced by a singlet for the 4-phenyl group in the PMR spectrum). Thus the β-propionate is shown in one of its momentary conformations of the aromatic and ester groups (334).



334

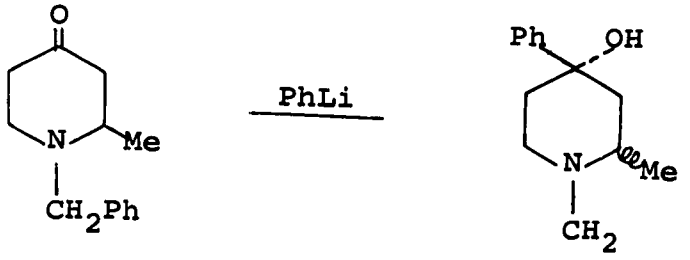
Epimer formation in the α-propionate hydrochloride in $CDCl_3$ makes the spectrum difficult to disentangle from the

secondary methyl signals; however, the same reasoning that applied to the acetate derivative is again appropriate. That is, the existence of a skew boat is probably due again to axial protonation because of the similarity of one of the ester signals to that of the β-propionate. In the case of the propionate, the epimeric proportions appeared to be more nearly equal, but this is difficult to ascertain due to signal overlap distortion.

N-BENZYL-2-METHYL-4-PHENYL-4-PIPERIDINOL

Earlier in this work (p. 94) it has been shown that the benzylic methylene protons would exhibit a pattern of non-equivalence when in a particular relationship to an adjacent methyl group. It was considered that this fact may be of some value in the assignment of the stereochemistry of the 2-methyl-4-piperidinol series.

N-benzyl-2-methyl-4-piperidone (105), previously prepared by two separate routes, was reacted with phenyllithium to yield N-benzyl-2-methyl-4-phenyl-4-piperidinol (335).

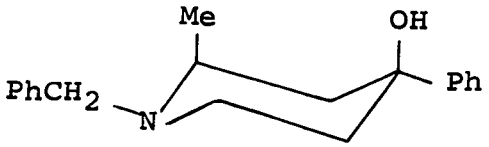


105 335

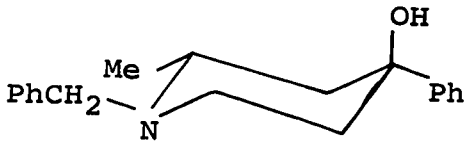
The PMR spectrum of the total free base in $CDCl_3$ displayed evidence of two isomers by duplicate 2-methyl signals

at δ1.27 and δ1.22 in a ratio of 2:1 respectively. As well, the benzylic methylene protons exhibited a multiplet consisting of a singlet at δ3.50 and an AB quartet with doublets at δ3.17 and δ3.97 (J=13.5 Hz).

The two possible isomers (336) and (337) which have a similar stereochemistry to that of the α- and β-1,2-dimethyl-4-phenyl-4-piperidinols described previously were expected



336



337

to exhibit similar benzylic methylene signals to those of the N-benzyl-2,5-dimethyl-4-piperidone also previously described (p. 94).

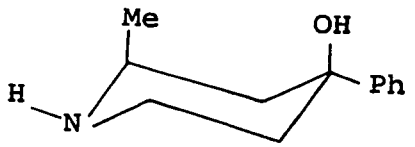
The trans 2-Me/4-Ph configuration shown in (336) possesses an axial 2-methyl group which will not interfere with the benzylic methylene protons, hence they appear as a singlet at δ3.50. In the cis 2-Me/4-Ph configuration (337), however, the methylene protons display non equivalence and appear as an AB quartet or pair of doublets at δ3.17 and δ3.97.

Fractional crystallization, as the hydrobromide salt, from ethanol/ether produced the isomer whose benzyl methylene protons displayed an AB quartet. As already mentioned this isomer was thought to have the cis 2-Me/4-Ph configuration (termed the β-form).

The α-isomer could not be obtained as a salt but was finally obtained by chromatography on a column, small, filled with Woelm neutral (activity 1) alumina. The base mixture of alcohols were eluted with chloroform. Five fractions were collected. The first fraction contained nearly pure α-N-benzyl-2-methyl-4-phenyl-4-piperidinol (336) as shown by a singlet at δ3.50 in the PMR spectrum for the benzyl methylene protons. Fractions two and three were composed of mixtures of the two isomers, while fractions four and five contained nearly pure β-N-benzyl-2-methyl-4-phenyl-4-piperidinol (337).

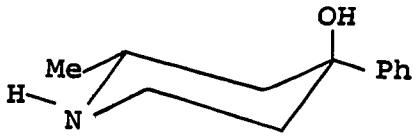
It was thought that if the N-benzyl group could be catalytically reduced to give the nor compound and then this methylated again, that the trans isomer would produce the trans 1,2-dimethyl-N-phenyl-4-piperidinol analogue, which, if previous assignments are correct, should have an equatorial 2-methyl orientation.

Hydrogenation of the trans isomer (336) with palladium charcoal at room temperature and pressure gave a product whose PMR spectrum ($CDCl_3$) indicated, by the lack of a singlet at δ3.50, that the trans 2-methyl-4-phenyl-4-piperidinol (338) had been produced.



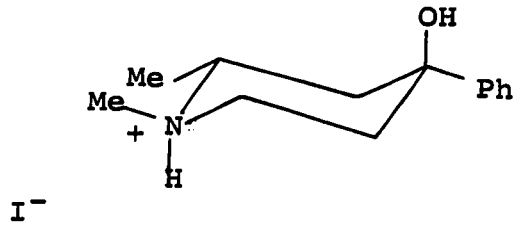
338

Subsequent debenzylation of the cis isomer (337) by the same technique produced a product whose PMR spectrum also indicated that the cis 2-methyl-4-phenyl-4-piperidinol (339) had been produced.



339

The cis isomer thus produced (339) was then reacted with one equivalent of methyl iodide in the hopes of obtaining monomethylation and hence the cis 1,2-dimethyl-4-phenyl-4-piperidinol (304) as the hydroiodide salt. Unfortunately the



304

PMR of the total product in DMSO-d_6 indicated that both monomethyl and dimethyl (the quaternary salt) and, presumably, some unreacted nor compound were present in the total product. The small sample available precluded fractional cyrstallization to prove that, in fact, the cis isomer had been produced.

The small quantities of the two N-benzyl-2-methyl-4-phenyl-4-piperidinol isomers prevented further study of the

inter-relationship to the N-methyl series, hence the sole evidence presented here concerning the benzylic methylene proton signals is the only proof to date of the stereochemistry of this series.

PHARMACOLOGICAL RESULTS AND DISCUSSION

The routine screening of some of the compounds prepared in this thesis for analgesic potency was carried out by Dr. E.L. May (Bethesda, Maryland) using the hot plate method.

There are limitation to this hot plate test, unfortunately, for although it offers a quick and convenient method for routine screening of analgesic compounds, it is relatively non-specific. The test does not distinguish between narcotic analgesics and other drugs which have a depressant action upon the central nervous system. The tranquillizing agent haloperidol, for example, has a lower hot plate ED_{50} value (0.84 mg./kg.) in mice than has pethidine (28.0 mg./kg.) as reported by Janssen and Jageneaueu (1956), and Janssen et al. (1959).

An empirical method of establishing whether a compound has morphine-like actions is to test the analogue in which the N-methyl group is replaced by an N-phenethyl function. Then, if the compound does in fact possess analgesic properties, this change should produce a pronounced increase in activity (Janssen and Eddy, 1959; Portoghese, 1965).

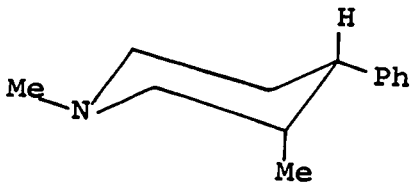
Therefore, with these limitations of the hot plate test in mind, a consideration of the pharmacological data available at the time of writing this thesis will now be made. All compounds were tested as the hydrochloride salts, but their structures are drawn in the following section as the base and with the piperidine ring in the chair form with the 4-phenyl group equatorial only as a convenience in

expressing the overall structure.

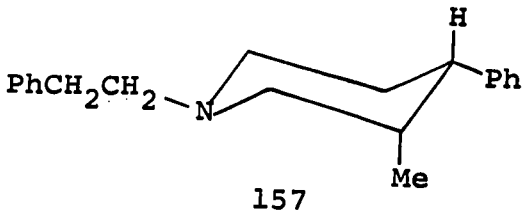
ANALOGUES OF PRODINE LACKING A 4-OXYGENATED FUNCTION:

Earlier it was shown that the diastereoisomeric forms of prodine have significant activity when tested by the hot plate method, and in all cases when the ester function was altered, the results indicated that the ethyl ester (prodine itself) is associated with the highest activity. Further it has been shown that the β-isomer was generally the more active. Also of interest is the fact that replacement of the N-methyl group by an N-phenethyl moiety resulted in an increase in potency (although in this series the methyl esters were shown to be more active than the ethyl ester derivatives) thus substantiating the morphine-like activity of the series (Beckett et al., 1959).

In the present study, therefore, N-methyl and N-phenethyl analogues of β-prodine were prepared, but now lacking the 4-oxygenated function. One of these derivatives, β-1,3-dimethyl-4-phenylpiperidine (141) was found to be half as active (ED_{50} 8.6 mg./kg.) as pethidine (ED_{50} 4.7 mg./kg.) when examined by the hot plate assay. However, when the β-N-phenethyl-3-methyl-4-phenyl-piperidine (157) was also



141



157

tested it was found to be inactive to 100 mg./kg. These results indicate, then, that the analogue (141) is not morphine-like in its action and may have a general C.N.S. depressant effect.

γ-PROMEDOL ANALOGUES:

The γ-isomer of 1,2,5-trimethyl-4-phenyl-4-propionyl-oxypiperidine (200) is used clinically in Russia under the

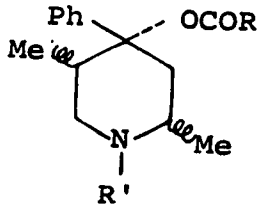
200

name promedol. It has been reported (Nazarov et al., 1956) as having twice the activity of morphine (unfortunately the exact method of analysis was not available, but the test animals were rats, a fact that may account for some differences), which is itself four times more active (ED_{50} 1.2 mg./kg., than pethidine when examined by the hot plate method (Jacobson and May, 1965).

In our studies (Table XXIX) the γ-promedol isomer was found to be just slightly less active than morphine and three times more active than pethidine. The acetyloxy derivative (194), although prepared by Nazarov et al. (1956), was not found to have been tested for analgesic potency by these workers.

194

TABLE XXIX. ANALGESIC ACTIVITY OF N-ALKYL-1,2,5-TRIMETHYL-4-PHENYL-4-ACETOXY (AND 4-PROPIONOXY)-PIPERIDINE HYDROCHLORIDES BY THE HOT PLATE METHOD (SUBCUTANEOUS INJECTION)



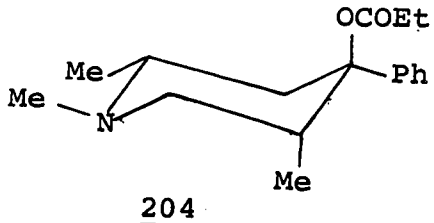
(HCl)

Isomer	R	R'	Pharmacological activity ED_{50} mg./kg.
γ	Me	Me	6.2
γ	Me	CH_2CH_2Ph	2.8
γ	Et	Me	1.6
γ	Et	CH_2CH_2Ph	0.9
β	Me	Me	0.8
β	Et	Me	0.2
α	Me	Me	2.6
α	Et	Me	0.6

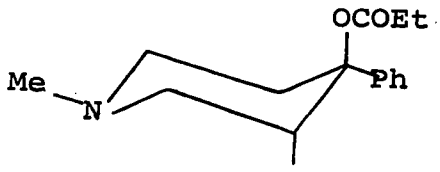
This acetyloxy analogue (194) showed a marked decrease in analgesic potency as compared to the propionyloxy form (200), a characteristic which has been found common to most analgesic series. Replacement of the N-methyl group by N-phenethyl resulted in in increase in potency (although the propionyloxy ester is again more potent than the acetyloxy derivative—a fact that is opposite to the findings of Beckett and coworkers (1959). These results provide good evidence that promedol is a morphine-like analgesic, that is, it interacts with the same receptor(s) as morphine. It therefore should be antagonized by nalorphine—this was not done in the present studies, nor could any references to this technique be found in the Russian literature available.

OTHER PROMEDOL SERIES ANALOGUES:

Referring to the β- and α-isomers of Table XXIX (the N-phenethyl analogues could not be prepared in this series), the two ester types are in very good agreement. In both series the potency ranking is: β>α>γ. Also, the propionyloxy esters are more potent than the acetyloxy, as was generally the case in N-methyl analgesic series. β-Promedol (isopromedol), which has been shown earlier to have the configuration and preferred conformation (204) is similar to that of β-prodine (36). It is significant, therefore, that the β-promedol isomer is equipotent with β-prodine (ED_{50} 0.2 mg./kg.), and about five times more active than α-prodine (ED_{50} 0.9 mg./kg.) in the same test.



204



36

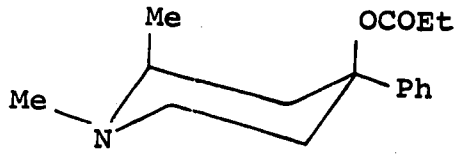
These results are in conflict with those reported by the Russian workers, Nazarov et al. (1954), who reported that in rats the α-promedol isomer as being the most potent, followed by the β- and finally the γ-forms (see earlier).

1,2-DIMETHYL-4-PHENYL-4-PIPERIDINOL ESTERS:

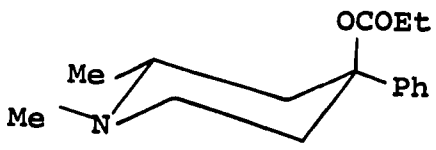
This series was originally planned as a hybrid between the 3-methyl prodine type analgesics and the 2,5-dimethyl promedol analogues.

The analgesic potency was determined, again by the hot plate method, and the results are tabulated in Table XXX.

The data in Table XXX appear to show a lack of sensitivity to the orientation of the 2-methyl group in the propionyloxy esters of α- (333) and β- (334) 1,3-dimethyl-4-phenyl-4-piperidinol. The analogues are shown here

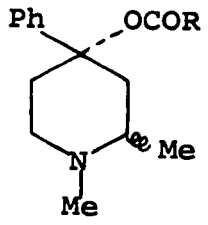


333



334

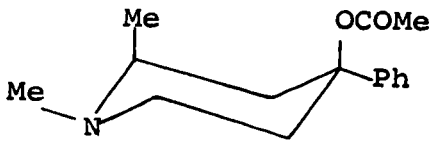
TABLE XXX. ANALGESIC ACTIVITY OF SOME ISOMERIC 1,2-DIMETHYL-4-PHENYL-4-ACETYLOXY (AND PROPIONYLOXY)-PIPERIDINES (AS HYDROCHLORIDES) BY THE HOT PLATE METHOD. (SUBCUTANEOUS INJECTION)



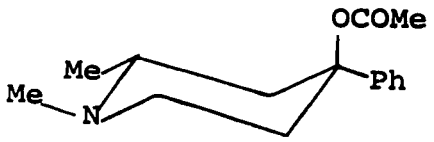
Isomer	R	Pharmacological Activity ED_{50} mg./kg.
α	OCOMe	2.4
β	OCOMe	4.9
α	OCOEt	1.3
β	OCOEt	1.4

in the chair form with the 4-phenyl group equatorial, but this was shown not to necessarily be the case when the salt is examined (see later).

The α- (330) and β- (329) acetyloxy esters (shown again



330



329

in the chair form) displayed some difference in activity, but both were significantly less potent than the propionate derivatives.

To ascertain that the 2-methyl group does enhance activity, therefore, it would be necessary to test the analgesic potency of the acetyloxy (326) and propionyloxy (340) derivatives of N-methyl-4-phenyl-4-piperidinol, a series which

326

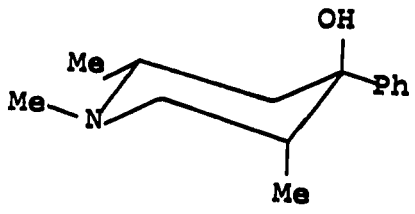
340

lacks any piperidine ring alkyl substitution, under the same conditions. Unfortunately data on the latter esters were not yet available at the time of writing this thesis.

ALCOHOL ANALOGUES:

In the promedol series the γ- (55) and β- (73) alcohols were tested for analgesic activity, with the finding that the relative activity as compared to the esters was very low.

55

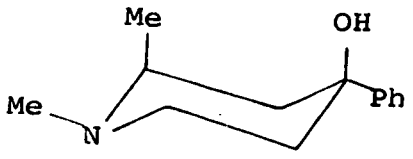


173

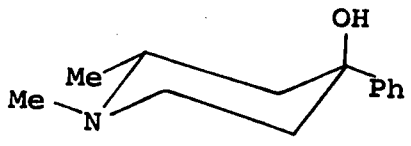
The γ-promedol alcohol had an ED_{50} of 56.3 mg./kg. while the β-form had an ED_{50} of 35.4 mg./kg. Shvetsov and Kucherov (1959) reported the β-isomer as being twice as active as the γ-form, which agrees roughly with the results obtained above. In the Russian paper the γ-promedol alcohol was claimed as being twice as active as morphine (test and animal not specified); however, this was certainly not found to be the case in the present assay, where the γ-form was found to be only one-fifth as active as morphine.

The anomalous results obtained between the two assays could certainly be attributed to the type of animal used and the test employed, for significant differences are found among analgesics which depend largely upon the animal used. A prime example of this is nalorphine (N-allyl morphine) which is an analgesic in man but is ineffective as an analgesic in dogs, rats, cats and rabbits in the tests used.

Turning then to the 1,2-dimethyl-4-phenyl-4-piperidinol series, both the α- (303) and β- (304) forms were found to be inactive to 100 mg./kg. in the hot plate test.



303



304

The far lower potency (or inactivity) of the 4-hydroxy derivatives as compared to the 4-propionyloxy analogues has

been a general finding for 4-phenyl-piperidine analgesics and strengthens the conclusion that the promedol esters have a morphine-like action.

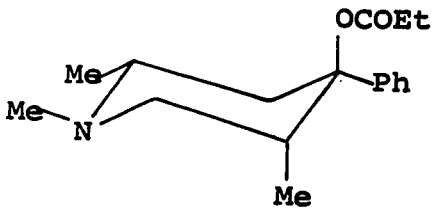
The question arises as to whether or not the results can be interpreted, in terms of differences between isomers of the prodine and promedol types, as an event that occurs at the receptor. If this is the case then it must be assumed that drug transport factors play only a secondary role.

In the case of the prodine isomers, preliminary results indicate that their potency differences might be related to differences in their ease of penetration of the C.N.S. Portoghese and Larson (1968) found that in rat's brain the levels of β-prodine exceeded those of α-prodine when both had been administered by the same route at equal dosage levels. In a more recent paper (Abdel-Monem et al., 1970), no significant differences were observed between brain concentration and injected dose (in mice) and it was concluded that analgesic potency differences between the isomers were due to differences in their affinity for the receptor and not due to distribution and metabolism differences.

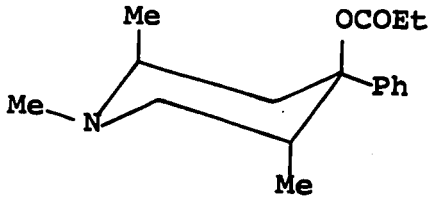
It is tentatively assumed, therefore, that the latter finding applies to all derivatives of 4-phenylpiperidines examined in this thesis since there is actually little gross difference between the basic structure of the various analogues, yet significant differences in activity between isomers is seen.

TENTATIVE STEREO-STRUCTURE-ACTIVITY CONSIDERATIONS

It has been shown earlier that a cis 3-Me/4-Ph geometry is superior for analgesic potency over those isomers possessing these groups in a trans relationship. This fact was supported by results on the prodine derivatives and later for the promedol series of isomers. In the latter case the two most active forms, β- (204) and α- (205), which are shown



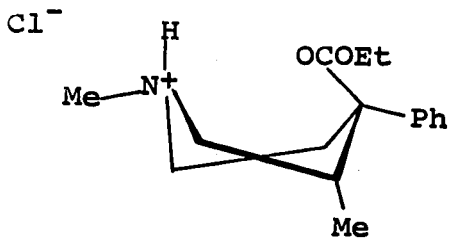
204



205

here in the chair conformation with the 4-phenyl equatorial, both have this cis 5-Me/4-Ph geometry.

In a previous paper, (Casy, 1968) it was argued that the preferred conformations of β-prodine hydrochloride and related compounds in polar solvents were skew boats (341).



341

It was postulated that conformations of this type represented an optimal arrangement of structural features in 4-phenylpiperidine analogues for association at the receptor (the

preferred conformation and the conformation at the receptor are not necessarily the same), and that derivatives which might have high skew boat populations may well be potent analgesics.

Thus the conformation of the promedol derivatives in D_2O may well be related to the likelihood of the skew boat form.

The γ-promedol acetate in D_2O will no doubt maintain the chair conformation since, as was shown earlier, any change from this form will result in less favourable orientations of all groups involved. Also, since the γ-isomer has the 5-Me/4-Ph trans it would be expected to be less active in view of the similarity to the less active trans 3-Me/4-Ph prodine isomer which also has been shown to maintain the chair conformation in D_2O.

The β-promedol acetyloxy derivative displays epimer formation for the hydrochloride in D_2O, and it has been argued that one of the epimers has a skew boat conformation (see earlier). This fact then serves to substantiate the expectation that high activity is associated with a skew boat conformation in a polar solvent.

It will be recognized, however, that the disposition of a skew boat form was observed for the salts of β-prodine and β-promedol derivatives and at physiological pH the drugs will have a significant concentration in the unionized basic form. However, the ability to form a skew boat in the salt does appear to be a factor associated with high activity.

The α-promedol acetate derivative (hydrochloride) in $CDCl_3$ has been shown earlier to have a preferred skew boat conformation. Therefore it is quite reasonable to conclude that in D_2O the same conformation will be present and, since the α-form also possesses high activity, the existence of a skew boat orientation is in fact anticipated in view of past experience.

The spectra of the propionate derivatives of α-, β-, and γ-isomers were more complex but similar conclusions can be proposed, in that significant skew boat populations in both the β- and α- esters are associated with high activity.

The role of the methyl substituent adjacent to the 4-carbon centre evidently plays a significant role in the mediation of analgesia either by

(i) its influence on conformation, or

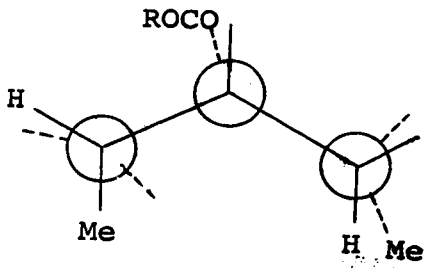
(ii) it may be important in its own right at the receptor surface.

Evidence for the latter factor is provided by the fact that α-1,2-dimethyl-4-phenyl-4-propionyloxypiperidine (333) is much less potent than both β-promedol and β-prodine. Evidence proposed earlier also points to the derivative (333) as having a preferred skew boat conformation, a condition that appears necessary for optimal activity. It is possible, though, that a detrimental influence by the 2-methyl group is responsible for the relatively low activity of this analogue.

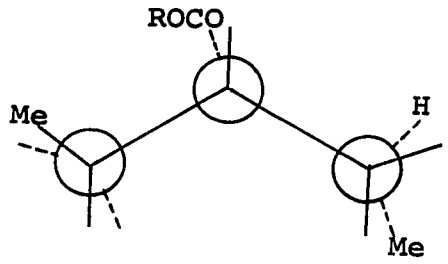
Therefore a consideration of the orientation of the

2-methyl group in both the promedol and 1,2-dimethyl series may provide a clue as to the effect on activity that the methyl group next to the nitrogen causes.

Taking the skew boat forms of α- and β-promedol, skewed in such a way that the 2- and 5-methyl groups move apart, it may be postulated, from experimental evidence, that the



β-promedol



α-promedol

orientation of the 2-methyl group in the β-isomer has little influence and drug-receptor uptake, since the activity is unchanged when this group is absent (β-prodine and β- promedol are equi-potent). The 2-methyl group orientation in the α-promedol isomer apparently is detrimental to drug-receptor uptake because the potency of α-promedol is <u>less</u> than that of either β-prodine or β-promedol.

A similar orientation of the 2-methyl group in α-1,2-dimethyl-4-phenyl-4-propionyloxypiperidine (<u>333</u>) is probable and in fact this analogue is decidedly less active than the β-prodine and β-promedol compounds. As mentioned previously, however, the effect of the 2-methyl group in this compound must be compared to an analogue lacking a piperidine ring substitutent altogether. Also the poor activity could also be due to the absence of a methyl group adjacent to the C-4

centre.

The chair conformations of α-prodine, γ-promedol and β-1,2-dimethyl-4-phenyl-4-propionyloxypiperidine are all associated with low activity; hence it is tentatively concluded, in the light of these limited observations, that an equatorial 2-methyl group has a detrimental influence on drug receptor uptake.

The higher activity associated with the α-1,2-dimethyl-4-phenyl-4-acetyloxypiperidine over that of the β-form, while the propionyloxy derivatives appear to be equally potent, can only be explained by assuming that the α- (skew boat) isomer has a better drug receptor uptake. In the light of past evidence no rationale for this fact is immediately apparent.

Unfortunately, analgesic potency results on α-promedol alcohol and the three isomeric promedol 4-H analogues was not yet available at the time of writing this thesis. Also absent are the activities of the isomers of 1,2-dimethyl-4-phenylpiperidine (4-H) analogues.

EXPERIMENTAL

EXPERIMENTAL

All melting points were measured on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman Infrared Spectrophotometer Model 10-A. PMR spectra were determined on a Varian Associates Model A-60D or HA-100 spectrometer. Elemental analyses were carried out by the microanalytical laboratories of the Department of Chemistry or by the Faculty of Pharmacy, University of Alberta. Equivalent weights were determined by non aqueous titration of the base compounds with acetous perchloric acid, using Oracet Blue B as an indicator. Dried solvents were distilled from lime and stored over type 4A molecular sieves or were dehydrated with freshly pressed sodium wire. Commercial chemicals were not further purified unless otherwise specified.

4-PIPERIDONE SYNTHESIS

(2-CARBOMETHOXY-n-PROPYL)-METHYLAMINE

A solution of methyl methacrylate (344 g.; 3.4 mole) in absolute methanol (200 ml.) was added slowly with stirring to a cooled solution of 33% methylamine (319 g.; 3.4 mole) in absolute methanol (200 ml.) over a period of three hours. After standing three days the methanol was evaporated and the product fractionally distilled under reduced pressure to give the title compound (225 g.; 52%) as a colourless mobile oil, b.p. 68 - 70°/20 mm. (Howton, 1945, reported b.p. 48.8 - 49.5°/8 mm.)

IR spectrum (film):

νmax 1740 (C=O str.), 3340 (NH str.) cm^{-1}

Anal. calcd. for $C_6H_{13}NO_2$ C,54.94; H,9.98

Found: C,55.10; H,10.23

(2-CARBOMETHOXYETHYL)-(2-CARBOMETHOXY-n-PROPYL)-METHYLAMINE

(2-Carbomethoxy-n-propyl)-methylamine (225 g.; 1.75 mole) was added in one lot to methyl acrylate (150 g.; 1.75 mole) and the mixture left for ten days. The resulting amber liquid was fractionally distilled to give the title compound (270 g.; 80%) b.p. 90 - 93°/2 mm. (Howton, 1945, reported b.p. 105 - 107°/2 mm.)

IR spectrum (film):

νmax 1740 (C=O str.), NH band (3340 cm^{-1}) disappeared

Anal. calcd. for $C_{10}H_{19}NO_4$ C,55.27; H,8.81

Found: C,55.10; H,8.76

It gave a picrate from ethanol which melted at 88 - 89° (Howton, 1945, reported m.p. 88.4 - 89°)

1,3-DIMETHYL-4-PIPERIDONE (65)

(2-Carbomethoxyethyl)-(2-carbomethoxy-n-propyl)-methylamine (110 g.; 0.51 mole) was added to a stirred solution of sodium sand (14.; 0.61 mole) in xylene (200 ml.) warmed gently to about 50°. Reaction started after about 30 g. of the diester had been added, at which time the addition was stopped until the reaction began to subside. The addition was then resumed at a rate sufficient to maintain gentle reflux; when all the diester had been added the red mixture was refluxed for four hours. The resulting product was cooled and added gently with stirring to 20% aqueous hydrochloric acid (200 ml.), during which time CO_2 evolution began. One drop of this solution gave a dark red colour with 2% ethanolic ferric chloride solution. After 2 hours reflux the evolution of CO_2 became negligible and a negative result was obtained with ferric chloride solution. The aqueous phase was evaporated to small bulk (until NaCl started to separate) and made alkaline with solid sodium hydroxide, sufficient water was added to effect complete solution and then the mixture was continuously extracted with chloroform for 12 hours. The $CHCl_3$ was dried ($NaSO_4$) and evaporated and the residue fractionally distilled

to give the title compound (32 g.; 46%) as an oil b.p. 79 - 82°/25 mm. (Howton, 1945, reported b.p. 43 - 43.4°/ 5.5 mm.)

It formed a hydrochloride from ethanol-ether which melted at 195° (reported m.p. 194.9-195.3°).

It also gave a methiodide from acetone which melted at 182-183° (Hassan and Casy, 1969, reported 184-185°).
Anal. Calcd. for $C_8H_{16}INO$ C,35.71; H,5.99.
Found: C,36.11; H,6.19

ALTERNATE PREPARATION OF 1,3-DIMETHYL-4-PIPERIDONE (65)

(2-Carbomethoxy-n-propyl)-(2-carbomethoxyethyl)-methylamine (150 g.; 0.69 mole) was added dropwise to a stirred suspension of sodium hydride (61% emulsion; 3.0 g.; 0.71 mole) in dry xylene (200 ml.). After the initial vigorous reaction had subsided the mixture was refluxed for 3 hours and then cooled and poured onto 20% hydrochloric acid (300 ml.). The product, after decarboxylation was complete, was treated as before and then fractionally distilled to give: 1,3-dimethyl-4-piperidone (42 g.; 42%) b.p. 76-79°/20 mm. The IR was identical with the previous sample of the same compound.

ALTERNATIVE PREPARATION OF 1,3-DIMETHYL-4-PIPERIDONE (65)

Dimethylsulfoxide was distilled from calcium hydroxide, b.p. 84°/18 mm. (Bloomfield, 1961), and used as a solvent in the cyclization of the previously prepared diester (100 g.; 0.41 mole) which was added dropwise with stirring to a warm

suspension of benzene-washed sodium hydride (10 g.; 0.42 mole) in 100 ml. of the above dried dimethylsulfoxide. When all the diester had been added the mixture was refluxed until the evolution of hydrogen ceased (6 hr.). The bulk of the solvent was removed on a rotary evaporator and then 20% hydrochloric acid (150 ml.) was added cautiously and the mixture refluxed overnight. The aqueous phase was removed at low pressure until a solid started to separate. Solid sodium hydroxide was added to basify the mixture and then it was extracted with 5 × 100 ml. of $CHCl_3$. The $CHCl_3$ was dried (Na_2SO_4) and evaporated. The residue was fractionally distilled under vacuum to yield 1,3-dimethyl-4-piperidone (18 g.; 35%), b.p. 80-82°/22 mm. The infrared spectrum was identical to the ketone prepared earlier.

ALTERNATE PREPARATION OF 1,3-DIMETHYL-4-PIPERIDONE (65)

(21.7 g.; .1 mole) of the diester was added slowly from a dropping funnel to sodium amide (4.9 g.; 0.11 mole) suspended in toluene (100 ml). Ammonia was noticed coming from the top of the condensor. When the addition was complete the mixture was refluxed for 6 hours at which time the evolution of ammonia was found to be very slight. The total mixture was poured cautiously onto 20% hydrochloric acid (100 ml.) and the aqueous layer refluxed 4 hours, after which time a negative ferric chloride test was obtained. The mixture was carefully made alkaline with solid sodium hydroxide and the base extracted with chloroform (4 × 100 ml.). The $CHCl_3$ was

dried (Na_2SO_4) and evaporated and the residue distilled to give the title compound (2.5 g.; 20%) as an oil b.p. 76-79°/23 mm. The IR spectrum was identical to previous samples of the same compound.

ALTERNATE METHOD TO PRODUCE 1,3-DIMETHYL-4-PIPERIDONE (65)

Sodium (5.1 g.; 0.22 mole) was added to anhydrous methanol (200 ml.) and allowed to react completely. Then the excess methanol was removed and the resulting sodium methoxide suspended in toluene (150 ml.). This mixture was warmed to about 60° and then (2-carbomethoxy-n-propyl)-(2-carbomethoxyethyl)-methylamine (43.4 g.; 0.2 mole) was added slowly from a dropping funnel. When all the diester had been added the mixture was poured onto 20% hydrochloric acid (200 ml.). The aqueous layer was separated and refluxed for 6 hours, after which time a negative test with ferric chloride solution was obtained. The mixture was then basified cautiously with sodium hydroxide and extracted with $CHCl_3$ (4 × 150 ml.). The $CHCl_3$ was dried (Na_2SO_4) and evaporated, and the residue distilled to give the title compound (7.6 g.; 30%) as an oil b.p. 76-78°/20 mm. The IR spectrum was identical to the same compound prepared previously.

ALTERNATE METHOD TO PRODUCE 1,3-DIMETHYL-4-PIPERIDONE (65)

Sodium (12.5 g.; 0.54 mole) was added to rapidly stirring liquid ammonia (approx. 400 ml.) in a three necked flask suspended in a dry ice and acetone bath and fitted

with a dry ice and acetone condenser. To the resulting blue solution was added dropwise, from a pressure equalizing funnel, (2-carbomethoxy-n-propyl)-(2-carbomethoxy-ethyl)-methylamine (108 g.; 0.50 mole). After the blue colour of the sodium ammonia solution was discharged the mixture was stirred for an additional two hours. The condenser and cooling bath were removed and the ammonia allowed to evaporate overnight. The resulting semisolid mass was diluted with ether (200 ml.) and refluxed without a condensor to remove the residual ammonia and allow the ether to evaporate. To this mixture was then added 20% hydrochloric acid (375 ml.) and the solution refluxed 3 hours until carbon dioxide evolution ceased. The aqueous layer was evaporated under reduced pressure until a solid began to separate; the mixture basified with ammonium hydroxide solution and the free base extracted with 5 × 100 ml. $CHCl_3$. The $CHCl_3$ was dried (Na_2SO_4) and evaporated and the residue distilled to yield 1,3-dimethyl-4-piperidone (30 g.; 47%) b.p. 60=62°/16 mm.

The IR proved identical with that produced earlier (Mistryokov et al., 1961, gave b.p. 62-64°/12 mm.).

MONOETHYL-2-ALLYLMALONATE

Diethyl malonate (120 g.; 0.75 mole) was added dropwise, with stirring to a warm solution of sodium ethoxide prepared by dissolving sodium (17.3 g.; 0.75 mole) in absolute ethanol (250 ml.). The resulting solution was cooled, allyl bromide (106 g.; 0.88 mole) added slowly from a dropping funnel and

then the mixture was refluxed 3 hours. After cooling a solution consisting of potassium hydroxide (42.5 g.; 0.76 mole) in absolute alcohol (300 ml.) was added in one lot and the mixture left to sit overnight at room temperature. The alcohol was removed by distillation and the residue dissolved in water and washed with ether (2 × 50 ml.) and then acidified with concentrated hydrochloric acid. The oil which separated was washed with water and extracted with ether (3 × 100 ml.). After drying (Na_2SO_4) the ether was removed at reduced pressure to give crude 2-allyl derivative of ethyl malonic acid (60 g.; 47%).

IR spectrum (film):

νmax 1720 (acid C=O str.), 1750 (ester C=O str.), 3340 (OH str.) cm^{-1}.

The crude material was not analyzed but the PMR spectrum displayed a complex multiplet between δ6.2 and δ4.8 which was indicative of the allyl function. A triplet at δ1.28 and a quartet at δ4.20 which integrated for approximately 3 and 2 protons respectively gave evidence of the monoethyl ester, and as well, a singlet at δ3.42, which disappeared upon the addition of D_2O, substantiated that an acid function was also present. The crude material was therefore used in the next step.

ETHYL α-ALLYLACRYLATE

The monoethyl ester of 2-allyl malonic acid (60 g.; 0.35 mole) was cooled in ice and neutralized by the addition of

diethylamine (25.6 g.; 0.35 mole). Then aqueous 37% formaldehyde (46 ml.; 0.35 mole) was added slowly from a dropping funnel. Carbon dioxide was evolved, and after 12 hours, without stirring, two layers had formed. The lower layer was saturated with anhydrous potassium carbonate, the upper layer separated, washed with dilute hydrochloric acid and extracted with ether (3 × 100 ml.). After drying (Na_2SO_4) the ether was evaporated and the residue distilled to give ethyl-α-allylacrylate (30 g.; 61%) b.p. 60-68°/20 mm. (Mannich and Ritsert, 1924, reported b.p. 60°/16 mm.)

IR spectrum (film):

νmax. 1720 (C=O str.), 1635 (C=C str.) cm^{-1}.

PMR spectrum ($CDCl_3$):

Broad singlet at δ6.21 integrated for 2 protons which was not present in the starting material was thus due to the vinylic methylene protons. OH absorption at δ3.42 absent.

Anal. Calcd. for $C_8H_{12}O_2$ C,68.54; H,8.63.

Found: C,68.40; H,8.52.

(2-CARBOETHOXY-n-PENT-4-ENYL)-METHYLAMINE

Mono ethyl α-allylacrylate (30 g.; 0.21 mole) was added, dropwise, with stirring to a 33% solution of methylamine (20 g.; 0.21 mole) in absolute ethanol (100 ml.) and refluxed gently for 12 hours. The ethanol was removed under reduced pressure and the residue distilled to give the title compound (21 g.; 59%) b.p. 90-95°/20 mm. (Ziering *et al.*, 1957, reported 105-110°/30 mm.)

IR spectrum (film):

νmax 1740 (C=O str.), 3340 (NH str.) cm^{-1}.

PMR spectrum ($CDCl_3$):

δ2.42 (N-Me singlet).

It gave a hydrochloride from ethanol-ether, m.p. 98-99°.

Anal. calcd. for $C_9H_{17}NO_2 \cdot HCl$ C,52.04; H,8.73; N,6.74.

Found: C,52.06; H,8.54; N,6.64.

(2-CARBOETHOXY-4-PENTENYL)-(2-CARBOETHOXYETHYL)-METHYLAMINE (79)

Ethyl-2-allyl-3-methylaminopropionate (21 g.; 0.12 mole) was added to ethyl acrylate (36 g.; 0.36 mole) in absolute ethanol (100 ml.) and refluxed for 48 hours. The ethanol and unreacted ethyl acrylate were removed at reduced pressure and the residue fractionally distilled to yield the title compound (15 g.; 46%), b.p. 118-120°/0.5 mm. (Ziering, 1957, reported b.p. 141-144°/4 mm.)

IR spectrum (film):

νmax 1740 cm^{-1} (C=O str.), no NH str. band (3340 cm^{-1}).

Anal. calcd. for $C_{14}H_{25}NO_4$ C,61.97; H,9.29; N,5.16.

Found: C,62.00; H,9.18; N,5.32.

ATTEMPTED PREPARATION N-METHYL-3-ALLYL-4-PIPERIDONE (81)

(2-Carboethoxy-4-pentenyl)-(2-carboethoxyethyl)-methylamine (15 g.; 0.055 mole) was added, slowly from a dropping funnel, to sodium sand (1.4 g.; 0.061 mole) in dry xylene (50 ml.). When the addition was complete the mixture was refluxed for 12 hours at which time it was poured onto 20%

hydrochloric acid (100 ml.). The aqueous phase was separated and refluxed for 12 hours. The solvent was removed under pressure and the residue dissolved in a minimum volume of water, basified with solid sodium hydroxide, and extracted with chloroform (2 × 100 ml.). The chloroform was dried (Na_2SO_4) and evaporated to a solid residue (0.5 g.), m.p. 98-100°. This proved not to be the expected title compound but a hemiacetal: 2,5-dimethyl tetrahydrofuro(2,3-c)piperidin-7a-ol, m.p. 97-98° (McElvain, 1956, gave m.p. 95-96°).

IR spectrum (nujol mull):

νmax 3110 cm^{-1} (OH str.); 1080 cm^{-1} (COC str.), no absorption in the carbonyl region.

Anal. calcd. for $C_9H_{17}NO_2$ C,63.12; H,10.01; N,8.18.

Found: C,62.95; H,9.85; N,8.43.

It gave a methiodide from acetone, m.p. 177-180° (McElvain, 1956, gave m.p. 176-179°).

ALLYLDIMETHYLANILINIUM BROMIDE (70)

Allylbromide (121 g.; 1 mole) in ethyl acetate (100 ml.) was mixed with N,N-dimethylaniline (121 g.; 1 mole) and allowed to sit overnight. The title compound crystallized out as fine plates (200 g.), m.p. 126-127°. (Tarbell and Vaughan, 1943, gave m.p. 126-127°)

N-METHYL-3-ALLYL-3-CARBOMETHOXY-4-PIPERIDONE (80)

N-methyl-3-carbomethoxy-4-piperidone (supplied by Smith, Kline and French Laboratories, Philadelphia) (24 g.; 0.14 mole)

in dry benzene (100 ml.) was added dropwise to a stirred suspension of sodium amide (5.5 g.; 0.142 mole) in dry benzene (100 ml.), protected from moisture. When the addition was complete the mixture was refluxed for 4 hours, cooled to room temperature, and allyldimethylanilinium bromide (34 g.; 0.14 mole) added in one lot. The resulting mixture was refluxed and stirred with an overhead mercury sealed stirring apparatus for 48 hours, cooled, and added to water (100 ml.). The benzene layer was separated, washed with water (4 × 100 ml.), and dried (Na_2SO_4). The solvent was evaporated and the residue fractionally distilled under reduced pressure to give dimethylaniline, b.p. 90-93°/25 mm. as the first fraction and then N-methyl-3-allyl-3-carbomethoxy-4-piperidone (16.5 g.; 56%), b.p. 95-97°/1.8 mm. (McElvain and Barnett, 1956, reported b.p. 85-105°/.25 mm.)

IR spectrum (film):

νmax 1720 (ketone C=O str.), 1740 (ester C=O str.) cm^{-1}.

The compound was not analyzed but used directly in the next step.

ATTEMPTED PREPARATION N-METHYL-3-ALLYL-4-PIPERIDONE (81)

N-methyl-3-allyl-3-carbomethoxy-4-piperidone (16.5 g.; 0.078 mole) was added to 20% hydrochloric acid (100 ml.) and refluxed for 12 hours. The aqueous phase was removed and the solid residue dissolved in a minimum volume of water, basified with strong ammonium hydroxide solution, extracted with $CHCl_3$ (3 × 100 ml.). The $CHCl_3$ was dried (Na_2SO_4) and

evaporated to leave a solid which proved identical with the hemiacetal, 2,5-dimethyl tetrahydrofuro (3,2c) piperidin-7a-ol, previously isolated, and had a m.p. and mixed m.p. of 98-100°.

(2-CARBOMETHOXY-n-PROPYL)-BENZYLAMINE

Methyl methacrylate (500 g.; 5 mole) in absolute methanol (200 ml.) was slowly added from a dropping funnel to benzylamine (428 g.; 4 mole) in absolute methanol (200 ml.), and the mixture allowed to set 60 days at room temperature. The ethanol and unreacted methyl methacrylate was removed at reduced pressure and the residue fractionally distilled to give the title compound (828 g.; 90%), b.p. 166-168°/20 mm. (Carabateas, 1962, reported b.p. 150-155°/17 mm.)

IR spectrum (film):

νmax. 1740 (C=O str.), 3340 (NH str.) cm^{-1}.

Anal. Calcd. for $C_{12}H_{17}HO_2$ C,59.13; H,7.44.

Found: C,59.04; H,7.18.

(2-CARBOMETHOXYETHYL)-(2-CARBOMETHOXY-n-PROPYL)-BENZYLAMINE

(2-Carbomethoxy-n-propyl)-benzylamine (725 g.; 3.5 mole) was added to methyl acrylate (450 g.; 5.25 mole) and gently refluxed for 26 hours. The unreacted methylacrylate was removed at reduced pressure and the total crude material reserved. This diester could not be distilled at 0.5 mm. without decomposition therefore the crude material was used. The PMR spectrum indicated that all the acrylate was removed.

(Carabatias, 1962, gives 140-145°/0.3 mm.) Yield (730 g.; 72%).

IR spectrum (film):

νmax. 1740 cm^{-1} (C=O str.), NH band (3340 cm^{-1}) absent.

Anal. Calcd. for $C_{16}H_{23}NO_4$ C,65.51; H,7.90.

Found: C,65.70; H,7.65.

Therefore the crude material from the reaction is sufficiently pure without distillation.

N-BENZYL-3-CARBOMETHOXY-5-METHYL-4-PIPERIDONE (93)

The (2-carbomethoxymethyl)-(2-carboethoxy-n-propyl)-benzylamine (170 g.; 0.58 mole) was added dropwise to a suspension of sodium methoxide in xylene (200 ml.) prepared by dissolving sodium (14.1 g.; 0.61 mole) in absolute methanol (200 ml.) and then removing the methanol at reduced pressure. When about 25 g. of the diester had been added, the reaction began, and the addition of the diester was then continued at a sufficient rate to maintain reflux. When all the diester had been added, the mixture was refluxed for 4 hours, cooled to room temperature and poured onto 20% hydrochloric acid (400 ml.). The fluffy white solide which separated was collected, washed with ether (3 × 300 ml.) and dried to give the title compound (130 g.; 89%) as the hydrochloride, m.p. 188-189°.

IR spectrum (film of base):

νmax. 1670,1725,1755 (C=O str., tautomeric forms), 1625 (C=C str.) cm^{-1}.

PMR spectrum (base in $CDCl_3$):

δ0.98 (secondary 5-methyl), δ1.16 (secondary 5-methyl) (see p. 73).

Anal. calcd. for $C_{15}H_{19}NO_3$ C,68.94; H,7.33.

Found: C,69.19; H,7.10.

N-BENZYL-3-METHYL-4-PIPERIDONE (88)

The N-benzyl-3-carbomethoxy-5-methyl-4-piperidone isolated from the last step was suspended in concentrated hydrochloric acid (800 ml.) and the mixture refluxed vigorously for 24 hours. After 3 hours the N-benzyl-3-carbomethoxy-5-methyl-4-piperidone had completely dissolved and carbon dioxide was being slowly evolved. After the 24 hour reflux period a negative test ferric chloride solution indicated that decarboxylation was essentially complete. The aqueous layer was reduced in volume at low pressure, solid NaOH was cautiously added until the solution became basic to litmus. The free base was extracted with $CHCl_3$ (10 × 100 ml.), the $CHCl_3$ dried (Na_2SO_4) and evaporated. The residue remaining was fractionally distilled under vacuum to yield the title compound (230 g.; 61%), b.p. 130-132°/1.2 mm. (Carabatias et al., 1962, reported b.p. 110-115°/0.3 mm.)

IR spectrum (film):

νmax. 1725 cm^{-1} (C=O str.).

Anal. calcd. for $C_{13}H_{17}NO$ C,76.81; H,8.43.

Found: C,76.73; H,8.11.

(2-CARBOMETHOXY-n-PROPYL)-PHENETHYLAMINE (101)

Methyl methacrylate (2.6 g.; 2.16 mole) in absolute methanol (400 ml.) was added all at once to 2-phenethylamine (262 g.; 2.16 mole) in absolute methanol (400 ml.) and the mixture set aside for three months at room temperature. The methanol was removed under reduced pressure and the residue distilled to give the title compound (311 g.; 68%), b.p. 130-134°/2 mm. (Beckett et al., 1959, reported b.p. 116-118°/0.6 mm.)

IR spectrum (film):

νmax. 1740 (C=O str.), 3340 (NH str.) cm^{-1}.

Equiv. calcd. for $C_{16}H_{19}NO_2$ 221.3.

Found: 222.

It gave a picrate from ethanol, m.p. 95-96° (Beckett et al. reported m.p. 96.5°).

(2-CARBOMETHOXY-n-PROPYL)-(2-CARBOMETHOXYETHYL)-PHENETHYLAMINE (102)

(2-Carbomethoxy-n-propyl)-phenethylamine (310 g.; 1.4 mole) was added to methyl acrylate (172 g.; 2 mole) and the mixture refluxed for 8 days. The unreacted methyl acrylate was removed under reduced pressure, and the residue fractionally distilled under vacuum to give the title compound (400 g.; 93%), b.p. 174-175°/1.5 mm. (Beckett et al. gave 155-157°/.25 mm.)

IR spectrum (film):

νC=O 1725 cm^{-1}. Virtually no N-H stretching.

Equiv. calcd. for $C_{17}H_{25}NO_4$ 307.4.

Found: 309.

The product was not further purified but used directly in the cyclization step.

ATTEMPTED PREPARATION OF (2-CARBOMETHOXY-n-PROPYL)-(2-CARBOMETHOXYETHYL)-PHENETHYLAMINE (102)

(2-Carbomethoxy-n-propyl)-phenethylamine (158 g.; 0.715 mole) was added to methyl acrylate (74 g.; 0.86 mole) and heated without a solvent in an autoclave at 850 lbs./sq.in. in a nitrogen atmosphere at 105° for 6 hours. (Pressure went from 600 lbs./sq.in. at 25° to 850 lbs./sq.in. after heating to 105°.) The product was then fractionally distilled under vacuum; however, only the starting materials could be recovered.

N-PHENETHYL-3-METHYL-4-PIPERIDONE (103)

(2-Carbomethoxy-n-propyl)-(2-carbomethoxyethyl)-phenethylamine (46 g.; 0.15 mole) was added dropwise to a stirred suspension of sodium sand (3.71 g.; 0.16 mole) in dry toluene (200 ml.). When all the diester had been added the mixture was refluxed 12 hours, by which time all the sodium had disappeared. The product was cooled and poured onto water (100 ml.) and acidified with concentrated hydrochloric acid and then refluxed for 10 hours, after which time a negative test was obtained with ferric chloride solution. The bulk of the water was removed at reduced pressure until a solid began to separate. The mixture was cautiously basified with strong ammonium hydroxide solution, and extracted with $CHCl_3$

(5 × 100 ml.). The $CHCl_3$ was dried (Na_2SO_4) and evaporated and the residue fractionally distilled under vacuum to give the title compound (10 g.; 31%), b.p. 138-141°/1 mm. (Beckett et al., 1959, reported b.p. 123-125°/0.3 mm.)

It gave a picrate from ethanol which melted at 174-174.5° (Beckett et al., 1959, reported m.p. 169.5-170.5°).

It also gave a hydrochloride from ethanol-ether, m.p. 171-172° (decomposition) (Beckett, 1960, reported m.p. 171-172°).

IR spectrum HCl (nujol mull):

νmax. 1735 cm^{-1} (C=O str.).

Anal. calcd. for $C_{14}H_{19}NO \cdot HCl$ C,66.26; H,7.94; N,5.52.

Found: C,66.33; H,7.99; N,5.72.

ALTERNATE PREPARATION OF N-PHENETHYL-3-METHYL-4-PIPERIDONE (103)

1,3-Dimethyl-4-piperidone methiodide (10 g.; 0.037 mole), prepared earlier, was added to 2-phenethylamine (4.5 g; 0.037 mole) in water (4.7 ml.; 0.27 mole), mixed well to effect solution, and then allowed to sit overnight. The oil which separated was extracted with ether (3 × 100 ml.), washed with water (2 × 50 ml.), and then dried (Na_2SO_4). The ether was then evaporated and the residue fractionally distilled to give the title compound (4.5 g.), b.p. 122-125°/0.4 mm. The IR and PMR spectra showed this to be identical with that prepared earlier.

N-BENZYL-2,5-DIMETHYL-4-PIPERIDONE (126)

1,2,5-Trimethyl-4-piperidone methiodide (56.7 g.; 0.2 mole), prepared by refluxing the ketone (kindly supplied by Dr. N.S. Prostakov) with excess methyl iodide in acetone, was added to benzylamine (20.8 g.; 0.2 mole) in water (20 ml.; 1.1 mole) and shaken until solution was complete. The mixture was then allowed to stand overnight; the next day an oily layer had separated. The reaction was diluted with ether, the ether separated, dried and evaporated. The residue was fractionally distilled under vacuum to give two fractions: b.p. 117-123°/0.5 mm. (10 g.), and b.p. 123-126°/0.5 mm. (21 g.). The IR showed them to be identical, therefore they were bulked (Mistryukov et al., 1961, reported 112-117°/1 mm.).
Anal. calcd. for $C_{14}H_{19}NO$ C,77.43; H,8.82.
Found: C,77.73; H,8.52.

ATTEMPTED PREPARATION N-BENZYL-2,5-DIMETHYL-4-PIPERIDONE (126)

1,2,5-Trimethyl-4-piperidone methiodide (5.7 g.; 0.02 mole) was added to benzylamine (2.1 g.; 0.02 mole) in water (0.36 ml.; 0.02 mole) and shaken until solution was complete. The mixture was allowed to stand overnight, then diluted with ether and a solid separated. Neither the ether layer nor the solid which separated proved to be the desired compound, and it was tentatively identified as a complex mixture of the open chain alkene plus unreacted starting materials.

N-PHENETHYL-2,5-DIMETHYL-4-PIPERIDONE (129)

1,2,5-Trimethyl-4-piperidone methiodide (28.3 g.; 0.1 mole) was added to 2-phenethylamine (12.1 g.; 0.1 mole), mixed well to effect solution, and then let stand overnight. A solid separated (10 g.) which was separated and recrystallized from ligroin m.p. 73.5-74°.

IR spectrum (nujol):

νmax. 1715 (C=O str.), 1600 (C=C str.), 690,750 (mono subs. benzene) cm^{-1}.

Anal. calcd. for $C_{15}H_{21}NO$ C,77.85; H,9.15.

Found: C,77.87; H,8.97.

(2-CARBOMETHOXYISOPROPYL)-METHYLAMINE

Methyl crotonate (212 g.; 2.12 mole) was slowly added from a dropping funnel to a stirred solution of 33% methylamine (200 ml.; 2.12 mole) in absolute ethanol (200 ml.). After the addition was complete the mixture was refluxed 8 hours. The ethanol was removed under reduced pressure and the residue fractionally distilled under vacuum to yield the title compound (200 g.; 74%), b.p. 64-66°/16 mm. (Morsch, 1932, gave 64-66°/10 mm.)

IR spectrum (film):

νmax. 1740 (C=O str.), 3350 (NH str.) cm^{-1}.

Anal. calcd. for $C_6H_{13}NO_2$ C,54.94; H,9.99.

Found: C,54.87; H,9.83.

(2-CARBOMETHOXYETHYL)-(2-CARBOMETHOXYISOPROPYL)-METHYLAMINE

(2-Carbomethoxyisopropyl)-methylamine (200 g.; 1.53 mole) was added to methyl acrylate (172 g.; 2.00 mole) and the mixture allowed to stand at room temperature for 10 days. The unreacted methyl acrylate was removed under reduced pressure and the residue fractionally distilled under vacuum to give the title compound (223 g.; 67.3%), b.p. 97-99°/0.07 mm. (Mistryukov and Aronova, 1966, reported b.p. 127-130°/6 mm.)
IR spectrum (film):
νmax. 1740 cm^{-1} (C=O str.), no NH band (3340 cm^{-1}).

It gave a methyliodide from acetone m.p. 131-132°.
Anal. calcd. for $C_{11}H_{22}INO_4$ C,36.78; H,6.17; N,3.90.
Found: C,36.71; H,6.39; N,3.97.

1,2-DIMETHYL-4-PIPERIDONE (90)

(2-Carbomethoxyethyl)-(2-carbomethoxyisopropyl)-methylamine (35 g.; 0.15 mole) was added slowly from a dropping funnel to a stirred suspension of potassium ethoxide, prepared by dissolving potassium (14.4 g.; 0.37 mole) in absolute ethanol (50 ml.) and then removing the excess ethanol under reduced pressure. After the addition was complete the mixture was refluxed with stirring overnight. Dilute hydrochloric acid (200 ml.) was added cautiously (excess potassium in this reaction makes this step hazardous). The aqueous layer separated and the toluene extracted with 20% hydrochloric acid (5 × 100 ml.), and the combined aqueous layers refluxed for 15 hours; at which time a negative test with ferric chloride

solution was obtained. The aqueous layer was evaporated under reduced pressure until a solid started to separate, then solid sodium hydroxide was cautiously added to basify the mixture. Enough water was added to effect solution of the solid separated and then the mixture was extracted with chloroform (8 × 100 ml.). The chloroform was dried (Na_2SO_4) and evaporated, and the residue fractionally distilled under vacuum to give the title compound (8.3 g.; 43%), b.p. 56-59°/1 mm. (Mistryukov and Aronova, 1966, gave b.p. 55-57°/7 mm.; Ganellin and Spickett gave 52.5°/4.5 mm.)

IR spectrum (film):

νmax. 1725 cm^{-1} (C=O str.).

It gave a picrate from ethanol m.p. 176-177° (Nazarov, 1948, reported m.p. 175.5-176.5°).

Anal. calcd. for $C_{13}H_{16}N_4O_8$ C,36.78; H,6.17.

Found: C,36.94; H,6.12.

It also formed a methiodide from acetone, m.p. 185-186°.

Anal. calcd. for $C_8H_{16}INO$ C,35.71; H,5.99.

Found: C,35.39; H,5.96.

It also gave a hydrobromide from ethanol which proved to be the diethy ketal derivative, m.p. 149-151°.

IR spectrum (nujol mull):

νmax. 1040 cm^{-1} (COC str.), C=O str. 1725 cm^{-1} absent.

PMR spectrum ($CDCl_3$):

δ1.62 (2-methyl doublet), δ1.22 and 1.27 ($OCH_2\underline{Me}$ two overlapping triplets), δ3.54 (center of two $O\underline{CH_2}Me$ overlapping quartets).

Anal. calcd. for $C_{11}H_{23}NO_2HBr$ C,46.81; H,8.57; N,4.96.
Found: C,47.09; H,8.75; N,4.98.

ATTEMPTED PREPARATION OF N-BENZYL-2-METHYL-4-PIPERIDONE

1,2-Dimethyl-4-piperidone methiodide (20 g.; 0.075 mole), prepared by gently refluxing 1,2-dimethyl-4-piperidone with an excess of methyl iodide in acetone overnight (see later), was mixed with benzylamine (7.65 g.; 0.075 mole) in water (6.75 ml.; 0.375 mole) and let stand overnight. The resulting dark brown solution was extracted with ether, washed with water, and dried (Na_2SO_4). The ether was evaporated and the residue fractionally distilled. Decomposition was extensive and the distillate collected had b.p. 80-140°/2 mm.
IR spectrum (film):
No carbonyl absorption, OH (small) 3300 cm^{-1}.

Evidently the reaction had not worked and the product was discarded.

ATTEMPTED PREPARATION OF (2-CARBOMETHOXYISOPROPYL)-(2-CARBOMETHOXY-n-PROPYL)-METHYLAMINE

(2-Carbomethoxyisopropyl)-methylamine (25 g.; 0.17 mole), prepared as previously described, was added to methyl methacrylate (35 g.; 0.35 mole) and the mixture allowed to sit for three months. The product was fractionally distilled under vacuum to give three fractions, whereupon decomposition of the pot mixture began and the distillation was stopped. The first two fractions proved to be methyl methacrylate and

and methyl crotonate by NMR spectral comparisons with authentic samples, and the third fraction, the unreacted mono ester; again determined by NMR. The appearance of methyl crotonate indicated breakdown of the original mono ester, therefore the reaction was not further investigated.

(2-CARBOMETHOXYISOPROPYL)-BENZYLAMINE

Methyl crotonate (83 g.; 0.83 mole) was added dropwise to a stirred solution of benzylamine (89 g.; .83 mole) in absolute methanol (200 ml.) and then the mixture was refluxed for 12 hours. The methanol was removed under reduced pressure and the residue distilled to give the title compound (135 g.; 79%), b.p. 120-123°/0.6 mm.

IR spectrum (film):

νmax. 1745 (C=O str.), 3350 (NH str.) cm^{-1}.

Anal. calcd. for $C_{12}H_{17}NO_2$ C,69.53; H,8.27.

Found: C,70.10; H,8.19.

It gave a hydrochloride from ethanol-ether, m.p. 99-101°.

Anal. calcd. for $C_{12}H_{17}NO_2 \cdot HCl$ C,59.14; H,7.44; N,5.75.

Found: C,59.26; H,7.38; N,5.69.

(2-CARBOMETHOXYETHYL)-(2-CARBOMETHOXYISOPROPYL)-BENZYLAMINE

(2-Carbomethoxyisopropyl)-benzylamine (135 g.; 0.65 mole) was added to methyl acrylate (224 g.; 2.6 mole) in absolute methanol (300 ml.) and the mixture gently refluxed for 36 hours. The methanol and unreacted methyl acrylate were removed under reduced pressure and the residue fractionally

distilled under vacuum to give the title compound (170 g.; 89%), b.p. 145-150°/0.5 mm.

IR spectrum (film):

νmax. 1740 cm^{-1} (C=O str.), no NH band (3350 cm^{-1}).

Anal. calcd. for $C_{16}H_{23}NO_4$ C,65.51; H,7.90; N,4.785.

Found: C,65.51; H,8.04; N,4.95.

N-BENZYL-2-METHYL-4-PIPERIDONE (110)

(2-Carbomethoxyethyl)-(2-carbomethoxyisopropyl)-benzylamine (160 g.; 0.55 mole) was added slowly from a dropping funnel to a warm (60°) stirred suspension of sodium methoxide in toluene (500 ml.), prepared by dissolving sodium (15 g.; .65 mole) in dry methanol (200 ml.), then removing the excess methanol under reduced pressure and adding the toluene. After the mixture began to reflux gently the diester addition was continued at a slower rate just sufficient to maintain reflux. When the addition was complete the mixture was refluxed for 14 hours, cooled, and poured onto an ice-water mixture. A white solid separated which was collected, washed with ether (100 ml.), dried, and then dissolved in 20% hydrochloric acid (300 ml.) and refluxed for 6 hours. The mixture did not give a positive test with ferric chloride solution, thus the evolution of CO_2 was monitored by bubbling the gas coming out of the top of the condensor through a solution of lime water; the absence of cloudiness was taken to mean that decarboxylation was complete. The aqueous phase was reduced in volume under low pressure until a solid began to separate,

then strong ammonia solution was added until the mixture was strongly basic. The base was extracted with $CHCl_3$ (5 × 100 ml.), which was dried (Na_2SO_4) and evaporated. The residue was fractionally distilled under vacuum to yield the title compound (45 g.; 40%), b.p. 138-143°/0.05 mm.

IR spectrum (film):

νmax. 1715 (C=O str.) 715 and 680 (monosubstituted benzene) cm^{-1}.

Anal. calcd. for $C_{13}H_7NO$ C,76.81; H,8.43; N,6.89.

Found: C,76.59; H,8.39; N,7.08.

It gave a hydrochloride from ethanol-ether which proved to be the diethyl ketal derivative, m.p. 149-151°. (Casy, 1964, found this to occur in analogues of this type.)

IR spectrum (nujol):

νmax. 1045 cm^{-1} (COC str.).

NMR spectrum ($CDCl_3$):

δ3.70 ($O\underline{CH_2}Me$ quartet), δ1.11 ($OCH_2\underline{Me}$ triplet).

Anal. calcd. for $C_{17}H_{27}NO_2 \cdot HCl$ C,65.06; H,8.99; N,4.46.

Found: C,64.96; H,8.96; N,5.10.

4-NITRO-2-METHYLPYRIDINE-1-OXIDE (112)

α-Picoline-1-oxide (150 g.; 0.75 mole) was dissolved in a mixture of sulfuric acid (830 g.; 8.45 mole) and nitric acid (180 g.; 1.43 mole), and the solution was heated 3.5 hours at 128-130° in an oil bath. The reaction mixture was cooled and poured onto ice with vigorous stirring and then cautiously neutralized with sodium carbonate. When crystals of sodium sulphate began to separate the neutralization was

stopped and the precipitate of 4-nitro-2-methylpyridine-1-oxide was collected, washed with ice water and dried. Yield 140 g., m.p. 154-156° (Ochiai, 1953, gave 153-154°).

IR spectrum (nujol mull):

νmax. 1510 (NO_2 str.) cm^{-1}.

PMR spectrum ($CDCl_3$):

δ2.57 (2-methyl singlet), δ8.40 - 7.85 (aromatic multiplet).

Anal. calcd. for $C_6H_6N_2O_3$ C,46.75; H,3.93; N,18.18.

Found: C,46.81; H,4.12; N,18.31.

4-METHOXY-2-METHYLPYRIDINE-1-OXIDE (113)

To (140 g.; 1 mole) of 4-nitro-2-methylpyridine-1-oxide in methanol (1 litre) was added a solution of sodium (24 g.; 1 mole) in methanol (1.2 litre) in small portions. When the addition was complete the mixture was allowed to stand overnight. Crystals of sodium nitrate separated, which were filtered and washed with a little methanol. The combined methanol solution was further concentrated and the sodium nitrate filtered off. This procedure was repeated several times until crystals of 4-methoxy-2-methylpyridine-1-oxide began to separate and the mother liquors remaining no longer gave off NO_2 gas when dropped in concentrated H_2SO_4. The methanol was evaporated completely to leave the crude title compound which was recrystallized from methanol-ether to give the title compound (140 g.), m.p. 79-81° as the monohydrate.

IR spectrum (nujol mull):

νmax. 3480 (OH str.), 1050 (COC str.) cm^{-1}.

PMR spectrum:

δ2.37 (2-methyl singlet), δ3.84 (4-methoxy singlet), δ3.57 (H_2O crystallization).

Anal. calcd. for $C_7H_9NO_2 \cdot H_2O$ C,53.50; H,7.05.

Found: C,53.50; H,6.80.

4-METHOXY-2-METHYLPYRIDINE (114)

4-Methoxy-2-methylpyridine-1-oxide (139 g.; 0.89 mole) was dissovled in a mixture of glacial acetic acid (1500 ml.) and acetic anhydride (250 ml.). 10% palladium charcoal (25 g.) was added and the mixture hydrogenated at room temperature and pressure until the theoretical amount of hydrogen was absorbed. (In another trial where impure material was used the $NaNO_2$ that slowly released NO_2 from the reducing mixture interfered with hydrogen absorption. Therefore a useful technique was to bubble hydrogen gas through the mixture for several minutes to displace all the NO_2 prior to hydrogenation.)

The mixture was filtered and evaporated to dryness, diluted with water and made alkaline with sodium carbonate. The liberated base was extracted with chloroform (4 × 100 ml.). The chloroform was dried (Na_2SO_4) and evaporated. The crude base remaining was fractionally distilled to give the title compound (40 g.), b.p. 184°.

IR spectrum (film):

νmax. 1040 cm^{-1} (COC str.), 3400 cm^{-1} (OH str.; may account for poor analysis below).

PMR spectrum:

δ2.5 (2-methyl singlet); δ3.82 (4-methoxy singlet).

Anal. calcd. for C_7H_9NO C,68.25; H,7.36.

Found: C,67.56; H,7.31.

It gave a hydrochloride from ethanol-ether, m.p. 223-225°.

Anal. calcd. for $C_7H_9NO \cdot HCl$ C,53.83; H,6.45.

Found: C,53.56; H,6.42.

It also gave a methiodide from acetone-ether, m.p. 168-170°.

Anal. calcd. for $C_8H_{12}NOI$ C,36.24; H,4.56.

Found: C,36.47; H,4.30.

The bulk of the product was converted to a benzylbromide (115), m.p. 157-159°.

Anal. calcd. for $C_{14}H_{16}NOBr$ C,57.18; H,5.48; N,4.76.

Found: C,57.46; H,5.49; N,4.94.

1-BENZYL-2-METHYL-4-METHOXY-1,2,5,6-TETRAHYDROPYRIDINE (116)

The 2-methyl-4-methoxypyridine benzylbromide (40 g.; 0.136 mole) was suspended in methanol (35 ml.) and cooled to -15°. N/1 sodium hydroxide (165 ml.) was slowly added and the temperature kept to -15°. The ice bath was removed and sodium borohydride (10 g.; 0.264 mole) was rapidly added. The temperature rose slowly to 35° during the next 20 minutes and then the mixture was heated at 70° for 1.5 hours. The flask was cooled, saturated with sodium chloride and extracted with ether (3 × 100 ml.). The ether was dried (Na_2SO_4) and evaporated and the residue distilled to give the title compound

(15.5 g.; 52%), b.p. 132-134°/0.5 mm.

IR spectrum (film):

νmax. 1600 (C=C str.), 1035 (COC str.)

PMR spectrum ($CDCl_3$):

δ1.18 (2-methyl doublet), δ1.08 (5-methyl doublet, minor), δ3.73 (centre of N-methylene AB quartet). (See discussion, p. 90).

Anal. calcd. for $C_{14}H_{19}NO$ C,77.38; H,8.81.

Found: C,77.36; H,8.80.

N-BENZYL-2-METHYL-4-PIPERIDONE (110)

The 1-benzyl-2-methyl-4-methoxy-1,2,5,6-tetrahydropyridine (15 g.) was refluxed with 20% hydrochloric acid (200 ml.) for 2 hours. The bulk of the acid was removed under reduced pressure, the residue made basic with strong ammonia solution and extracted with chloroform (4 × 100 ml.). The chloroform was dried (Na_2SO_4) and evaporated to leave a residue which was fractionally distilled under reduced pressure to give the title compound (10.5 g.), b.p. 138-142°/0.5 mm. The IR spectrum was identical with that previously prepared.

Anal. calcd. for $C_{13}H_{17}NO$ C,76.81; H,8.43; N,6.89.

Found: C,76.21; H,8.52; N,6.60.

N-ALKYL-3-METHYL-4-PHENYL-4-PIPERIDINOL AND DERIVATIVES

1,3-DIMETHYL-4-PHENYL-4-PIPERIDINOL (33) and (34)

Lithium metal (1.7 g.; 0.24 mole) was hammered out into a thin sheet, cut into small pieces and dropped into a three necked flask containing sodium dried ether (100 ml.). Bromobenzene (18.8 g.; 0.12 mole) was added slowly from a dropping funnel to the rapidly stirred lithium; after the initial reaction began, the bromobenzene was added at a rate sufficient to maintain gently reflux. When the addition was complete, the mixture was refluxed with stirring for 2 hours. The mixture was cooled in an ice bath and 1,3-dimethyl-4-piperidone (12.7 g.; 0.1 mole), dissolved in dry ether (100 ml.), was added dropwise. When the addition was complete the mixture was refluxed for eight hours, cooled, and poured onto crushed ice and glacial acetic acid (20 ml.). The solid which separated was washed with ether and suspended in water, basified with solid sodium hydroxide, and extracted with $CHCl_3$ (3 × 100 ml.). The chloroform was dried (Na_2SO_4) and evaporated and the residue let stand overnight in a desiccator. The solid which separated was collected, washed with petroleum ether, and recrystallized from ligroin. The base had m.p. 98-99° (Ziering and Lee, 1947, gave m.p. 97-99° for the α-isomer). M.p. and mixed m.p. with an authentic sample of α-prodine alcohol proved this to be the α-isomer.

IR spectrum (nujol):

νmax. 3265 cm^{-1} (OH str.), no C=O band (1710 cm^{-1}).

Anal. calcd. for $C_{13}H_{19}NO$ C,76.06; H,9.33; N,6.82.
Found: C,76.05; H,9.10; N,7.02.

Fractional crystallization of the mother liquors remaining from isolation of the α-prodinol and seeding with an authentic sample of the β-isomer* yielded a very small amount of β-1,3-dimethyl-4-phenyl-4-piperidinol hydrochloride, m.p. 218-219.5°.

Anal. calcd. for $C_{13}H_{19}NO.HCl$ C,64.58; H,8.34; N,5.80.
Found: C,64.86; H,8.35; N,5.79.

α-1,3-DIMETHYL-4-PHENYL-4-ACETYLOXYPIPERIDINE (41)

Acetyl chloride (1.9 g.; 0.24 mole) was added slowly to a rapidly stirred solution of α-1,3-dimethyl-4-phenyl-4-piperidinol (2.5 g.; 0.12 mole) in dry benzene (50 ml.) and then refluxed for 4 hours. The mixture was cooled to room temperature and the solid filtered off to give the title compound (2.4 g.), m.p. 210-211°. Recrystallized from methanol-ether had m.p. 215-216° (Casy, 1968, reported 216-218°).

IR spectrum (nujol):
νmax. 1745 cm^{-1} (C=O), no νOH absorption.
Anal. calcd. for $C_{15}H_{21}NO_2 \cdot HCl$ C,63.48; H,7.81; N,4.93.
Found: C,63.39; H,7.69; N,4.60.

---

*(Kindly supplied by Hoffman-LaRoche Laboratories, New Jersey.)

β-1,3-DIMETHYL-4-PHENYL-4-ACETYLOXYPIPERIDINE (42)

Acetyl chloride (3 g.; 0.4 mole) was added slowly to a rapidly stirred solution of β-1,3-dimethyl-4-phenyl-4-piperidinol (4 g.; 0.2 mole) in dry benzene (50 ml.) and then refluxed for 4 hours. The mixture was cooled to room temperature and the solid filtered off to give the title compound (2.8 g.). One recrystallization from methanol-ether gave m.p. 210-212° (Casy, 1968, gave 211-213°).

IR spectrum (nujol):

νmax. 1745 cm^{-1} (C=O), no νOH absorption.

Anal. calcd. for $C_{15}H_{21}NO_2 \cdot HCl$ C,63.48; H,7.81; N,4.93.

Found: C,63.71; H,7.58; N,4.73.

α-1,3-DIMETHYL-4-PHENYL-4-PROPIONYLOXYPIPERIDINE (52)

Propionyl chloride (5 g.; 0.06 mole) was added slowly to a rapidly stirred solution of α-1,3-dimethyl-4-phenyl-4-piperidinol (6.1 g.; 0.03 mole) in dry benzene (100 ml.). The mixture was refluxed for 4 hours, cooled and the solid filtered off to yield the title compound (5.8 g.). One recrystallization from the ethanol-ether gave material m.p. 217-218° (Ziering and Lee, 1947, gave 220-221°).

IR spectrum (nujol):

νmax. 1745 cm^{-1} (C=O), no νOH band.

Anal. calcd. for $C_{16}H_{23}NO_2 \cdot HCl$ C,64.52; H,8.12; N,4.70.

Found: C,64.73; H,8.06; N,4.65.

β-1,3-DIMETHYL-4-PHENYL-4-PROPIONYLOXYPIPERIDINE (53)

Propionyl chloride (1 g.; 0.011 mole) was added slowly to a rapidly stirred solution of β-1,3-dimethyl-4-phenyl-4-piperidinol (1 g.; 0.005 mole) in dry benzene (25 ml.). The mixture was refluxed 4 hours, cooled to room temperature and the solid filtered off to give the title compound (1.1 g.). One recrystallization from ethanol gave material m.p. 203-204° (Ziering et al., 1957, reported 199-200°).

IR spectrum (nujol):

νmax. 1745 cm^{-1} (C=O), no νOH band.

Anal. calcd. for $C_{16}H_{23}NO_2 \cdot HCl$ C,64.52; H,8.12; N,4.70.

Found: C,64.73; H,8.05; N,4.64.

DEHYDRATION OF α-1,3-DIMETHYL-4-PHENYL-4-PIPERIDINOL (33)

α-1,3-Dimethyl-4-phenyl-4-piperidinol (8 g.) was added to a mixture of concentrated hydrochloric acid (66 ml.) and glacial acetic acid (124 ml.) and then refluxed 12 hours. The acids were removed completely under reduced pressure to leave a solid (7.8 g.) which proved to be a mixture of 1,3-dimethyl-4-phenyl-1,2,5,6-tetrahydropyridine and 1,5-dimethyl-4-phenyl-1,2,5,6-tetrahydropyridine hydrochlorides.

IR spectrum (nujol):

νmax. 1590 cm^{-1} (C=C str.), no νOH absorption.

UV spectrum (ethanol):

λmax. 235 mμ.; log ε 3.940.

PMR spectrum ($CDCl_3$):

δ1.00 (5-methyl doublet), δ5.87 (C-3H triplet), δ1.13 (3-methyl

singlet).

The isomers were not separated but used directly in the next step.

β-1,3-DIMETHYL-4-PHENYLPIPERIDINE (141)

The isomeric tetrahydropyridines (6 g.) obtained earlier were subjected to hydrogenation at room temperature and pressure over 10% palladium charcoal (0.4 g.) in ethanol (50 ml.). When the theoretical amount of hydrogen was absorbed the catalyst was filtered off and the ethanol evaporated to yield the title compound (5.9 g.), m.p. 236-237°. Recyrstallization from ethanol-ether yielded crystals melting at 243-244°.

IR spectrum (nujol):

νmax. C=C (1590 cm^{-1}) much reduced.

PMR spectrum ($CDCl_3$):

δ1.14 (3-methyl doublet) shifts to δ0.73 in the base.

Anal. calcd. for $C_{13}H_{19}N \cdot HCl$ C,69.34; H,8.81.

Found: C,69.21; H,8.89.

No evidence of a second isomer could be obtained from the mother liquors.

N-METHYL-4-PHENYL-4-PIPERIDINOL (159)

N-methyl-4-piperidone (10.8 g.; 0.11 mole) was added dropwise to a stirred suspension of phenyllithium in dry ether (50 ml.), prepared from lithium (3.46 g.; 0.24 mole) and bromobenzene (27.6 g.; 0.24 mole). When the addition was complete the mixture was refluxed 6 hours and then decomposed

in the usual manner. The base crystallized out in the fridge overnight and was collected, washed with benzene and then recrystallized from benzene to yield the title compound (8 g.), m.p. 110° (Schmidle and Mansfield, 1956, reported 115-116°).
Anal. calcd. for $C_{12}H_{17}NO$ C,75.35; H,8.96; N,7.32.
Found: C,75.11; H,9.03; N,7.32.

N-METHYL-4-PHENYLPIPERIDINE (160)

Raney nickel (prepared by the method of Vogel, 1964) (5 g.) in ethanol was added to N-methyl-4-piperidinol (0.5 g.; 0.0025 mole) in absolute ethanol (100 ml.) and the mixture rapidly stirred and refluxed for 6 hours. The nickel was filtered off and the ethanol evaporated to give the title compound (0.5 g.) as an oil.
IR spectrum (film):
No OH stretching observed.

It gave a hydrochloride from ethanol-ether m.p. 197-198°.
Anal. calcd. for $C_{12}H_{17}N \cdot HCl$ C,68.07; H,8.57; N,6.62.
Found: C,68.16; H,8.57; N,6.63.

It also gave a picrate from ethanol, m.p. 238-240° (Schmidle and Mansfield, 1955, gave 239-240°).

N-METHYL-4-PHENYL-1,2,5,6-TETRAHYDROPYRIDINE

N-methyl-4-phenyl-4-piperidinol (4 g.; 0.021 mole) was added to a mixture of concentrated hydrochloric acid (66 ml.) and glacial acetic acid (124 ml.) and refluxed 6 hours. The aqueous phase was removed under reduced pressure and

the residue remaining recrystallized from ethanol-ether to give the title compound (2.5 g.), m.p. (hydrochloride) 253-254° (McElvain, 1950, gave m.p. 248-250°).

IR spectrum (nujol):

νmax. 1590 cm^{-1} (C=C str.), no OH band.

UV spectrum (ethanol):

λmax. 242 mμ.; log ε 4.135.

Anal. calcd. for $C_{12}H_{15}N \cdot HCl$ C,68.72; H,8.02; N,6.68.

Found: C,68.85; H,7.84; N,6.74

ALTERNATE PREPARATION OF N-METHYL-4-PHENYLPIPERIDINE (160)

N-methyl-4-phenyl-1,2,5,6-tetrahydropyridine hydrochloride (1 g.), obtained previously, was dissolved in absolute ethanol (100 ml.) and hydrogenated over 10% palladium charcoal (0.1 g.) at room temperature and pressure. When the theoretical amount of hydrogen had been taken up, the catalyst was filtered off, and the ethanol evaporated to yield the title compound (1 g.). Recrystallization from ether-ethanol gave m.p. 197-198° which agrees with that prepared previously.

Mixed m.p. 197-198°, and IR spectra were identical.

ATTEMPTED PREPARATION OF α-1,3-DIMETHYL-4-PHENYLPIPERIDINE (137)

Raney nickel suspension (10 g.) in ethanol was added to a solution of α-1,3-dimethyl-4-phenyl-4-piperidinol (1 g.; 0.05 mole) in absolute ethanol, and the mixture rapidly stirred and refluxed for 4 hours. The nickel catalyst was removed by filtration and the ethanol evaporated to leave a

solid (1 g.). M.p. and mixed m.p. with the starting material 96-98°. IR spectrum (nujol mull) was identical with the starting material.

β-N-ETHYL-3-METHYL-4-PHENYLPIPERIDINE (148)

N-ethyl-5-methyl-1,2,5,6-tetrahydropyridine hydrochloride (1 g.) (supplied by Dr. A.D. Parulkar) was dissolved in absolute ethanol (100 ml.) and hydrogenated over 10% palladium charcoal (0.1 g.) at room temperature and pressure. When the theoretical amount of hydrogen had been absorbed, the catalyst was filtered off and the ethanol evaporated. The solid residue was recrystallized from ethanol-ether to give the title compound (0.9 g.) which melted at 260-263°.

IR spectrum (nujol mull):

νmax. 1605 cm^{-1} (C=C str.) diminished.

PMR spectrum ($CDCl_3$):

δ1.12 (3-methyl-doublet) shifting to δ0.95 when the proton was removed.

Anal. calcd. for $C_{14}H_{21}N \cdot HCl$ C,70.12; H,9.25; N,5.84.
Found: C,70.38; H,9.14; N,5.53.

No evidence of a second isomer was noticed.

β-N-ETHYL-3-METHYL-4-PHENYLPIPERIDINE

N-ethyl-3-methyl-1,2,5,6-tetrahydropyridine hydrochloride (1 g.) (supplied by Dr. A.D. Parulkar) was dissolved in ethanol (100 ml.) and hydrogenated over 10% palladium charcoal (0.1 g.) at room temperature and pressure. When the

theoretical amount of hydrogen was absorbed the catalyst was filtered off and the ethanol evaporated. The solid remaining was recrystallized from ethanol-ether to give the title compound (0.8 g.) which melted at 261-263°. The IR and PMR spectra showed this to be identical to the same compound previously prepared from the trisubstituted alkene.

β-3-METHYL-4-PHENYLPIPERIDINE (152)

N-benzyl-5-methyl-1,2,5,6-tetrahydropyridine hydrochloride (1 g.) (supplied by Dr. A.P. Parulkar) was dissolved in absolute ethanol (100 ml.) and hydrogenated over 10% palladium charcoal (0.1 g.) at room temperature and pressure. When the theoretical amount of hydrogen was absorbed (in this case 2 equivalents of hydrogen were absorbed since the N-benzyl group was also reductively cleaved) the catalyst was filtered off and the ethanol evaporated. The solid remaining was recrystallized from ethanol-ether to yield the title compound (0.7 g.) which melted at 216-217°.

IR spectrum (nujol mull):

νmax. 1600 cm^{-1} (C=C str.) diminished.

PMR spectrum ($CDCl_3$):

δ1.05 (3-methyl doublet), shifted to δ0.95 when proton removed from nitrogen.

Anal. calcd. for $C_{12}H_{17}N \cdot HCl$ C,68.07; H,8.57; N,6.62.

Found: C,67.79; H,8.48; N,6.79.

β-3-METHYL-4-PHENYLPIPERIDINE (152)

N-benzyl-3-methyl-1,2,3,6-tetrahydropyridine hydrochloride (1 g.) (supplied by Dr. A.P. Parulkar) was dissolved in absolute ethanol (100 ml.) and hydrogenated over 10% palladium charcoal (0.1 g.) at room temperature and pressure. When the theoretical amount of hydrogen had been absorbed (2 equivalents) the catalyst was filtered off and the ethanol evaporated. The solid remaining was recrystallized from ethanol-ether to give the title compound which melted at 216-217°. The IR and PMR spectra were identical to the same compound prepared previously from the tetrasubstituted alkene.

β-1,3-DIMETHYL-4-PHENYL-4-CHLOROPIPERIDINE (164)

Freshly distilled thionyl chloride (2 ml.; 0.03 mole) was added slowly from a dropping funnel to a stirred, cooled (0°) solution of β-1,3-dimethyl-4-phenyl-4-piperidinol (2.5 g.) in dry chloroform (50 ml.) over a period of 30 minutes. The mixture was refluxed 4 hours, and the solvents evaporated to give the title compound (2.6 g.). It was recrystallized from ethanol-ether and had m.p. 153-154° (Casy, 1961, reported 154°).

IR spectrum (nujol mull):

No OH absorption band.

PMR spectrum ($CDCl_3$):

δ1.13 (3-methyl doublet), shifted to δ0.97 when the free base was liberated. This large shift is indicative of the β-configuration and conformation.

Anal. calcd. for $C_{13}H_{18}ClN \cdot HCl$ C,60.01; H,7.36.
Found: C,59.92; H,7.30.

ATTEMPTED PREPARATION OF α-1,3-DIMETHYL-4-PHENYL-4-CHLORO-PIPERIDINE

Freshly distilled thionyl chloride (2 ml.; 0.03 mole) was added slowly from a dropping funnel to a stirred, cooled (0°) solution of α-1,3-dimethyl-4-phenyl-4-piperidinol (2.5 g.; 0.012 mole) in dry chloroform (50 ml.) over a 20 minute period. The mixture was then refluxed for 4 hours and the solvents evaporated to leave a solid (2.4 g.).

IR spectrum (nujol mull):

νmax. 1600 cm^{-1} (C=C str. intense), no OH absorption band.

PMR spectrum ($CDCl_3$):

δ1.57 (3-methyl singlet), δ5.75 (vinylic proton), integral showed that the tetrasubstituted alkene was in a ratio of 2:3 as compared to the trisubstituted alkene.

β-1,3-DIMETHYL-4-PHENYLPIPERIDINE (141)

Raney nickel suspension (10 g.) was added to a solution of β-1,3-dimethyl-4-phenyl-4-piperidinol (1 g.; 0.05 mole) in absolute ethanol (100 ml.) and the mixture rapidly stirred and refluxed for 4 hours. The nickel catalyst was filtered off and the ethanol evaporated to leave an oil (1 g.) which would not solidify.

IR spectrum (film):

No OH absorption band.

It gave a hydrochloride from ethanol-ether m.p. 243-243.5° which was identical to that prepared earlier (mixed m.p. and IR).

PMR spectrum ($CDCl_3$):

δ0.85 (3-methyl doublet), δ7.40 (aromatic).

Anal. calcd. for $C_{13}H_{19}N \cdot HCl$ C,69.35; H,8.81.

Found: C,69.21; H,8.89.

N-PHENETHYL-3-METHYL-4-PHENYL-4-PIPERIDINOL (154)

N-2-phenethyl-3-methyl-4-piperidone (10.8 g.; 0.05 mole) was added slowly to a stirred suspension of phenyllithium in dry ether (200 ml.), prepared from lithium (0.77 g.; 0.011 mole) and bromobenzene (8.65 g.; 0.011 mole). When the addition was complete the mixture was refluxed for 2 hours, cooled, and poured onto ice and glacial acetic acid (20 ml.). The semisolid mass which separated was removed with a spatula, suspended in water, washed with ether and basified with strong ammonia solution. The free base was then extracted with $CHCl_3$ (5 × 100 ml.), which was dried (Na_2SO_4) and evaporated to give the title compound (8 g.). The base was recrystallized from acetone-petroleum ether to yield the α-N-2-phenethyl-3-methyl-4-phenyl-4-piperidinol, m.p. 98-102°, and mixed m.p. with authentic sample of the α-isomer 98-102°. (Beckett et al., 1959, reported 105-106°.)

IR spectrum (nujol mull):

νmax. 3240 (OH str.), 1620 (C=C) cm^{-1}. Peaks at 690, 740, 770 and 780 cm^{-1} were attributed to the monosubstituted benzene

rings. No (C=O str.) present.

PMR spectrum ($CDCl_3$):

δ0.64 (3-methyl doublet).

Anal. calcd. for $C_{20}H_{25}NO$ C,81.32; H,8.53.

Found: C,81.56; H,8.78.

It gave a hydrochloride from ethanol-ether, m.p. 216-217°.

PMR spectrum ($CDCl_3$):

δ0.68 (3-methyl doublet, small shift when proton removed indicative of equatorial orientation).

Anal. calcd. for $C_{20}H_{25}NO \cdot HCl$ C,72.38; H,7.59.

Found: C,71.95; H,7.63.

DEHYDRATION OF N-PHENETHYL-3-METHYL-4-PHENYL-4-PIPERIDINOL (154)

The α-isomer of N-phenethyl-3-methyl-4-phenyl-4-piperidinol (5 g.) obtained from the preceding reaction was dissolved in a mixture consisting of concentrated hydrochloric acid (66 ml.) and glacial acetic acid (124 ml.). The mixture was refluxed for 4 hours and then the aqueous phase reduced in volume under low pressure. The residue was made alkaline with strong ammonia solution and extracted with chloroform (2 × 100 ml.). The chloroform was dried (Na_2SO_4) and evaporated to leave a mixture of the tri- (155) and tetrasubstituted (156) alkenes (30:70 ratio).

IR spectrum (film):

νmax. 1625 cm^{-1} (intense C=C str.).

PMR spectrum ($CDCl_3$):

δ5.66 (broad triplet for C-3 vinylic proton); δ1.59 (broad

singlet for C-3-methine group); δ1.24 (C-5-methyl doublet).
UV spectrum (ethanol):
λmax. 235 mμ.; log ε=3.926.

It gave a hydrochloride from ethanol-ether which melted at 217-222° (wide due to two isomeric forms).
Anal. calcd. for $C_{20}H_{23}N \cdot HCl$ C,76.54; H,7.71.
Found: C,76.76; H,8.02.

β-N-PHENETHYL-3-METHYL-4-PHENYLPIPERIDINE (157)

The mixture of the tetrahydropyridine hydrochloride (2 g.) previously prepared was dissolved in ethanol (100 ml.) and hydrogenated over 10% palladium charcoal at room temperature and pressure. When the theoretical amount of hydrogen had been absorbed the catalyst was filtered off and the ethanol reduced in volume to approximately 10 ml. Ether was added and crystals of the title compound (2 g.) separated readily, m.p. 235-236°.
IR spectrum (nujol mull):
νmax. 1610 cm^{-1} (C=C small), aromatic peaks at 685 and 740 cm^{-1} for monosubstituted benzene.
PMR spectrum ($CDCl_3$):
δ1.11 (3-methyl doublet), δ5.64 (aromatic singlet),
(Base): δ0.78 (3-methyl doublet—large shift indicative of axial methyl group, hence β-isomer).
Anal. calcd. for $C_{20}H_{25}N \cdot HCl$ C,76.05; H,8.31.
Found: C,76.01; H,8.50.

N-ALKYL-2,5-DIMETHYL-4-PHENYL-4-PIPERIDINOL AND DERIVATIVES

ATTEMPTED SEPARATION OF CIS AND TRANS 1,2,5-TRIMETHYL-4-PIPERIDONE HYDROCHLORIDE (122)

The commercial sample of 1,2,5-trimethyl-4-piperidone (supplied by Dr. N.S. Prostakov) was converted to the hydrochloride in ethanol. Fractional crystallization of the salt from ethanol-ether gave pure trans 1,2,5-trimethyl-4-piperidone, m.p. 189-190° (Hassan and Casy, 1970, reported 189-190°).

PMR spectrum (DMSO-d_6):

δ1.39 (2-methyl doublet), δ0.94 (5-methyl doublet), δ2.83 (N-methyl singlet).

Anal. calcd. for $C_8H_{15}NO \cdot HCl$ C,54.11; H,9.03; N,7.89.
Found: C,54.29; H,8.96; N,8.15.

The cis isomer could not be isolated in a pure state by crystallization.

Similarly was prepared the hydrobromide of 1,2,5-trimethyl-4-piperidone. Again fractional crystallization from ethanol-ether produced only trans 1,2,5-trimethyl-4-piperidone hydrobromide.

PMR spectrum (DMSO-d_6):

δ1.38 (2-methyl doublet), δ0.95 (5-methyl doublet), δ1.73 (N-methyl singlet).

Anal. calcd. for $C_8H_{15}NO \cdot HBr$ C,43.25; H,7.26; N,6.31.
Found: C,43.40; H,7.26; N,6.20.

ISOMERIZATION OF 1,2,5-TRIMETHYL-4-PIPERIDONE (123)

1,2,5-Trimethyl-4-piperidone (50 g.; 0.35 mole) was heated over Woelm neutral (activity grade 1) alumina (5 g.) for 45 minutes on a steam bath and then distilled from the alumina b.p. 36-38°/0.1 mm. PMR spectral analysis showed that no significant amount of isomerization had occurred. Thus another lot of 1,2,5-trimethyl-4-piperidone (50 g.; 0.35 mole) was heated over alumina (5 g.) for 2 hours and then distilled. The PMR this time showed a considerable amount of the cis isomer present (see discussion p. 123 Heating under the same conditions for 12 hours did not change the ratio from that obtained after 2 hours (see Nazarov and Shvetsov, 1959).

1,2,5-TRIMETHYL-3,3,5-TRIDEUTERO-4-PIPERIDONE (180)

Sodium (2.3 g.; 0.1 mole) cut into small pieces was added cautiously to deuterium oxide (40 ml.; 0.5 mole). When all the sodium had dissolved, 1,2,5-trimethyl-4-piperidone (14.1 g.; 0.1 mole) in dry carbon tetrachloride (100 ml.) (distilled from phosphorous pentoxide and stored over type 4A molecular sieves) was added all at once. The flask was securely stoppered and then shaken for 24 hours on a mechanical shaker. The carbon tetrachloride layer was separated and the aqueous layer extracted with more dry carbon tetrachloride (2 × 50 ml.). The combined extracts were dried (Na_2SO_4) and evaporated to give the title compound (48 g.).

PMR spectrum (CCl_4):

δ0.92 (5-methyl singlet); δ1.01 (5-methyl singlet of cis isomer).

1,2,5-TRIMETHYL-4-PHENYL-4-PIPERIDINOL

1,2,5-Trimethyl-4-piperidone (56.4 g.; 0.4 mole) was added slowly from a dropping funnel to a stirred solution of phenyllithium, prepared from lithium (6.72 g.; 0.96 mole) and bromobenzene (75.4 g.; 0.48 mole) in 100 ml. dry ether. When the addition was complete, the mixture was stirred overnight and then refluxed 4 hours, cooled and poured onto ice and glacial acetic acid (50 ml.). The aqueous layer was separated and washed with ether (2 × 100 ml.) and then basified with solid sodium hydroxide. The free base was extracted with $CHCl_3$ (4 × 100 ml.) which was dried (Na_2SO_4) and evaporated to give an isomeric mixture of the title compound (57 g.). The residue was diluted with a small amount of petroleum ether and set in the fridge. The next day crystals of the γ-1,2,5-trimethyl-4-phenyl-4-piperidinol separated. These were collected and the mother liquors were diluted with more petroleum ether. In all 4 crops of the γ-isomer were isolated this way (total 33 g.), m.p. 106-107°.

It gave a hydrochloride from ethanol-ether m.p. 159-160° (Nazarov et al., 1956, gave base m.p. 107-108°; hydrochloride 158-159°).

It also gave a methiodide from acetone, m.p. 223-225°. Anal. calcd. for $C_{15}H_{24}INO$ C,49.87; H,6.70; N,3.88.

Found: C,49.93; H,6.72; N,4.07.

The petroleum ether was evaporated and the residue diluted with acetone. HCl gas was bubbled in until the solution was acidic to litmus. From this, β-1,2,5-trimethyl-4-phenyl-4-piperidinol (4.5 g.) was isolated after storage at 0° for several days, m.p. 233-235°. (Nazarov et al., 1956, reported 233-236°.) The free base had m.p. 106-109°. (Nazarov et al., 1956, reported 106-107°.)

It gave a methiodide from acetone m.p. 232-234°.
Anal. calcd. for $C_{15}H_{24}NOI$ C,49.87; H,6.70; N,3.88.
Found: C,49.74; H,6.66; N,3.69.

The mother liquors remaining after the acetone was evaporated were dissolved in ethanol and diluted with ether. After storage at 0° for several weeks was isolated the α-1,2,5-trimethyl-4-phenyl-4-piperidinol as the hydrochloride (6.8 g.) m.p. 125-129° (reported 173-174°), free base m.p. 101-102° (reported 102-103°). Several different crops of the α-isomer hydrochloride from repetitions of this reaction were found to have melting points of 101-102°, 103-105° and 100-101°.

It gave a methiodide from acetone m.p. 278-280°.
Anal. calcd. for $C_{15}H_{24}NOI$ C,49.87; H,6.70; N,3.88.
Found: C,50.04; H,6.74; N,4.04.
Anal. calcd. for (γ)$C_{14}H_{21}NO\cdot HCl$ C,65.77; H,8.67; N,5.47.
Found: C,65.49; H,8.66; N,5.30.
Anal. calcd. for (β)$C_{14}H_{21}NO\cdot HCl$ C,65.77; H,8.67; N,5.47.
Found: C,65.57; H,8.72; N,5.36.
Anal. calcd. for (α)$C_{14}H_{21}NO\cdot HCl$ C,65.77; H,8.67; N,5.47.

Found: C,65.49; H,8.56; N,5.40.

CHROMATOGRAPHY OF ISOMERIC 1,2,5-TRIMETHYL-4-PHENYL-4-PIPERIDINOLS

Woelm neutral alumina (750 g.) (activity grade 1) was made into a slurry in dry chloroform and packed in a 75 × 5 gm. glass column. The crude isomeric mixture of the 1,2,5-trimethyl-4-phenyl-4-piperidinols (15 g.), previously prepared, was adsorbed onto the top of the column and eluted with dry chloroform. The flow rate was adjusted to 1 ml./ 3 min. and 200 fractions of 20 ml. each were collected by a Buchler automatic fraction collector.

PMR analysis showed the following separation:

fraction	isomeric composition	weight
1-30	-	0.2
31-83	γ only	5.8
84-110	γ (and perhaps δ)	2.2
115-130	α, β	1.2
140-190	α, β, γ	5.0

From fractions 31-110 pure γ-1,2,5-trimethyl-4-phenyl-4-piperidinol was isolated from chloroform-petroleum ether. The δ-isomer could not be isolated from the mixture. Evaporation of the solvents and dilution with acetone-HCl yielded the β-isomer after several days storage at 0°. The acetone was evaporated and the residue diluted with ethanol-ether and seeded with some of the α-isomer previously isolated (m.p. 100-101°). Crystallization proceeded slowly for 2 weeks to

yield the α-1,2,5-trimethyl-4-phenyl-4-piperidinol m.p. 101-102°. The mother liquors remaining (4.9 g.) would not yield the missing δ-isomer.

1,2,5-TRIMETHYL-3,3,5-TRIDEUTERO-4-PHENYL-4-PIPERIDINOL (168)

1,2,5-Trimethyl-3,3,5-trideutero-4-piperidone (14 g.; 0.1 mole) was added dropwise to a stirred solution of phenyllithium in dry ether (200 ml.), prepared from lithium (1.7 g.; 0.22 mole) and bromobenzene (18 g.; 0.11 mole). When the addition was complete, the mixture was allowed to stir overnight and then refluxed for 4 hours, cooled, and poured onto ice and glacial acetic acid (50 ml.). The aqueous layer was separated and the ether layer washed with dilute acetic acid (2 × 50 ml.). The combined aqueous layers were reduced in volume to about 50 ml., then basified with strong ammonia solution, and extracted with chloroform (5 × 100 ml.). The chloroform was dried (Na_2SO_4) and evaporated to leave a residue which, when diluted with a small amount of petroleum ether and set in the fridge overnight, gave 1,2,5-trimethyl-3,3,5-trideutero-4-phenyl-4-piperidinol. Dilution of the mother liquor with more petroleum ether produced another crop of the γ-isomer, m.p. 103-104°. In all, 8 g. of the γ-isomer were collected.

It gave a hydrochloride from ethanol-ether, m.p. 152-154°. Anal calcd. for $C_{14}H_{18}D_3NO \cdot HCl$ C,64.97; H,D,9.44; N,5.41. Found: C,64.97; H,D,9.74; N,5.26.

The solvent was evaporated and the residue diluted with

acetone/HCl. Storage in the fridge for several days gave crystals of β-1,2,5-trimethyl-3,3,5-trideutero-4-phenyl-4-piperidinol hydrochloride (1.8 g.), m.p. 228-229°.
Anal. calcd. for $C_{14}H_{18}D_3NO \cdot HCl$ C,64.97; H,D,9.44; N,5.41.
Found: C,64.69; H,9.43; N,5.40.

The acetone was evaporated and the residue diluted with ethanol-ether and several weeks of storage at 0° yielded crystals of α-1,2,5-trimethyl-3,3,5-trideutero-4-phenyl-4-piperidinol hydrochloride (0.3 g.), m.p. 110-120°. (PMR analysis at 100 MHz showed this isomer to be contaminated with some of the β- and γ-isomers.
Anal. calcd. for $C_{14}H_{18}D_3NO \cdot HCl$ C,64.97; H,D,9.44; N,5.41.
Found: C,64.90; H,D,9.48; N,5.61.

γ-1,2,5-TRIMETHYL-4-PHENYL-4-ACETYLOXYPIPERIDINE (192)

Acetyl chloride (3.5 g.; 0.46 mole) was added dropwise with stirring to γ-1,2,5-trimethyl-4-phenyl-4-piperidinol (5 g.; 0.23 mole) in dry benzene. When the addition was complete the mixture was refluxed 12 hours. The solvents were evaporated to leave an oil which would not solidify readily.
IR spectrum (film):
νmax. 3400 cm^{-1} (medium OH), 1740 cm^{-1} (C=O strong).

The mixture of alcohol and ester was dissolved in water (10 ml.), just basified with dilute ammonia solution, and the free base extracted with chloroform (2 × 100 ml.). The chloroform was dried (Na_2SO_4) and evaporated and the residual oil diluted with petroleum ether. Crystals separated over-

night (0.3 g.) which proved to be the γ-alcohol base (m.p., IR identical with authentic sample). The solvent was evaporated and ethanolic HCl added, dilution with ether gave the title compound as the hydrochloride salt (1.3 g.), m.p. 223-226° (Prostakov et al., 1956, gave m.p. 223-224°).

IR spectrum (nujol mull):

νmax. 1740 cm^{-1} (C=O), no OH absorption band apparent.

Anal. calcd. for $C_{16}H_{23}NO_2 \cdot HCl$ C,64.52; H,8.12.

Found: C,64.72; H,8.39.

β-1,2,5-TRIMETHYL-4-PHENYL-4-ACETYLOXYPIPERIDINE (194)

Acetyl chloride (1.6 g.; 0.02 mole) was added dropwise to a stirred solution of β-1,2,5-trimethyl-4-phenyl-4-piperidinol (0.5 g.; 0.0022 mole) in dry benzene (100 ml.), let stir for 4 hours at room temperature and then refluxed for 12 hours. The solvent was evaporated and the residue dissolved in methanol and diluted with ether. Crystals separated (0.4 g.) after storage overnight at 0° which proved to be the title compound, m.p. 181-183°.

IR spectrum (nujol mull):

νmax. 1740 cm^{-1} (C=O str.), OH absorption band not apparent.

Anal. calcd. for $C_{16}H_{23}NO_2 \cdot HCl$ C,64.52; H,8.12; N,4.70.

Found: C,64.49; H,8.08; N,4.60.

α-1,2,5-TRIMETHYL-4-PHENYL-4-ACETYLOXYPIPERIDINE (198)

Acetyl chloride (2 g.; 0.025 mole) was added dropwise to a solution of α-1,2,5-trimethyl-4-phenyl-4-piperidinol (0.5 g.; 0.022 mole) in dry benzene (100 ml.) then refluxed 12 hours. The solvent was evaporated, the residue dissolved in ethanol and diluted with ether. Crystals of the title compound separated as the hydrochloride (0.4 g.), m.p. 197-198°.

IR spectrum (nujol mull):

νmax. 1745 cm^{-1} (C=O), no OH absorption band apparent.

Anal. calcd. for $C_{16}H_{23}NO_2HCl$ C,64.52; H,8.12; N,4.70.

Found: C,64.25; H,8.21; N,4.47.

γ-1,2,5-TRIMETHYL-4-PHENYL-4-PROPIONYLOXYPIPERIDINE (201)

Propionyl chloride (5 g.; 0.54 mole) was added dropwise to a stirred solution of γ-1,2,5-trimethyl-4-phenyl-4-piperidinol (5.7 g.; 0.27 mole) in dry benzene (50 ml.) and the mixture refluxed 18 hours. The solvent was evaporated to leave an oil which would not readily solidify.

IR spectrum (film):

νmax. 3390 (medium OH str.), 1740 (C=O str.).

Fractional crystallizstion of the alcohol-ester mixture from ethanol-ether gave the title compound (3.8 g.), m.p. 202-203° (Nazarov et al. reported 222-223°). Further purification would not raise the melting point.

IR spectrum (nujol mull):

νmax. 1740 cm^{-1} (C=O), OH (3390 cm^{-1}) absent.

Anal. calcd. for $C_{17}H_{25}NO_2 \cdot HCl$ C,65.46; H,8.40.

Found: C,65.14; H,8.66.

β-1,2,5-TRIMETHYL-4-PHENYL-4-PROPIONYLOXYPIPERIDINE (204)

Propionyl chloride (2 g.; 0.026 mole) was added dropwise with stirring to a solution of β-1,2,5-trimethyl-4-phenyl-4-piperidinol (0.5 g.; 0.0022 mole) in dry benzene (50 ml.) and let stir for 6 hours, then refluxed 48 hours. The solvent was removed and the residue dissolved in ethanol and diluted with ether. The first solid that separated proved to be a mixture m.p. 110-120° of starting alcohol and ester (IR evidence). Fractional crystallization of the mother liquors produced the title compound (0.8 g.), m.p. 180-183° (hygroscopic) (Nazarov et al., 1956, reported m.p. 181-182°).
IR sprectrum (nujol mull):
νmax. 1735 cm^{-1} (C=O str.), OH absorption band not apparent.
Anal. calcd. for $C_{17}H_{25}NO_2 \cdot HCl$ C,65.46; H,8.40; N,4.49.
Found: C,65.47; H,8.38; N,3.94.

α-1,2,5-TRIMETHYL-4-PHENYL-4-PROPIONYLOXYPIPERIDINE (205)

Propionyl chloride (2 g.; 0.026 mole) was added dropwise to a stirred solution of α-1,2,5-trimethyl-4-phenyl-4-piperidinol (0.5 g.; 0.023 mole) in dry benzene (100 ml.) and refluxed 12 hours. The solvent was removed, the residue dissolved in absolute ethanol and diluted with ether. Crystallization began at once but IR evidence showed some alcohol remained, therefore the solvents were removed, the residue dissolved in water (10 ml.), brought to pH 9 with ammonium

hydroxide solution, and extracted with $CHCl_3$ (2 x 50 ml.). The $CHCl_3$ was dried (Na_2SO_4) and evaporated to leave an oil which was chromatographed through a column (1 x 25 cm.) filled with 20 cm. Woelm alumina (neutral, activity grade 1) and eluted with 75% chloroform, 25% ether at a flow rate of 1 ml./minute. The first and second 300 ml. fractions were evaporated and displayed no (OH) absorption in the spectrum but a strong (C=O) band at 1740 cm^{-1}. The two fractions were bulked, dissolved in ethanolic HCl, and diluted with ether. Crystals separated after several days to give the title compound (0.35 g.), m.p. 184-186° (Nazarov et al., 1956, reported 227-229° and 101-108°. This diversity of m.p. data is commented on in the discussion, p. 160.

Anal. calcd. for $C_{17}H_{25}NO_2 \cdot HCl$ C,65.46; H,8.40; N,4.49.
Found: C,65.38; H,8.11; N,4.24.

ACTION OF THIONYL CHLORIDE ON β-1,2,5-TRIMETHYL-4-PHENYL-4-PIPERIDINOL

Freshly distilled thionyl chloride (0.6 g.; 0.005 mole) was added slowly to a cooled, stirred solution of β-1,2,5-trimethyl-4-phenyl-4-piperidinol (0.44 g.; 0.002 mole) in $CHCl_3$ (50 ml.). When the addition was complete the mixture was refluxed 4 hours at which time the solvents were removed and the total hydrochloride salt isolated (0.4 g.) to give 1,2,5-trimethyl-4-phenyl-1,2,5,6-tetrahydropyridine hydrochloride as the sole product, m.p. 178-179°.

IR spectrum (nujol mull):

νmax. 1600 cm^{-1} (strong C=C str.), no OH band apparent.

PMR spectrum, base ($CDCl_3$):

δ5.53 (vinylic proton), δ1.07 and δ0.83 (2- and 5-methyl doublets).

UV spectrum, hydrochloride (ethanol):

λmax. 242 mμ, log ε 3.92.

Anal. calcd. for $C_{14}H_{19}N \cdot HCl$ C,70.72; H,8.48; N,5.89.
Found: C,70.72; H,8.37; N,5.90.

It gave a methiodide from acetone, m.p. 119-121°.

PMR spectrum (DMSO-d_6):

δ3.24, δ3.64 (N-methyl singlets), δ1.56, δ1.03 (2- and 5-methyl doublets).

Anal. calcd. for $C_{15}H_{22}NI$ C,52.49; H,6.46; N,4.08.
Found: C,52.68; H,6.69; N,3.75.

ATTEMPTED PREPARATION OF γ-1,2,5-TRIMETHYL-4-PHENYL-4-CHLORO-PIPERIDINE

Freshly distilled thionyl chloride (2.4 g.; 0.02 mole) was added dropwise to a cooled, stirred solution of γ-1,2,5-trimethyl-4-phenyl-4-piperidinol (2.2 g.; 0.01 mole) in dry chloroform (50 ml.). When the addition was complete the mixture was gently refluxed 3 hours. The solvents were evaporated under reduced pressure and the residue made slightly alkaline with dilute ammonium hydroxide solution. The free base was extracted with chloroform which was dried (Na_2SO_4) and evaporated. The residue proved not to be the 4-chloro-

derivative, but a mixture of tri- and tetrasubstituted alkenes.

IR spectrum (film):

No OH band apparent, 1605 cm^{-1} (strong C=O str.).

PMR spectrum, base ($CDCl_3$):

δ5.53 (C3 proton triplet); δ1.55 (broad C-5-methyl singlet).

The alkene isomers were not separated; the crude material had m.p. 174-179°.

Anal. calcd. for $C_{14}H_{19}N \cdot HCl$ C,70.72; H,8.48; N,5.89.
Found: C,70.50; H,8.30; N,6.01.

ATTEMPTED PREPARATION OF γ-1,2,5-TRIMETHYL-4-PHENYL-4-CHLORO-PIPERIDINE

Freshly isolated thionyl chloride (2.4 g.; 0.02 mole) was added as before to a solution of γ-1,2,5-trimethyl-4-phenylpiperidine (2.2 g.; 0.01 mole) in dry chloroform (50 ml.). This time the mixture was not refluxed but instead was stirred for 2 hours at room temperature. The free base isolated proved to be a mixture of unreacted alcohol and tri- and tetrasubstituted alkenes.

IR spectrum (film):

νmax. 3390 (OH str.), 1605 (C=C str.) cm^{-1}.

DEHYDRATION OF γ-1,2,5-TRIMETHYL-4-PHENYL-4-PIPERIDINOL

γ-1,2,5-trimethyl-4-phenyl-4-piperidinol (5 g.) was added to a mixture of concentrated hydrochloric acid (66 ml.) and glacial acetic acid (124 ml.) and the total refluxed for

8 hours. The aqueous phase was removed under reduced pressure and the liberated free base (NH_4OH) extracted with chloroform (3 × 100 ml.). The chloroform was dried (Na_2SO_4) and evaporated to leave an oil (4.5 g.) which had PMR and IR spectra nearly identical to the mixture of 1,2,5-trimethyl-1,2,5,6-tetrahydropyridine and 1,3,6-trimethyl-1,2,5,6-tetrahydropyridine produced previously by the action of thionyl chloride. Fractional crystallization produced nearly pure 1,2,5-trimethyl-4-phenyl-1,2,5,6-tetrahydropyridine hydrochloride, m.p. 175-179°.

PMR spectrum ($CDCl_3$):

δ5.53 (vinylic proton), δ1.07 and δ0.83 (2- and 5-methyl doublets).

It gave a methiodide from acetone, m.p. 117-119°.

PMR spectrum (DMSO-d_6):

δ3.24, δ3.62 (N-methyl singlets), δ1.56, δ1.03 (2- and 5-methyl doublets).

DEHYDRATION OF γ-1,2,5-TRIMETHYL-4-PHENYL-4-PIPERIDINOL METHIODIDE (268)

The methiodide of γ-1,2,5-trimethyl-4-phenyl-4-piperidinol (7 g.), prepared by the action of excess methyl iodide on the γ-promedol alcohol, was added to a mixture of concentrated hydrochloric acid (66 ml.) and glacial acetic acid (124 ml.) and then refluxed 4 hours. The aqueous phase was removed under pressure to leave a solid, m.p. 108-114°, whose PMR showed it to be a mixture of the tri- and tetra-

substituted alkenes. Fractional crystallization of the methiodide yielded a fraction enriched in the trisubstituted alkene, whose PMR was nearly identical to the methiodide of β-1,2,5-trimethyl-4-phenyl-1,2,5,6-tetrahydropyridine prepared previously.

ALTERNATE DEHYDRATION OF γ-1,2,5-TRIMETHYL-4-PHENYL-4-PIPERIDINOL

γ-1,2,5-trimethyl-4-phenyl-4-piperidinol (1.2 g.; 0.085 mole) was added to concentrated sulphuric acid (2.5 g.; 0.026 mole) and heated over a steam bath 5 hours, by which time the solution had gone very dark. Water (15 ml.) was added and the solution strongly basified with 20% sodium hydroxide solution. The free base was extracted with chloroform (2 × 50 ml.), which was dried (Na_2SO_4) and evaporated to leave a residue (1.0 g.).

IR spectrum (film):

3300 (small OH str.), 1605 cm^{-1} (very small C=C str.) cm^{-1}.

PMR spectrum ($CDCl_3$):

Peak multiplicity made analysis impossible but evidence of trisubstituted alkene was apparent by a signal at δ5.55 (C-3-H triplet). Thus the reaction was not stereospecific for production of 1,3,6-trimethyl-4-phenyl-1,2,5,6-tetrahydropyridine as suggested in the literature (Prostakov, 1965).

1,2,5-TRIMETHYL-4-PHENYLPIPERIDINE (271)

Hydrogenation of the total alkene mixture hydrochloride (5 g.), derived previously from the dehydration of γ-1,2,5-trimethyl-4-phenyl-4-piperidinol, was effected at room temperature and pressure over palladium charcoal (0.5 g.) in ethanol. When the theoretical amount of hydrogen was absorbed the catalyst was filtered off and the solvent evaporated to leave an isomeric mixture of the title compound (5 g.). Fractional crystallization from ethanol-ether yielded one isomer (hydrochloride), m.p. 265-267°, which was later tentatively identified as α-1,2,5-trimethyl-4-phenylpiperidine.

IR spectrum (nujol mull):

νmax. 1595 cm^{-1} (small due only to aromatic ring).

PMR spectrum ($CDCl_3$):

δ1.12 and δ1.68 (2- and 5-methyl doublets).

Anal. calcd. for $C_{14}H_{21}N \cdot HCl$ C,70.12; H,9.25; N,5.84.

Found: C,70.01; H,9.05; N,6.14.

ATTEMPTED PREPARATION OF γ-1,2,5-TRIMETHYL-4-PHENYL-PIPERIDINE (273)

Raney nickel (10 g.) was added to a solution of γ-1,2,5-trimethyl-4-phenyl-4-piperidinol (1 g.) in absolute ethanol (300 ml.) and the mixture rapidly stirred and refluxed for 4 hours. The nickel catalyst was filtered off and the ethanol evaporated to leave an oil which crystallized to give the starting alcohol (1 g.), m.p. 103-104°.

IR spectrum (nujol mull):

νOH (strong) 3150 cm^{-1}. IR identical with starting alcohol.

It gave a hydrochloride from ethanol-ether, m.p. 156-158°, undepressed by admixture of authentic γ-promedol alcohol.

β-1,2,5-TRIMETHYL-4-PHENYLPIPERIDINE (272)

Raney nickel (2 g.) was added to a solution of β-1,2,5-trimethyl-4-phenyl-4-piperidinol (0.2 g.) in absolute ethanol (50 ml.) and refluxed with rapid stirring for 12 hours. The catalyst was filtered off and the ethanol evaporated to leave an oil which would not solidify.

IR spectrum (film):

OH absorption band (3140 cm^{-1}) absent.

PMR spectrum ($CDCl_3$):

δ1.02 and 0.73 (5- and 2-methyl doublets).

It gave a hydrochloride from ethanol-ether, m.p. 206-209°.

Anal. calcd. for $C_{14}H_{21}N \cdot HCl$ C,70.12; H,9.25; N,5.84.

Found: C,70.31; H,9.28; N,5.88.

γ-1,2,5-TRIMETHYL-4-PHENYLPIPERIDINE (273)

Raney nickel (2 g.) was added to a solution of α-1,2,5-trimethyl-4-phenyl-4-piperidinol (0.2 g.) in absolute ethanol (50 ml.) and refluxed with rapid stirring for 12 hours. The nickel catalysti was filtered off and the ethanol evaporated to leave an oil.

IR spectrum (film):

νmax. 3410 cm^{-1} (very small OH).

PMR spectrum ($CDCl_3$):

δ0.60 and δ1.04 (2- and 5-methyl doublets).

It gave a hydrochloride from ethanol-ether after several days storage at 0°, m.p. 149-151°.

IR spectrum, hydrochloride (nujol mull):

OH absorption band (3140 cm^{-1}) absent.

Anal. calcd. for $C_{14}H_{21}N \cdot HCl$ C,70.12; H,9.25; N,5.84.

Found: C,69.89; H,9.34; N,5.90.

The PMR spectrum indicated that this α-promedol alcohol isomer had isomerized to produce the γ-promedol hydrocarbon analogue.

N-PHENETHYL-2,5-DIMETHYL-4-PHENYL-4-PIPERIDINOL (245)

N-phenethyl-2,5-dimethyl-4-piperidone (10 g.; 0.046 mole) was added slowly by a spatula to a stirred solution of phenyl lithium in dry ether (100 ml.) prepared from lithium (0.75 g.; 0.12 mole) and bromobenzene (9.4 g.; 0.06 mole). When the addition was complete the mixture was refluxed overnight, cooled, and poured onto ice and glacial acetic acid (10 ml.). The semi-solid mass that separated was removed, suspended in water (25 ml.), basified with solid sodium hydroxide and extracted with $CHCl_3$ (3 × 100 ml.). The $CHCl_3$ was dried (Na_2SO_4), and evaporated to leave the title compound (15 g.) as a thick oil.

IR spectrum (film):

νmax. 3300 (broad OH str.), C=O (1710 cm^{-1}) virtually absent.

NMR spectrum ($CDCl_3$):

δ0.64 and δ1.03 (2- and 5-methyl doublets), evidence of only one isomer.

The free base crystallized out from chloroform-petroleum ether m.p. 98-100°.

Anal. calcd. for $C_{21}H_{27}NO$ C,81.51; H,8.80.

Found: C,81.51; H,8.57.

It gave a hydrochloride from ethanol-ether m.p. 198-199°.

PMR spectrum ($CDCl_3$):

δ0.63 and 1.10 (2- and 5-methyl doublets).

Anal. calcd. for $C_{21}H_{27}NO \cdot HCl$ C,72.91; H,8.16.

Found: C,72.89; H,8.09.

ATTEMPTED PREPARATION OF N-PHENETHYL-2,5-DIMETHYL-4-PHENYL-4-PROPIONYLOXYPIPERIDINE (249)

Propionyl chloride (1 g.; 0.011 mole) was added to a solution of N-2-phenethyl-2,5-dimethyl-4-piperidinol (1.5 g.; 0.005 mole) in dry benzene (50 ml.) and the mixture refluxed 7 hours. The solvent and excess propionyl chloride were removed under vacuum to leave a solid (1.1 g.), m.p. 196-197°.

IR spectrum (nujol mull):

νmax. 3300 cm^{-1} (OH str.), no C=O absorption band apparent. Therefore the unreacted alcohol was recovered as the hydrochloride salt.

ATTEMPTED PREPARATION OF N-2-PHENETHYL-2,5-DIMETHYL-4-PHENYL-4-PROPIONYLOXYPIPERIDINE (249)

Propionic anhydride (20 g.; 0.15 mole) was added to a solution of N-2-phenethyl-2,5-dimethyl-4-piperidinol (5 g.; 0.016 mole) in dry pyridine (100 ml.) and refluxed for 20 hours. The pyridine was removed under low pressure. Then water (5 ml.) was added to decompose the unreacted propionic anhydride and the flask evaporated to dryness.

IR spectrum (nujol mull):

νmax. 3300 cm^{-1} (OH str.), no C=O absorption band was apparent. Thus reaction had failed and starting material recovered.

Similar reaction with acetic anhydride produced the same results, that is, the starting material only could be recovered.

N-PHENETHYL-2,5-DIMETHYL-4-PHENYL-4-ACETYLOXY (AND PROPIONYLOXY) PIPERIDINE (248) and (250)

N-phenethyl-2,5-dimethyl-4-piperidone (10 g.; 0.046 mole) was added from a spatula in small portions to a stirred solution of phenyllithium, prepared from lithium (0.78 g.; 0.11 mole) and bromobenzene (9.4 g.; 0.06 mole) in dry ether (250 ml.). When the addition was complete the mixture was refluxed overnight. Then approximately half the mixture was poured onto propionic anhydride (20 g.) and allowed to stir at room temperature for 2 hours. Water was added to decompose the excess anhydride and all the solvents evaporated to leave an oil. This was suspended in water, dilute ammonium hydroxide added to basify (pH 8) and extracted with

$CHCl_3$ (2 × 75 ml.) which was dried and evaporated to leave an oil.

IR spectrum (film):

νmax. 3410 cm^{-1} (small OH str.), 1740 cm^{-1} (medium C=O str.).

The base (5 g.) was put through a column (1 × 25 cm.) filled with 20 cm. Woelm alumina (neutral, activity grade 1) and eluted with chloroform at a flow rate of 5 ml./minute. The initial 100 ml. of eluate proved to be pure ester (2 g.) (IR evidence). The chloroform was evaporated, the base dissolved in ethanolic HCl and diluted with ether, crystals separated after storage at 0° to yield N-phenethyl-2,5-dimethyl-4-phenyl-4-propionyloxypiperidine hydrochloride (1.5 g.), m.p. 173-176°.

IR spectrum (nujol mull):

νmax. 1745 cm^{-1} (C=O str.), no OH absorption band apparent.

PMR spectrum ($CDCl_3$):

δ1.58 and 0.73 (2- and 5-methyl doublets), δ1.23 ($OCH_2\underline{Me}$ triplet), δ2.57 ($O\underline{CH_2}Me$ quartet).

Anal. calcd. for $C_{24}H_{31}NO_2 \cdot HCl$ C,71.71; H,8.03.

Found: C,71.71; H,8.00.

To half of the lithium complex remaining, acetic anhydride (20 g.) was added slowly from a dropping funnel with cooling and stirring. After the addition was complete, the mixture was allowed to stir for 2 hours at room temperature. A solid separated which was filtered off and dissolved in water (20 ml.), basified to pH 8 with dilute ammonium hydroxide solution, and extracted with chloroform. The chloroform was dried (Na_2SO_4) and evaporated to leave a residue (3 g.)

which was dissolved in ethanolic HCl and diluted with ether. Fractional crystallization produced the N-phenethyl-2,5-dimethyl-4-phenyl-4-acetyloxypiperidine hydrochloride (0.5 g.), m.p. 221-223°.

IR spectrum (nujol mull):

νmax. 1745 cm^{-1} (C=O str.), no OH absorption band apparent.

PMR spectrum ($CDCl_3$):

δ1.55 and δ0.73 (2- and 5-methyl doublets), δ2.26 (methoxy singlet).

Anal. calcd. for $C_{23}H_{29}NO_2 \cdot HCl$ C,71.21; H,7.79.
Found: C,70.93; H,7.99.

The similarity of the 2- and 5-methyl group PMR signals to γ-promedol indicated that the N-phenethyl analogues had the same configuration.

1,2,5-TRIMETHYL-5-BROMO-4-PIPERIDONE (207)

Aqueous 48% hydrochloric acid (109 g.; 0.65 mole) was added dropwise with cooling and stirring to 1,2,5-trimethyl-4-piperidone (50 g.; 0.355 mole). After stirring for 30 min. at 0°, bromine (28.4 g.; 0.355 mole) was added dropwise with stirring and an orange precipitate began to form. Methanol (20 ml.) was added. Storage overnight at room temperature did not produce crystallization, therefore acetone (20 ml.) and ether (20 ml.) were added. Crystals began to separate overnight in the fridge to yield the title compound. Subsequent dilution with ether produced a total of 50 g. of the product, m.p. 145-145.5° (Nazarov et al., 1959,

gave 143-144°).

IR spectrum (nujol mull):

νmax. 1730 cm^{-1} (C=O str.)

Anal. calcd. for $C_8H_{14}BrNO \cdot HBr$ C,31.93; H,5.02; N,4.65.

Found: C,32.02; H,5.17; N,4.80.

DEHYDROBROMINATION OF 1,2,5-TRIMETHYL-5-BROMO-4-PIPERIDONE (208)

Triethylamine (21.8 g.; 0.3 mole) was added gradually to 1,2,5-trimethyl-5-bromo-4-piperidone hydrochloride (30 g.; 0.1 mole). The salt would not dissolve (as reported by Nazarov, 1959), even upon gently warming, thus an additional amount of triethylamine (65 g.; 0.9 mole) was added to effect a suspension. The mixture was gently refluxed for 2 hours during which time solution occurred; however, at the same time a solid began to crystallize out. The dark yellow solid that formed during this time was filtered off and washed repeatedly with ether (7 × 200 ml.). The solid proved to be crude triethylamine hydrobromide, m.p. 233-240°; one crystallization gave material melting at 247-248°—undepressed by admixture of triethylamine hydrobromide (m.p. 247-248°). The combined ethereal washings were evaporated and the residue fractionally distilled under vacuum to give a fraction distilling at 100-104°/1 mm. (Nazarov et al., 1959, did not report a b.p.). (Yield, 8 g.)

IR spectrum (film):

νmax. 1640,1600 cm^{-1} (bands assigned to ketone and α,β-unsaturated bond), 3440 cm^{-1} (weak band, may be due to hydrate).

UV spectrum (ethanol):

λmax. 336 mμ., log ε=2.726 (Nazarov et al., 1959 gave λmax. 308 mμ., log ε=3.444).

PMR spectrum ($CDCl_3$):

δ1.21 (5-methyl doublet), δ1.63 (2-methyl singlet), δ6.77 (C-2-H singlet).

It gave a picrate from ethanol m.p. 132-145° (reported 152-154°).

Anal. calcd. for $C_8H_{13}NO \cdot C_6H_3N_3O_7$ C,45.65; H,4.38.

Found: C,45.77; H,4.54.

1,2,5-TRIMETHYL-4-PHENYL-1,2,3,4-TETRAHYDRO-4-PYRIDINOL (209)

Phenyllithium, prepared from lithium (0.84 g.; 0.12 mole) and bromobenzene (9.4 g.; 0.06 mole) in dry ether (50 ml.), was added slowly over 20 minutes from a dropping funnel to a stirred solution of 1,2,5-trimethyl-2,3-dihydro-4-pyridone (7.5 g.; 0.05 mole) in dry ethanol (50 ml.) in a dry ice and acetone bath (-78°). When the addition was complete, the cooling bath was removed, the flask allowed to attain room temperature and then stirred for an additional 15 minutes. The mixture was decomposed with water (20 ml.), the ether layer separated, dried (Na_2SO_4) and evaporated to leave the crude title compound as an oil (6 g.).

IR spectrum (film):

νmax. 3380 (OH str.), 1590 (broad band due to C=C) cm^{-1}, 695 and 750 cm^{-1} (monosubstituted benzene).

PMR spectrum ($CDCl_3$):

δ1.13 (5-methyl doublet, major isomer); δ1.38 (5-methyl doublet, minor isomer); δ1.55 (2-methyl singlet, major isomer); δ1.45 (2-methyl singlet, minor isomer).

The oil could not be induced to solidify (Nazarov reported a solid obtained from iso-octane, m.p. 105-107°) and would not give a satisfactory analysis. The PMR indicated the oil essentially to be the correct compound and thus it was used in the next step.

ATTEMPTED PREPARATION OF α/β-1,2,5-TRIMETHYL-4-PHENYL-4-PIPERIDINOL (210)

The crude 1,2,5-trimethyl-4-phenyl-1,2,3,4-tetrahydro-4-pyridinol (6 g.), prepared previously, was hydrogenated at room temperature and pressure over platinum oxide (Adam's catalyst) (0.2 g.) in absolute ethanol (200 ml.) for 18 hours. Although more than the theoretical amount of hydrogen was absorbed, PMR analysis showed the presence of the vinylic methyl group at δ1.55 remained. In an attempt to complete hydrogenation, palladium charcoal (0.3 g.) was substituted for the platinum catalyst and hydrogenation continued for 7 days (only a small amount of hydrogen absorbed). A sample of the total product displayed many unresolvable peaks in the PMR spectrum, as well as a strong signal for the vinylic methyl group. Therefore the reaction was discontinued.

BROMINATION OF 1,2,5-TRIMETHYL-4-PIPERIDONE IN METHANOL AND HYDROBROMIC ACID

Aqueous 48% hydrobromic acid (21.8 g.; 0.146 mole) was added dropwise with cooling (0°) and stirring to a solution of 1,2,5-trimethyl-4-piperidone (10 g.; 0.072 mole) in absolute methanol (100 ml.). After stirring for 30 minutes, bromine (11.4 g.; 0.072 mole) was added slowly from a dropping funnel and the mixture stirred overnight. Ether was added until crystallization started and the flask set in the fridge overnight. Crystals of bromo-1,2,5-trimethyl-4-piperidone hydrobromide (8 g.) were collected, m.p. 157-159°.

IR spectrum (nujol mull):

νmax. 1740 cm^{-1} (C=O str.).

PMR spectrum ($CDCl_3$):

Similar to the 5-bromo analogue obtained earlier except the spectrum showed evidence of either 3-bromo or starting material present as well.

Fractional crystallization produced a major amount of 1,2,5-trimethyl-5-bromo-4-piperidone (m.p. 145-146°) which had a PMR identical to the same product prepared earlier. Further crystallization of the mother liquors remaining produced a sample that was tentatively identified as a mixture of 1,2,5-trimethyl-4-piperidone and the 3-bromo product (as shown by analysis and PMR spectrum).

BROMINATION OF 1,2,5-TRIMETHYL-4-PIPERIDONE IN METHANOL

25% Hydrobromic acid in absolute methanol (24 ml.; 0.073 mole) was added dropwise to a cooled stirred solution of 1,2,5-trimethyl-4-piperidone (5 g.; 0.036 mole) in absolute methanol (50 ml.). After stirring 30 minutes, bromine (5.7 g.; 0.036 mole) was added slowly from a dropping funnel and then the mixture was stirred overnight. The bulk of the methanol was removed and ether was added until crystallization began. PMR spectra evidence of the total hydrobromide salt thus isolated showed it to be identical to that previously prepared in methanol and aqueous hydrobromic acid. Again it was not found possible to isolate the desired 1,2,5-trimethyl-3-bromo-4-piperidone.

N-ALKYL-2-METHYL-4-PHENYL-4-PIPERIDINOL AND DERIVATIVES

1,2-DIMETHYL-4-PHENYL-4-PIPERIDINOL (300)

1,2-Dimethyl-4-piperidone (25.4 g.; 0.2 mole) was added slowly from a dropping funnel to a stirred solution of phenyllithium in dry ether (150 ml.), prepared from lithium (3.4 g.; 0.48 mole) and bromobenzene (37.7 g.; 0.24 mole). When the addition was complete, the mixture was allowed to stir overnight and then refluxed 4 hours, cooled, and poured onto ice and glacial acetic acid (50 ml.). The ether layer was separated and washed once with 50 ml. dilute acetic acid.

The combined aqueous layers were reduced in volume at low pressure and then basified with strong ammonium hydroxide solution and extracted with chloroform (10 × 150 ml.). The chloroform was dried (Na_2SO_4) and evaporated to leave a residue (28 g.) which proved to be a mixture of isomers of the title compound.

The residue was diluted with petroleum ether and fractionally crystallized to give first an isomer (2.6 g.) melting at 106-108° which corresponded to the β-form isolated by Mistryukov et al. (1967), who reported m.p. 106-108°.
IR spectrum (nujol mull):
νmax. 3140 (OH str.), 690, 760 (monosubstituted benzene) cm^{-1}.

It gave a hydrochloride from ether/HCl which was extremely hygroscopic and would not give a good melting point (m.p. obtained 78-84°).

It also gave a methiodide from acetone m.p. 183-184°.
Anal. calcd. for $C_{14}H_{22}INO$ C,48.42; H,6.39; N,3.70.
Found: C,48.73; H,6.09; N,3.96.

It also gave a benzyl chloride quaternary salt from acetone m.p. 230-231°.
Anal. calcd. for $C_{20}H_{26}ClNO$ C,72.40; H,7.90; N,4.22.
Found: C,72.53; H,8.05; N,4.31.

The α-isomer would not crystallize out in a pure form thus the mother liquors remaining from the isolation of the β-isomer were chromatographed on a column (2 × 40 cm.) filled to 30 cm. with Woelm alumina (neutral, activity grade 1) and eluted with dry chloroform at a flow rate of 1 ml./

min. The first fraction proved to be unreacted ketone. The second band that was eluted was found to be a mixture of α- and β-isomers followed finally by pure α-isomer.

The α-isomer had m.p. 122-123° (Mistryukov and Aronova, 1967, reported 122-123°).

IR spectrum (nujol mull):

νmax. 3140 (OH str.), 690, 760 (mono subs. benzene) cm^{-1}.

It gave a hydrochloride from ethanol-ether, m.p. 193-194°.

Anal. calcd. for $C_{13}H_{19}NO \cdot HCl$ C,64.58; H,8.34; N,5.80.

Found: C,64.72; H,8.17; N,5.69.

It also gave a methiodide from acetone, m.p. 122-123°.

Anal. calcd. for $C_{14}H_{22}NOI$ C,48.42; H,6.39; N,3.70.

Found: C,48.79; H,6.42; N,3.70.

It gave a benzyl chloride quaternary salt from acetone, m.p. 221-222°.

Anal. calcd. for $C_{20}H_{26}NOCl$ C,72.40; H,7.90; N,4.22.

Found: C,72.11; H,7.72; N,4.31.

β-1,2-DIMETHYL-4-PHENYL-4-ACETYLOXY (AND PROPIONYLOXY) PIPERIDINE (329) and (334)

Acetyl chloride (1.6 g.) was added to a solution of β-1,2-dimethyl-4-phenyl-4-piperidinol (0.4 g.) in dry benzene (50 ml.) and refluxed overnight. Ether was added and crystals of β-1,2-dimethyl-4-phenyl-4-acetyloxypiperidine hydrochloride (0.35 g.) separated, m.p. 208-209°.

IR spectrum (nujol mull):

νmax. 1755 cm^{-1} (C=O str.), OH (3140 cm^{-1}) absent.

Anal. calcd. for $C_{15}H_{21}NO_2 \cdot HCl$ C,63.48; H,7.82; N,4.94.
Found: C,63.12; H,7.90; N,4.80.

It gave a methiodide from acetone, m.p. 234-236°.
Anal. calcd. for $C_{16}H_{24}INO$ C,49.36; H,6.21; N,3.59.
Found: C,50.19; H,6.17; N,3.99.

Similarly was prepared the β-1,2-dimethyl-4-phenyl-4-propionyloxypiperidine hydrochloride from propionyl chloride, m.p. 194-195°.
IR spectrum (nujol mull):
νmax. 1750 cm^{-1} (C=O str.), OH (3140 cm^{-1}) absent.
Anal. calcd. for $C_{16}H_{23}NO_2 \cdot HCl$ C,64.53; H,8.12; N,4.70.
Found: C,64.84; H,8.14; N,4.85.

α-1,2-DIMETHYL-4-PHENYL-4-ACETYLOXY (AND PROPIONYLOXY) PIPERIDINE (330) and (333)

Acetyl chloride (1.6 g.) was added to a solution of α-1,2-dimethyl-4-phenyl-4-piperidinol (0.5 g.) in dry benzene (50 ml.) and the mixture refluxed overnight. Ether was added to the benzene and crystals of α-1,2-dimethyl-4-phenyl-4-acetyloxypiperidine hydrochloride separated (0.44 g.), m.p. 184-185°.
IR spectrum (nujol mull):
νmax. 1750 cm^{-1} (C=O str.), OH (3140 cm^{-1}) absent.
Anal. calcd. for $C_{15}H_{21}NO_2 \cdot HCl$ C,63.48; H,7.81; N,4.94.
Found: C,63.58; H,7.68; N,5.20.

It gave a methiodide from acetone, m.p. 214-216°.
Anal. calcd. for $C_{16}H_{24}INO$ C,49.36; H,6.21; N,3.59.

Found: C,49.36; H,5.92; N,3.66.

Similarly was prepared α-1,2-dimethyl-4-phenyl-4-propionyloxypiperidine hydrochloride from propionyl chloride. Crystals were found to be very hygroscopic, m.p. 85-95°.
IR spectrum (nujol mull—difficult to make):
νmax. 1750 cm^{-1} (C=O str.), OH (3320 cm^{-1}) very weak, (probably atmospheric water absorbed when attempting to triturate).
Anal. calcd. for $C_{16}H_{23}NO_2 \cdot HCl$ C,64.53; H,8.12; N,4.73.
Found: C,64.31; H,8.11; N,4.73.

α-1,2-DIMETHYL-4-PHENYLPIPERIDINE

α-1,2-dimethyl-4-phenyl-4-piperidinol (0.2 g.) was added to a rapidly stirred suspension of Raney nickel (2 g.) in absolute ethanol (150 ml.) and refluxed 8 hours. The catalyst was filtered off and the ethanol evaporated to leave an oil, which proved to be the title compound, but which also was found to contain a small amount of the β-isomer (PMR evidence).
IR spectrum (film):
OH (3140 cm^{-1}) absent.

It gave a hydrochloride (hygroscopic) from ethanol-ether, m.p. 101-105°, which could not be obtained pure and free from contamination with a small amount of the β-isomer.
Anal. calcd. for $C_{13}H_{19}N \cdot HCl$ C,69.16; H,8.93; N,6.21.
Found: C,69.21; H,8.87; N,6.30.

It also gave a methiodide from acetone, m.p. sinters at 160°, melts at 172-174°.

Anal. calcd. for $C_{14}H_{22}IN$ C,50.76; H,6.70; N,4.23.
Found: C,51.07; H,6.64; N,4.36.

β-1,2-DIMETHYL-4-PHENYLPIPERIDINE (327)

β-1,2-dimethyl-4-phenyl-4-piperidinol (0.2 g.) was added to a rapidly stirred suspension of Raney nickel (2 g.) in absolute ethanol (150 ml.) and refluxed 4 hours. The catalyst was filtered off and the ethanol evaporated to leave the title compound as an oil.

IR spectrum (film):
νmax. OH (3140 cm^{-1}) absent.

It gave a hydrochloride from ethanol-ether, m.p. 174-175°.
Anal. calcd. for $C_{13}H_{19}N \cdot HCl$ C,69.16; H,8.93; N,6.21.
Found: C,69.24; H,9.03; N,6.32.

It also gave a methiodide from acetone, m.p. 164-165°.
Anal. calcd. for $C_{14}H_{22}IN$ C,50.76; H,6.70; N,4.23.
Found: C,50.59; H,6.99; N,4.32.

DEHYDRATION OF α-1,2-DIMETHYL-4-PHENYL-4-PIPERIDINOL (303)

α-1,2-dimethyl-4-phenyl-4-piperidinol (1 g.) was added to a mixture of concentrated hydrochloric acid (33 ml.) and glacial acetic acid (66 ml.) and refluxed for 4 hours. The solvents were evaporated completely under reduced pressure to give a mixture of alkene hydrochlorides, m.p. 192-194°, as evidenced by the PMR signals at δ1.16 and δ2.00 for the 2-methyl doublets and two vinylic signals at δ5.87 and δ6.05 (base in $CDCl_3$).

IR spectrum (nujol mull):

νmax. 1595 cm^{-1} (C=C str.), OH (3140 cm^{-1}) virtually absent.

Anal. calcd. for $C_{13}H_{17}N \cdot HCl$ C,69.79; H,8.11; N,6.26.

Found: C,69.70; H,8.45; N,6.53.

The two alkene components, 1,2-dimethyl-4-phenyl-1,2,5,6-tetrahydro-4-pyridinol and 1,6-dimethyl-4-phenyl-1,2,5,6-tetrahydro-4-pyridinol isomers, were not separated.

ATTEMPTED PREPARATION OF α-1,2-DIMETHYL-4-PHENYL-4-CHLORO-PIPERIDINE (317)

Fresh distilled thionyl chloride (1 g.; 0.008 mole) was added slowly from a dropping funnel to a stirred, cooled (0°) solution of α-1,2-dimethyl-4-phenyl-4-piperidinol (0.82 g.; 0.004 mole) in dry chloroform (100 ml.). When the addition was complete the mixture was refluxed for 4 hours. The solvent was evaporated to leave a solid which proved to be a mixture of alkene hydrochlorides, m.p. 185-186°. Mixed m.p. with the previously prepared α-alkene mixture 188-189°. IR spectrum (nujol mull) and PMR spectrum ($CDCl_3$) were identical with that previously prepared.

β-1,2-DIMETHYL-4-PHENYL-4-CHLOROPIPERIDINE (318)

Freshly distilled thionyl chloride (1 g.; 0.008 mole) was added slowly from a dropping funnel to a stirred, cooled (0°) solution of β-1,2-dimethyl-4-phenyl-4-piperidinol (0.82 g.; 0.004 mole) in dry chloroform (100 ml.). When the addition was complete the mixture was refluxed for 4 hours.

The solvent was evaporated to leave the title compound as the hydrochloride.

Recrystallization from ethanol-ether gave pure β-1,2-dimethyl-4-phenyl-4-chloropiperidine hydrochloride, m.p. 159-159.5°.

IR spectrum (nujol mull):

νmax. 1590 cm^{-1} (C=C str. weak); OH (3140 cm^{-1}) absent; 695 and 750 cm^{-1} (monosubstituted benzene).

Anal. calcd. for $C_{13}H_{18}NCl \cdot HCl$ C,60.01; H,7.36; N,5.38; Cl,27.25.

Found: C,60.09; H,7.39; N,5.40; Cl,27.27.

N-METHYL-4-PHENYL-4-ACETYLOXY PIPERIDINE (326)

Acetyl chloride (0.47 g.; 0.006 mole) was slowly added to N-methyl-4-phenyl-4-piperidinol (1 g.; 0.005 mole) in benzene (50 ml.) and the mixture gently refluxed 4 hours. The flask was allowed to sit at room temperature overnight and the solid which separated was then filtered off.

The infrared spectrum showed no OH absorption band but did show an intense C=O absorptions at 1740 cm^{-1} and an intense C=C band at 1590 cm^{-1}. The PMR spectrum (hydrochloride in $CDCl_3$) showed that a substantial amount of elimination had occurred by the appearance of a vinylic peak near δ5.4.

N-METHYL-4-PHENYL-4-ACETYLOXYPIPERIDINE (326)

N-methyl-4-piperidone (11.3 g.; 0.1 mole) was added dropwise to phenyllithium in dry ether (200 ml.), prepared from lithium (1.54 g.; 0.22 mole) and bromobenzene (17.3 g.; 0.11 mole). When the addition was complete the mixture was refluxed 4 hours and then cooled in ice, then acetic anhydride (22.4 g.; 0.22 mole) was added and the mixture again refluxed 1 hour. The reaction was poured onto ice and acetic acid (20 ml.). The ether layer was removed and the aqueous layer basified with dilute ammonium hydroxide until just slightly basic. This was extracted with $CHCl_3$ (2 × 100 ml.) which was then dried (Na_2SO_4) and evaporated to leave an oil (10 g.) which proved to be the title compound.

IR spectrum (film):

νmax. 1740 cm^{-1} (C=O str.).

It gave a hydrochloride from ethanol-ether which melted at 228-229° (Jensen et al., 1943, reported 233-234°).

Anal. calcd. for $C_{14}H_{19}NO_2 \cdot HCl$ C,62.33; H,7.47; N,5.19.

Found: C,62.16; H,7.40; N,4.77.

N-METHYL-4-PHENYL-4-PROPIONYLOXYPIPERIDINE (335)

N-methyl-4-piperidone (11.3 g.; 0.1 mole) was added dropwise to phenyllithium in dry ether (200 ml.), prepared from lithium (1.54 g.; 0.22 mole) and bromobenzene (17.3 g.; 0.11 mole). When the addition was complete the mixture was refluxed for 4 hours and then the flask was cooled in ice, propionic anhydride (28.6 g.; 0.22 mole) was added slowly

and then the reaction was refluxed gently for 1 hour. The mixture was poured onto ice and glacial acetic acid (20 ml.). The ether layer was removed and the aqueous layer just basified with dilute ammonium hydroxide. The free base was extracted with $CHCl_3$ (2 × 100 ml.), the $CHCl_3$ was dried (Na_2SO_4) and evaporated to leave an oil (10.5 g.) which proved to be the title compound.

IR spectrum (film):

νmax. 1740 cm^{-1} (C=O str.).

It gave a hydrochloride from ethanol-ether which melted at 189-190° (Jensen et al., 1943, reported 183-184°).

Anal. calcd. for $C_{15}H_{21}NO_2 \cdot HCl$ C,63.48; H,7.82; N,4.94.
Found: C,63.40; H,7.70; N,4.88.

N-BENZYL-2-METHYL-4-PHENYL-4-PIPERIDINOL (336) (337)

N-benzyl-2-methyl-4-piperidone (20.3 g.; 0.1 mole) was added slowly from a dropping funnel to phenyllithium in dry ether (300 ml.), prepared from lithium (1.68 g.; 0.24 mole) and bromobenzene (19 g.; 0.12 mole). When the addition was complete the mixture was refluxed gently overnight, and then poured onto ice and glacial acetic acid (50 ml.). The ether layer was removed and the aqueous layer basified with solid sodium hydroxide. The free base liberated was extracted with chloroform (3 × 100 ml.) which was then dried (Na_2SO_4) and evaporated to leave an oil (21 g.).

Fractional crystallization of the hydrobromide salt from ethanol-ether produced one isomer (termed β) which

melted at 200-201° (0.6 g.).

IR spectrum (nujol mull):

νmax. 3400 cm^{-1} (OH str.).

PMR spectrum (base in $CDCl_3$):

δ1.27 (2-methyl doublet), δ3.17 and δ3.97 (benzylic methylene AB quartet, J=13.5 Hz).

Anal. calcd. for $C_{19}H_{23}NO \cdot HBr$ C,62.99; H,6.77; N,3.87.
Found: C,62.64; H,6.44; N,3.70.

The mother liquors remaining were converted back to the free base and then 1 g. was chromatographed on a column (1 × 30 cm.) filled to 28 cm. with Woelm neutral (activity 1) alumina and eluted with chloroform at a flow rate of 1 ml./min. Five 25 ml. fractions were collected, after an initial 75 ml. of $CHCl_3$ had been eluted. The first fraction contained nearly pure α-isomer, followed by two fractions containing mixtures and finally the last two fractions containing the β-isomer.

Fractionaly crystallization as the hydrobromide from ethanol-ether produced essentially pure α-N-benzyl-2-methyl-4-piperidinol which melted at 189-190° (0.06 g.).

IR spectrum (nujol mull):

νmax. 3400 cm^{-1} (OH str.).

PMR spectrum (base in $CDCl_3$):

δ1.22 (2-methyl doublet), δ3.50 (benzylic methylene protons singlet).

Anal. calcd. for $C_{19}H_{23}NO \cdot HBr$ C,62.99; H,6.77; N,3.87.
Found: C,63.33; H,7.08; N,3.75.

α-2-METHYL-4-PHENYL-4-PIPERIDINOL (338)

Palladium charcoal (0.05 g.) was added to a solution of α-N-benzyl-2-methyl-4-phenyl-4-piperidinol (.06 g.) in absolute ethanol (50 ml.) and hydrogenated at room temperature and pressure for 24 hours, by which time the uptake of hydrogen had ceased. The catalyst was filtered off and the solvent evaporated to leave an oil.

PMR spectrum ($CDCl_3$):

δ1.08 (2-methyl doublet), singlet for benzylic methylene protons absent. The N-H proton was not clearly visible.

The product was not analyzed but used directly in the next step.

β-2-METHYL-4-PHENYL-4-PIPERIDINOL (339)

Palladium charcoal (0.1 g.) was added to a solution of β-N-benzyl-2-methyl-4-phenyl-4-piperidinol (0.4 g.) in absolute ethanol (50 ml.) and hydrogenated at room temperature and pressure for 24 hours, at which time the uptake of hydrogen ceased. The catalyst was filtered off and the ethanol evaporated to leave an oil (0.1 g.).

PMR spectrum ($CDCl_3$)

δ0.98 (2-methyl doublet), AB quartet of benzylic methylene protons absent; δ2.82 broad singlet which disappeared upon the addition of D_2O—may be N-H proton.

ATTEMPTED METHYLATION OF α-2-METHYL-4-PHENYL-4-PIPERIDINOL

Methyl iodide (.021 g.; 0.00015 mole) was added (using a microsyringe) to α-2-methyl-4-phenyl-4-piperidinol (approximately 0.03 g.; 0.00015 mole) in acetone (10 ml.) and the mixture let stir at room temperature overnight. The solvent was evaporated and the total product examined by PMR spectroscopy in DMSO-d_6. The small amount of sample made certain analysis impossible, however, the N-methyl region exhibited a multiplet which indicated that both the mono N-methyl product and as well the quaternary salt were likely present.

PHARMACOLOGY EXPERIMENTAL

Dr. E.L. May, Chief of the Medicinal Chemistry Section of the National Institute of Health, Bethesda, Maryland, carried out the routine screening for analgesic potency of some of the compounds prepared in the course of this work using an adaptation of the hot plate method.

Mice which have been delivered by Caesarian section (called Caesarian Derived General Purpose mice - C.D.G.P.) have been found, when kept under very sanitary conditions, to be much more sensitive to analgesics without significantly lowering the toxicity limits. This increase in the therapeutic limit (LD_{50}/ED_{50}) allows for examination of analgesics of low potency which would otherwise not be detected.

The actual method employed was based on a procedure outlined by Eddy and Leimbach (1953). The analgesic potency of all compounds was determined at the peak of activity. The onset, peak and duration of all active compounds were found to be in the vicinity of 3, 15 and 150 minutes respectively.

REFERENCES

REFERENCES

Abdel-Monem, M.M., Larson, D.L., Kupferberg, H.J., and Portoghese, P.S., Am. Chem. Soc. Abstr. Papers, Chicago Sept., 1970.

Ahmed, F.R., Barnes, W.H., and Kartha, G., Chem. Ind. (London), 485 (1959).

Ahmed, F.R., Barnes, W.H., and Masironi, L.A., Chem. Ind. (London), 97 (1962).

Ahmed, F.R., Barnes, W.H., and Masironi, L.A., Acta. Cryst., 16, 237 (1963).

Allinger, N.L., Allinger, J., DaRooge, M.A., and Greenberg, S., J. Org. Chem., 27, 4603 (1962).

Archer, S., Am. Chem. Soc. Abstr. Papers, 113rd Meeting, San Francisco, April 1958, p. 4M.

Baty, J.D., Jones, G., and Moore, C., J. Chem. Soc., 2645 (1967).

Becker, E.D., J. Chem. Ed., 42, 591 (1965).

Beckett, A.H., and Walker, J., J. Pharm. Pharmacol., 7, 1039 (1952).

Beckett, A.H., and Casy, A.F., J. Pharm. Pharmacol., 6, 986 (1954).

Beckett, A.H., and Walker, J., J. Pharm. Pharmacol., 6, 1039 (1955).

Beckett, A.H., in "Progress in Drug Research", (E. Jucker, ed.), Vol. 1, p. 455. Birkhauser Verlag, Basel, Switzerland (1959).

Beckett, A.H., Casy, A.F., and Harper, N.J., Chem. Ind. (London), 19 (1959).

Barfield, M., and Grant, D.M., J. Am. Chem. Soc., 85, 1899 (1963).

Beckett, A.H., Casy, A.F., and Kirk, G., J. Med. Pharm. Chem., 1, 37 (1959).

Beckett, A.H., Brit. Paten 832,490, April 13, 1960.

Beckett, A.H., and Casy, A.F., in "Progress in Medicinal Chemistry", (G.P. Ellis and G.B. West, eds.), Vol. 2, p. 43, Butterworths, London (1962).

Beckett, A.H., and Casy, A.F., in "Progress in Medicinal Chemistry", (G.P. Ellis and G.B. West, eds.), Vol. 4, p. 171, Butterworths, London (1965).

Beckett, A.H., Casy, A.F., and Iorio, M.A., Tetrahedron, 22, 2745 (1966).

Beecher, H.K., Pharmacol. Rev., 9, 59 (1957).

Benson, W.M., Cunningham, D.J., Hane, D.L., VanWinkle, S., Arch. Intern. Pharmacodyn., 109, 171 (1957).

Bhacca, N.S., and Williams, D.H., "Application of NMR Spectroscopy in Organic Chemistry", p. 18,185, Holden-Day, San Francisco (1964).

Bloomfield, J.J., J. Org. Chem., 26, 4112 (1961).

Bloomfield, J.J., and Fennessey, P.V., Tetrahedron Letters, 33, 2273 (1964).

Bonner, W.A., and Zderic, J.A., J. Am. Chem. Soc., 78, 3218 (1956).

Booth, H., Tetrahedron, 22, 615 (1966).

Braenden, O.J., Eddy, N.B., and Halbach, H., Bull. World. Health Organ., 13, 937 (1955).

Brignell, P.J., Katritzky, A.R., and Russell, P.L., J. Chem. Soc., 1459 (1968).

Carabateas, P.M., and Grumbach, L., J. Med. Pharm. Chem., 5, 913 (1962).

Carr, J.B., and Huitric, A.C., J. Org. Chem., 29, 2506 (1964).

Casy, A.F., J. Chem. Soc., 5057 (1961).

Casy, A.F., Beckett, A.H., Hall, G.H., Vallance, D.K., J. Med. Pharm. Chem., 4, 535 (1961).

Casy, A.F., Experientia, 20, 437 (1964).

Casy, A.F., Tetrahedron, 22, 2711 (1966).

Casy, A.F., Beckett, A.H., and Iorio, M.A., Tetrahedron, 23, 1405 (1967).

Casy, A.F., Iorio, M.A., and Pocha, P., J. Chem. Soc., 942 (1967).

Casy, A.F., J. Med. Chem., 11, 188 (1968).

Casy, A.F., Chatten, L.G., Khullar, K.K., J. Chem. Soc., 2491 (1969).

Casy, A.F., and Jeffery, W., unpublished data (1970).

Chang, F.F.C., Safar, P., and Lasagna, L., J. Pharmacol. Exp. Therap., 122, 370 (1958).

Cookson, R.C., Henstock, J., and Hudec, J., J. Am. Chem. Soc., 88, 1060 (1966).

DeKornfield, T.J., and Lasagna, L., J. Chronic Dis., 12, 252 (1960).

Demarco, P.V., Farkas, E., Doddrell, D., Mylari, B.L., and Wenkert, E., J. Am. Chem. Soc., 90, 5480 (1968).

Denton, J.E., and Beecher, H.K., J. Am. Med. Assoc., 141, 1146 (1949).

Eddy, N.B., and Leimbach, D., J. Pharmacol. Exp. Therap., 107, 385 (1953).

Eddy, N.B. Halbach, H., and Braenden, O.J., Bull. World Health Organ., 14, 353 (1956).

Eddy, N.B., Halbach, H., and Braenden, O.J., Bull. World Health Organ., 17, 569 (1957).

Eddy, N.B., and May, E.L., in "Synthetic Analgesics", Part II B, 6,7-Benzomorphans, Pergamon Press, Oxford (1966).

Eisleb, O., and Schaumann, O., Chem. Abstr., 33, 9442 (1939).

Eliel, E.L., in "Stereochemistry of Carbon Compounds", McGraw-Hill, New York (1962).

Eliel, E.L., Allinger, N.L., Angyal, S.J., and Morrison, G.A., in "Conformational Analysis", p. 436, Interscience Publishers, New York (1965).

Eliel, E., and Schroeter, S., J. Am. Chem. Soc., 87, 5031 (1965).

Eliel, E., and Gilbert, E., J. Am. Chem. Soc., 91, 5487 (1969).

Elpern, B., Gardner, L.N., and Gaumbach, L., J. Am. Chem. Soc., 79, 1951 (1957).

Ercoli, N., and Lewis, M.W., J. Pharmacol., 84, 301 (1945).

Fodor, G., and Nador, K., J. Chem. Soc., 721 (1953).

Foster, R.H.K., and Carmen, A.J., J. Pharmacol. Exp. Therap., 91, 195 (1947).

Ganellin, C.R., and Spickett, R.G.W., J. Med. Chem., 8, 619 (1965).

Garb, S., Crim, B.J., Thomas, G., "Pharmacology and Patient Care", 3rd Ed., p. 90, Springer, New York (1970).

Garbisch, E.W., J. Org. Chem., 27, 3363 (1962).

Garbisch, E.W., and Patterson, D.B., J. Am. Chem. Soc., 85, 3228 (1963).

Garbisch, E.W., J. Org. Chem., 30, 2109 (1965).

Garbisch, E.W., Chem. Comm., 806 (1967).

Gates, M., and Tschudi, G., J. Am. Chem. Soc., 74, 1109 (1952).

Goodman, L.S., and Gilman, A.Z., in "The Pharmacological Basis of Therapeutics", 3rd ed., p. 37, Macmillan, New York (1966).

Green, A.F., and Young, P.A., Brit. J. Pharmacol., 6, 572 (1951).

Grewal, R.S., Brit. J. Pharmacol., 7, 433 (1952).

Gulland, J.M., and Robinson, R., J. Chem. Soc., 980 (1923).

Hamlon, H.P., Okuda, S., Nakagawa, N., Tetrahedron Letters, 37, 2553 (1964).

Harper, N.J., Beckett, A.H., and Balon, A.D., J. Chem. Soc., 2704 (1960).

Harper, N.J., and Fullerton, S.E., J. Med. Pharm. Chem., 4, 297 (1961).

Harper, N.J., Chignell, C.F., and Kirk, G., J. Med. Chem., 7, 726 (1964).

Harris, S.C., and Blockus, L.F., J. Pharmacol. Exp. Therap., 104, 135 (1952).

Hassan, M.M.A., and Casy, A.F., Org. Mag. Res., 1, 389 (1969).

Hassan, M.M.A., and Casy, A.F., Org. Mag. Res., 2, 197 (1970).

Hassan, M.M.A., and Casy, A.F., unpublished data.

Hill, R.K., and Chan, T., Tetrahedron, 21, 2015 (1965).

House, H.O., in "Modern Synthetic Reactions", W.A. Benjamin, New York (1965).

Howard, T.J., and Morley, B., Chem. Ind. (London), 73 (1967).

Howton, D.R., J. Org. Chem., 10, 277 (1945).

Iorio, M.A., personal communication.

Isbell, H., Wikler, A., Eddy, N.B., Wilson, J.L., and Moran, C.F., J. Am. Med. Assoc., 135, 888 (1947).

Isbell, H., and Fraser, H.F., J. Pharmacol. Exp. Therap., 107, 524 (1953).

Jacobson, A.E., and May, E.L., J. Med. Chem., 8, 563 (1965).

Janssen, P.A.J., and Jageneau, A.H.M., J. Pharm. Pharmacol., 9, 981 (1957).

Janssen, P.A.J., and Eddy, N.B., J. Med. Pharm. Chem., 2, 31 (1959).

Janssen, P.A.J., Van de Westeringh, C., and Jageneau, A.H.M., Demoen, P.J.A., Hermans, B.K.F., Van Daell, G.H.D., Schellekens, K.H.L., Van der Eycken, C.A.M., and Niemegeers, C.J.E., J. Med. Pharm. Chem., 1, 281 (1959).

Janssen, P.A.J., in "Synthetic Analgesics", Part I, Diphenylpropylamines, Pergamon Press, London (1960).

Janssen, P.A.J., and Eddy, N.B., J. Med. Pharm. Chem., 2, 31 (1960).

Jensen, K., Lindquist, F., Rekling, E., and Wolffbrandt, C.G., Dansk. Tidskr. Farm., 17, 173 (1943); Chem. Abstr., 39, 2506 (1945).

Johnson, C.E., and Bovey, F.A., J. Chem. Phys., 29, 1012 (1958).

Kartha, G., Ahmed, F.R., and Barnes, W.H., Acta. Cryst., 13, 525 (1960).

Kawazoe, Y., Sato, Y., Natsume, M., Hasegawa, H., Okamoto, T., Tsuda, K., Chem. Pharm. Bull. (Tokyo), 10, 338 (1962).

Kawazoe, Y., and Tsuda, M., ibid, 15, 1405 (1967).

Keats, S., and Beecher, H.K., J. Pharmacol. Exp. Therap., 105, 109 (1952).

Khullar, K.K., Ph.D. Thesis, Alberta (1969).

Kirk, G., Ph.D. Thesis, London (1958).

Kugita, H., Inoue, H., Oine, T., Hayashi, G., and Nurimoto, S., J. Med. Chem., 1, 298 (1964).

Kuhn, R.A. and Bromley, R.B., J. Pharmacol. Exp. Therap., 101, 47 (1951).

Lasagna, L., and Beecher, H.K., J. Pharmacol. Exp. Therap., 112, 306 (1954).

Lemieux, R.U., and Stevens, J.D., Can. J. Chem., 43, 2059 (1965).

Lemieux, R.U., and Stevens, J.D., Can. J. Chem., 44, 249 (1966).

Lyle, R.E., Adel, R.E., and Lyle, G.G., J. Org. Chem., 24, 342 (1959).

Lyle, R.E., and Thomas, J.J., Tetrahedron Letters, 11, 897 (1969).

Mannich, C., and Ritsert, K., Ber., 57B, 116 (1924); Chem. Abstr., 18, 3360 (1924).

McElvain, S.M., and Stork, G., J. Am. Chem. Soc., 68, 1049 (1946).

McElvain, S.M., and Safranski, J.C., J. Am. Chem. Soc., 72, 3134 (1950).

McElvain, S.M., and Barnett, M.D., J. Am. Chem. Soc., 78, 3140 (1956).

Mellett, L.B., and Woods, L.A., in "Progress in Drug Research" (E. Jucker, ed.), Vol. 5, Birkhauser Verlag, Basel, Switzerland (1963).

Mistryukov, E.A., Aronova, N.I., and Kucherov, V.F., Bull. Acad. Sci. U.S.S.R., 866 (1961).

Mistryukov, E.A., and Aronova, N.I., Bull. Acad. Sci. U.S.S.R., 12, 2171 (1966).

Mitsui, S., Hebiguchi, K., and Saito, H., Chem. Ind. (London), 1746 (1967).

Mitsui, S., Kudo, Y., and Kobayashi, M., Tetrahedron, 25, 1921 (1969).

Morsch, K., Monatsh, 60, 50 (1932), Chem. Abstr., 26, 4030 (1932).

Moynehan, T.M., Schofield, K., Jones, R.A.Y., and Katritzky, A.R., J. Chem. Soc., 2637 (1962).

Nazarov, I.N., and Rudenko, V.A., Bull. Acad. Sci. U.S.S.R., 610 (1948); Chem. Abstr., 43, 2958h (1949).

Nazarov, I.N., Raigorodskaya, V.Ya., and Rudenko, V.A., Bull. Acad. Sci. U.S.S.R., 504 (1949); Chem. Abstr., 44, 3461 (1950).

Nazarov, I.N., and Rudenko, V.A., Chem. Abstr., 43, 2958 (1949).

Nazarov, I.N., Prostakov, N.S., and Shvetsov, N.I., J. Gen. Chem. U.S.S.R., 26, 3117 (1956).

Nazarov, I.N., Prostakov, N.S., and Mikheeva, N.N., J. Gen. Chem. U.S.S.R., 28, 2772 (1958).

Nazarov, I.N., and Shvetsov, N.I., Bull. Acad. Sci. U.S.S.R., 2059 (1959).

Noller, C.R., in "Chemistry of Organic Compounds", 3rd ed., p. 222, Saunders, Philadelphia (1965).

Ochiai, E., J. Org. Chem., 18, 534 (1953).

Orahovats, P.D., Lehman, E.G., and Chapin, E.W., J. Pharmacol. Exp. Therap., 119, 26 (1957).

Ouellette, R.J., J. Am. Chem. Soc., 86, 3089 (1964).

Pople, J.A., Schneider, W.B., and Bernstein, H.J., "High-Resolution Nuclear Magnetic Resonance", p. 410, McGraw-Hill, New York (1959).

Portoghese, P.S., J. Med. Chem., 8, 609 (1965).

Portoghese, P.S., and Larson, D.L., J. Pharm. Sci., 57, 711 (1968).

Prostakov, N.S., and Mikheeva, N.N., J. Gen. Chem. U.S.S.R., 31, 101 (1961).

Prostakov, N.S., and Mikheeva, N.N., Russ. Chem. Rev., 31, 556 (1962).

Prostakov, N.S., Zaitsev, B.E., Mikhailova, N.M., J. Gen. Chem. U.S.S.R., 34, 463 (1964).

Rader, C.P., J. Am. Chem. Soc., 91, 3248 (1969).

Richer, J.C., and Perrault, G., Can. J. Chem., 43, 18 (1965).

Robinson, D.L., and Theobald, D.W., Quart. Rev. (London), 21, 314 (1967).

Schaefer, J., in "Organic Reactions", (J.J. Bloomfield, ed.), Vol. 15, J. Wiley and Sons, New York (1967).

Schaumann, O., Brit. Med. J., ii, 1091 (1956).

Schmidle, C.J., and Mansfield, R.C., J. Am. Chem. Soc., 77, 5698 (1955).

Scott, A.I., in "Interpretation of the Ultraviolet Spectra of Natural Products", (D.H.R. Barton and W. Doering, eds.), Vol. 7, p. 58, Pergamon Press, New York (1964).

Shoolery, J.N., and Rogers, M.R., J. Am. Chem. Soc., 80, 5121 (1958).

Shvetsov, N.I., and Kucherov, V.F., Proc. Acad. Sci. U.S.S.R., 129, 451 (1959).

Siegal, S., and Smith, G., J. Am. Chem. Soc., 82, 6082 (1960).

Silverstein, R.M., and Bassler, G.C., in "Spectrometric Identification of Organic Compounds", 3rd ed., p. 87, John Wiley and Sons, New York (1968).

Sorokin, O.I., Bull. Acad. Sci. U.S.S.R., 424 (1961).

Sternhill, S., Quart. Rev. (London), 23, 236 (1969).

Takeda, M., Jacobson, A.E., and May, E.L., J. Org. Chem., 34, 4158 (1969).

Tarbell, D.S., and Vaughan, J.R., J. Am. Chem. Soc., 65, 231 (1943).

Thomas, C., Annual Review of NMR Spectroscopy (E.F. Mooney, ed.), Vol 3, p. 43 (1970).

Tori, K., and Komeno, T., Tetrahedron, 21, 309 (1964).

Tsuda, M., and Kawazoe, Y., Chem. Pharm. Bull. (Tokyo), 16, 702 (1968).

Vogel, A.I., in "Practical Organic Chemistry", 3rd ed., p. 870, Longmans, London (1964).

Weijlard, J., Orahovats, P.D., Sullivan, A.P., Purwue, G., Heath, F.K., and Pfister, K., J. Am. Chem. Soc., 78, 2342 (1956).

Wikler, A., A.M.A. Arch. Neurol. Psychiat., 67, 672 (1952).

Winter, C.A., Orahovats, P.D., and Lehman, E.G., Arch. Intern. Pharmacodyn., 110, 186 (1957).

Woolfe, G., and MacDonald, A.D., J. Pharm. Exp. Ther., 80, 300 (1944).

Yonezawa, T., Morishima, I., and Fukuta, K., Bull. Chem. Soc. Japan, 41, 2297 (1968).

Ziering, A., Berger, L., Heineman, S.D. and Lee, J., J. Org. Chem., 12, 834 (1947).

Ziering, A., and Lee, J., J. Org. Chem., 12, 911 (1947).

Ziering, A., Motchane, A., and Lee, J., J. Org. Chem., 22, 1521 (1957).