STUDIES IN ISOQUINOLINE CHEMISTRY RELATING TO MORPHINE ANALGESICS.

by

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Department of Chemistry

To my wife

Jane.

ACKNOWLEDGEMENT

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Finally, I am also most grateful to my wife for her continued help and understanding during the preparation of this work.

'Not poppy, nor mandragora,
Nor all the drowsy syrups of the world,
Shall ever medicine thee to that sweet sleep
Which thou owedst yesterday.'

William Shakespeare Othello, The Moor of Venice.
Act III, Scene III.

SUMMARY

Approaches to the synthesis of partially hydrogenated 8-ketoisoquinolines have been made via 5,6,7,8-tetrahydroisoquinoline and also via attempted Bischler-Napieralski cyclodehydration of a series of 3-oxygenated cyclohexenylphenylacetamide derivatives. This latter ring closure has been found not to take place and the former route also did not prove satisfactory.

The synthesis of ring-A bridged isoquinolines has been studied. Although thermal isomerisation of 2,5-dihydrophenylacetamides to give conjugated dienes followed by Diels-Alder reaction met with limited success, the Diels-Alder reaction of 1,2,3,4,7,8-hexahydro-6-methoxy-2-methylisoquinoline has been achieved with methyl vinyl ketone, phenyl vinyl ketone and 2-chloroacrylonitrile. The exo and endo cycloadducts have been separated by column and thin-layer chromatography and their stereochemistry assigned on the basis of n.m.r. studies.

Exo and endo ketone adducts have also been obtained from methyl vinyl ketone and 1,2,3,4,7,8-hexahydro-6-methoxy-2-formyl isoquinoline utilising potassium t-pentoxide in dimethylsulphoxide to effect conjugation.

The cycloadducts obtained from 1,2,3,4,7,8-hexahydro-6-methoxy-2-methylisoquinoline and 2-chloroacrylonitrile have been converted by base hydrolysis into 7-keto-1,2,3,4,-6,7,8,8a-octahydro-6-methoxy-2-methyl-6,8a-ethanoisoquinoline and this sequence effectively affords a method for the addition of the elements of ketene to the hexahydroisoquinoline system.

The synthesis of 1-benzyl-6-methoxy-1,2,3,4,5,8-hexahydroisoquinoline derivatives has been shown not to occur satisfactorily via Stevens rearrangement of an isoquinolinium salt, mixtures being given. However, partial Birch reduction of 1-benzylisoquinoline derivatives has been achieved. The

base-catalysed isomerisation and subsequent Diels-Alder reaction of the 2-methyl and 2-formyl-1-(4'-methoxybenzyl) compounds has been investigated and shown to give a mixture of Diels-Alder adducts and ene reaction products.

The Grignard reaction of the methyl vinyl ketone adducts from 1,2,3,4,7,8-hexahydro-6-methoxy-2-methylisoquinoline has been effected using n-propylmagnesium bromide and benzylmagnesium bromide. The stereochemistry of the resulting carbinols has been assigned on the basis of spectroscopic data. An acid-catalysed rearrangement of the tertiary carbinols has been shown to provide a novel synthesis of the [4,4,4]azapropellane system.

The 2-chloroacrylonitrile adduct obtained from 1,2,3,4,7,8-hexahydro-6-methoxy-2-methylisoquinoline and the benzyl carbinols derived from the M.V.K. Diels-Alder adducts have been found to have analgesic activity equivalent to morphine in the rat-tail pressure test.

CONTENTS

INTRODUCTION

INTRODUCTION

The aim of the work has been to synthesise certain novel compounds relating to the morphine analgesics. There are many reports in the literature, both of modifications of the relevant opium alkaloids themselves and of the synthesis and study of selected portions of the morphine skeleton. Unfortunately none of these approaches has produced an ideal analgesic drug totally free from unwanted side-effects.

In this introduction we attempt to review the main areas of previous work in this field.

The Opium Alkaloids

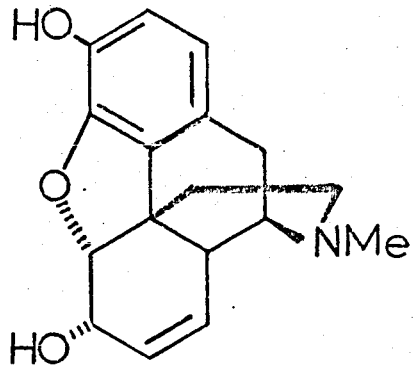
The distressing and isolating effect of pain has made its removal or alleviation one of the main objectives of medicine throughout the ages. Lack of knowledge of the fundamental physiology of pain and the mechanism by which the analgesic drugs exert their effect has hampered progress in the field of analgesia. Opium, the most ancient pain-relieving drug, still furnishes the most widely used potent analgesic agent, morphine(1), isolated by Friedrich Serturner in the nineteenth century. Since the isolation of morphine (1) twenty four other alkaloids have been isolated from poppy latex, the more important constituents being morphine (1) [9%]; codeine (2) [0.3%]; thebaine (3)[0.4%]; narcotine (4) [5.0%]; papaverine (5) [0.8%]; cryptopine (6) [0.01%]; laudanosine (7) [0.01%]; and narceine (8) [0.2%]. Two structural types can be discerned among the opium alkaloids:

1) Those related to 1-benzylisoquinolines exemplified by norlaudanosoline (9) and

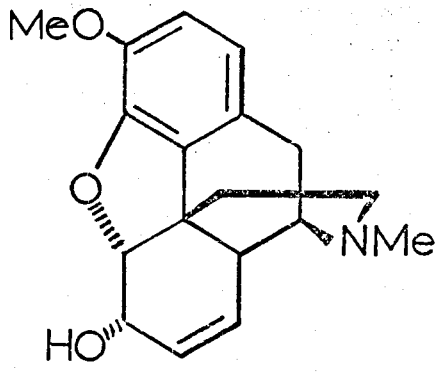
2) those incorporating the partially hydrogenated phenanthrene system common to morphine (1), codeine (2) and thebaine (3). These latter alkaloids can be regarded as being derived from the benzylisoquinoline (9) if the structure is depicted as (10).

Morphine

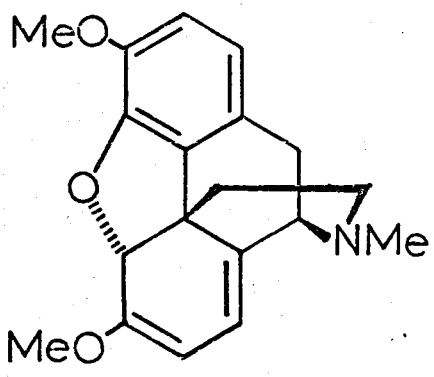
Morphine (1) is clearly the most important opium



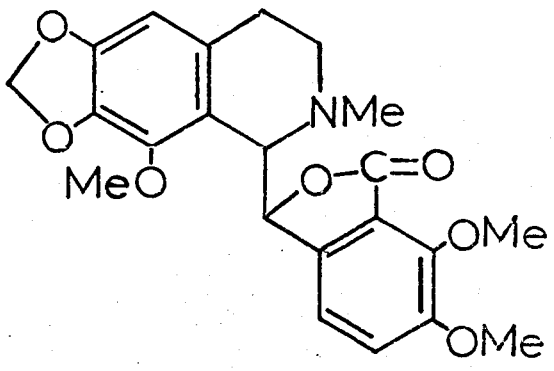
(1)
Morphine



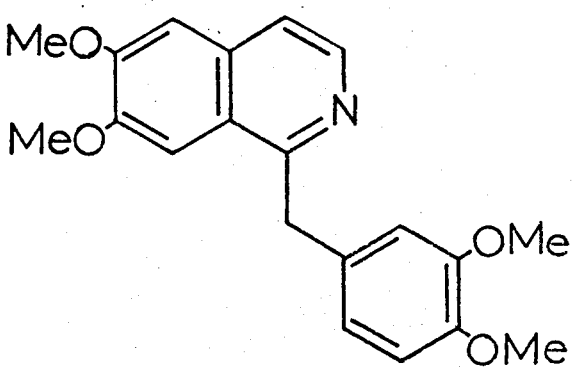
(2)
Codeine



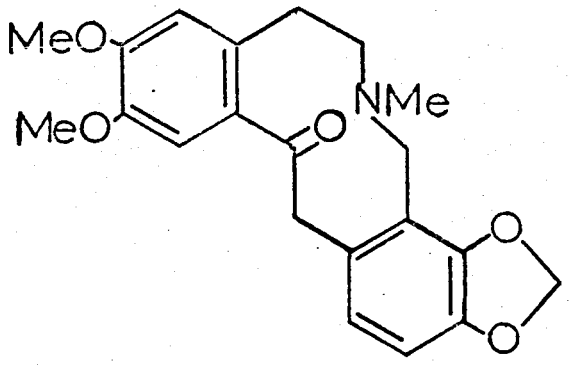
(3)
Thebaine



(4)
Narcotine

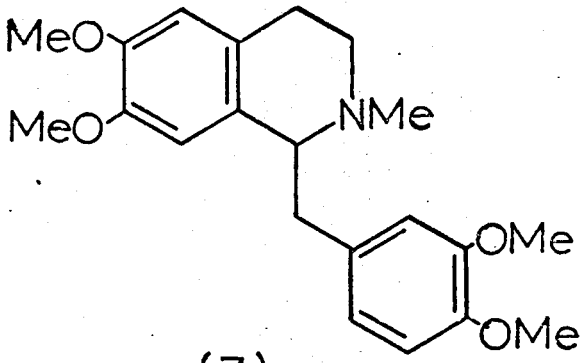


(5)
Papaverine



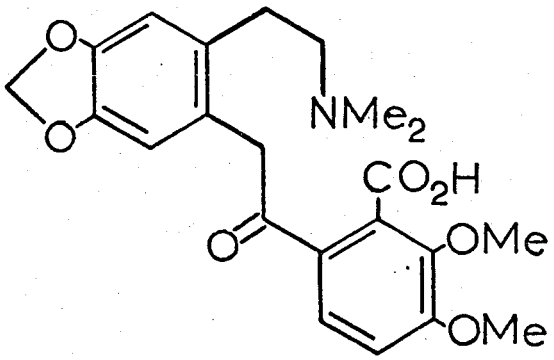
(6)

Cryptopine



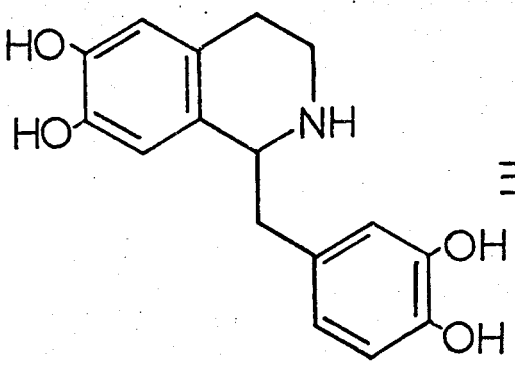
(7)

Laudanosine



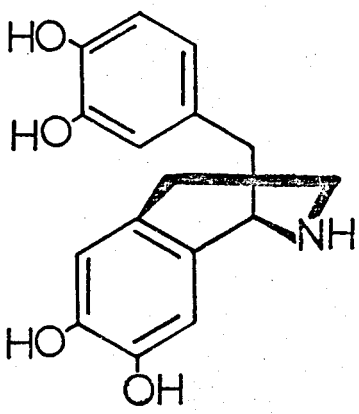
(8)

Narceine



(9)

Norlaudanosoline



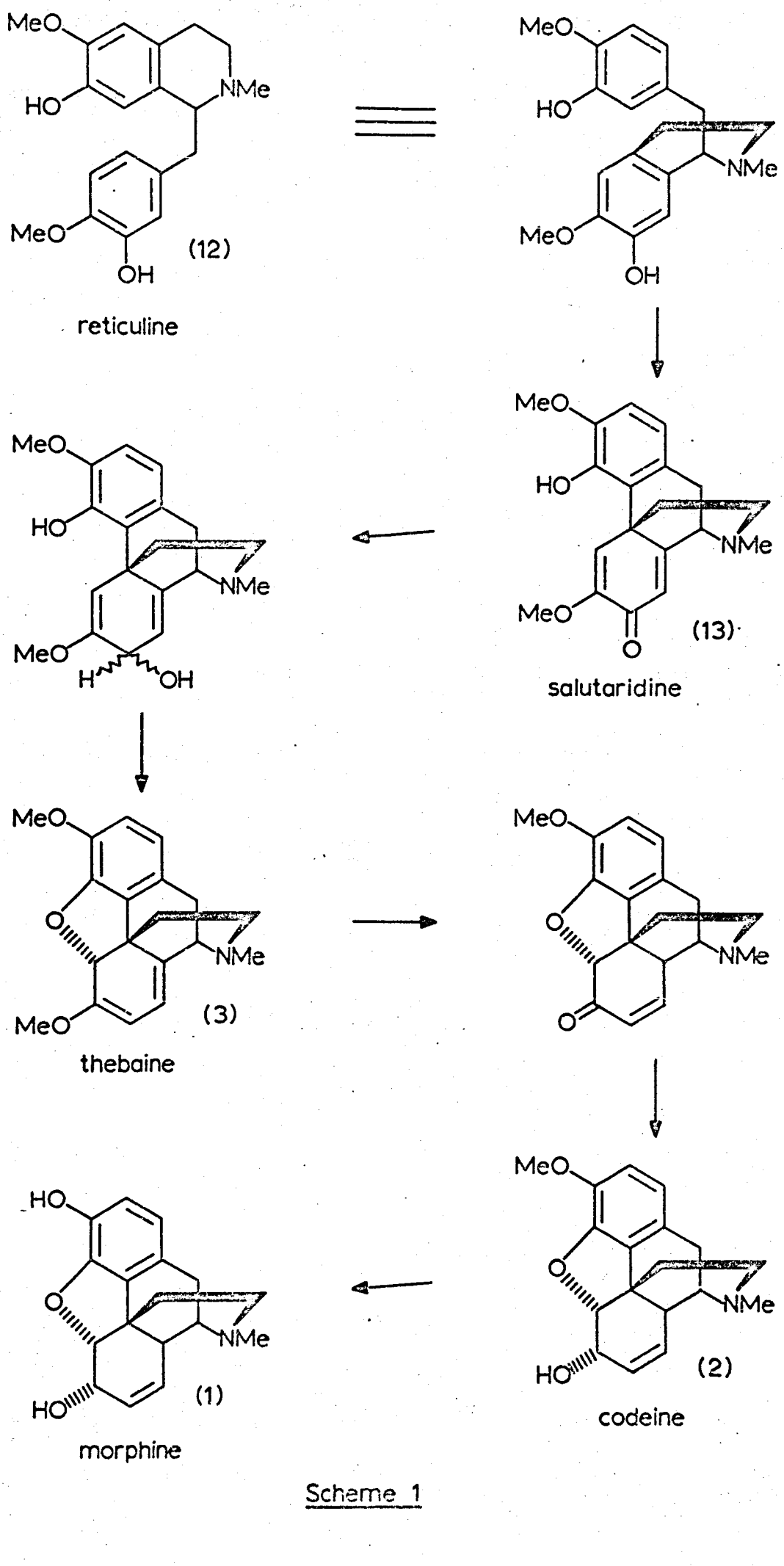
(10)

alkaloid because of its potent analgesic qualities. However its use is accompanied by several serious side-effects,[1,2] the most serious being its ability to produce physical and psychological dependence. The animal becomes dependent on the drug after repeated dosing. The observable symptom of physical dependence is the unpleasant withdrawal syndrome which manifests itself when the regular dose of the drug is withdrawn. Closely associated with dependence or addiction, is tolerance; in that the effective dose of drug required to elicit analgesia has to be increased after only a relatively short period of administration. Other serious side-effects associated with morphine and other analgesic agents that exert their effect in the central nervous system, include respiratory and cardiovascular depression, constipation and nausea. With the introduction of certain chemically related antagonists (see later p.18) it is now possible to counteract quickly the hazardous depressant reactions induced by morphine and morphine-like compounds. Removal of these side-effects, either by chemical modification of morphine or by the total synthesis of related compounds, has been a major target of medicinal chemists since the turn of the century. A totally synthetic analgesic agent would also obviate the present dependence on quantities of crude poppy latex (opium) from sources in the far east.

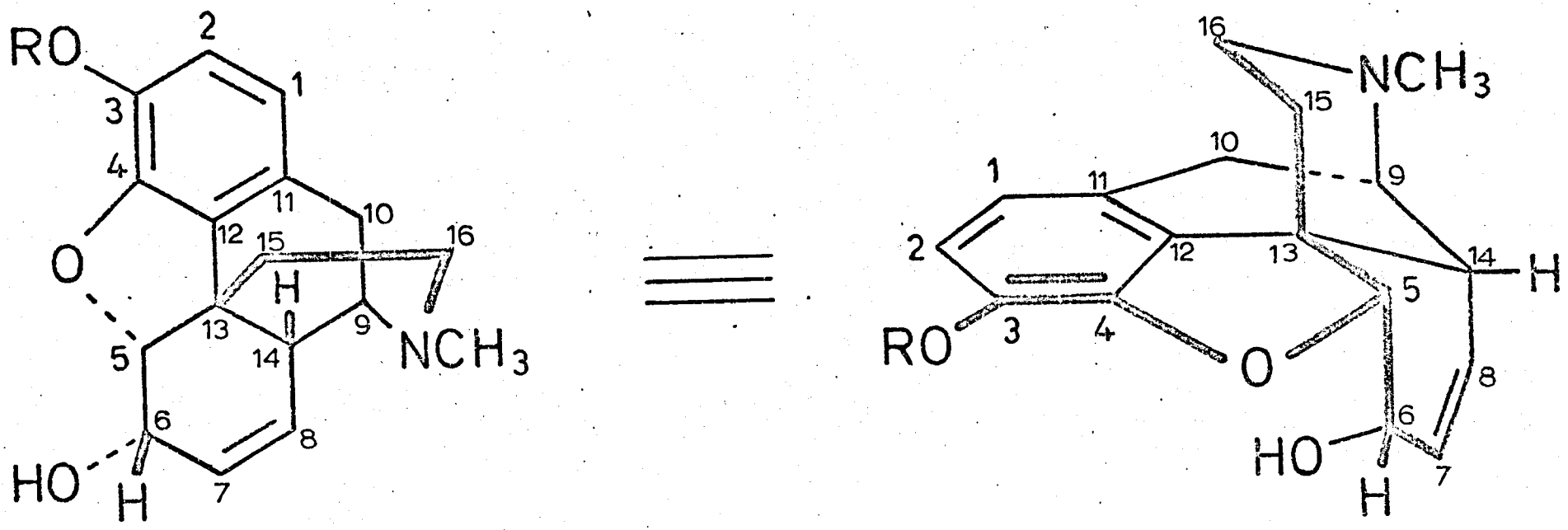
In 1925 the correct structure for morphine was proposed by Gulland and Robinson[3] and was later confirmed by the classic synthesis of the alkaloid by Gates and Tschudi.[4,5] Elucidation of the stereochemistry[6,7,8] and absolute configuration[9] have also been accomplished. It has been found that the hydrogens at carbons 5, 6 and 14 are cis orientated with respect to the iminoethano system likewise cis-fused to carbons 9 and 13 as depicted in structure (11).

Synthesis of the morphine system in which rings B and C are trans-fused has also been achieved.[10-13]

Upon completion of the structural picture, various biosynthetic studies directed at the clarification of the pathways involved in the formation of morphine and its congeners were undertaken. Tracer experiments have shown that morphine (1) is biosynthesised from salutaridine (13),


MeO
HO
NMe
MeO
OH
(12)
reticuline
MeO
HO
NMe
MeO
OH
MeO
HO
NMe
MeO
O
(13)
salutaridine
MeO
HO
NMe
MeO
H
OH
MeO
O
NMe
MeO
(3)
thebaine
MeO
O
NMe
O
HO
O
NMe
HO
(1)
morphine
MeO
O
NMe
HO
(2)
codeine

Scheme 1


RO
2
1
3
4
11
10
16
12
15
O
H
13
9
NCH3
5
14
6
8
HO
H
7
16
NCH3
15
10
1
11
9
2
12
13
14
H
5
RO
3
4
O
8
6
HO
H
7

(11)

formed via phenolic oxidation of reticuline (12), through thebaine (3) and codeine (2) as shown in scheme 1.[14] This biogenetic scheme has been duplicated in the laboratory by oxidising reticuline (12). The desired conversion was achieved by Barton[15] using tritium-labelled reticuline and constitutes a total synthesis of morphine and congeners analogous to the biogenetic route.

The natural alkaloid (1) clearly possesses complex molecular dimensions; it can be regarded as a derivative of phenanthrene, piperidine, dibenzofuran, isoquinoline, benzodihydrofuran, furan and other ring systems. Natural (-)-morphine is a laevorotatory T-shaped pentacyclic tertiary amine. Because of the 7,8 double bond, ring C assumes the half-chair conformation. Rings B and C form a cis-octalin system, rings C and D a trans-octahydroisoquinoline system. Structure (11) represents the absolute configuration and conformation of the natural alkaloid, which is 5(R), 6(S), 9(R), 13(S), 14(R).[16]

The strong analgesics reported to date can be classified as follows:-

a) morphine derivatives including ring-C bridged derivatives.
b) 4-phenylpiperidines.
c) 3,3-diphenylpropylamines.
d) morphinans.
e) benzomorphans.
f) miscellaneous.

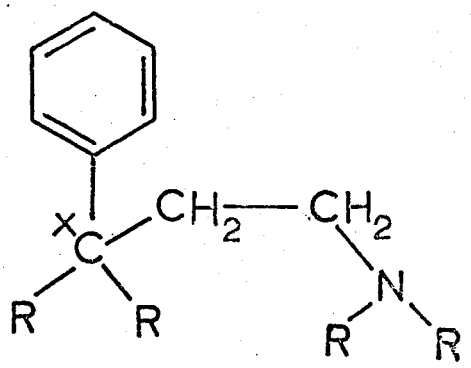
Classes a to f are related by the following common structural features:-[62,63]

i a quaternary carbon atom C_x

ii an aromatic nucleus linked to this carbon atom

iii a tertiary nitrogen atom two saturated carbon atoms removed from the quaternary carbon atom.

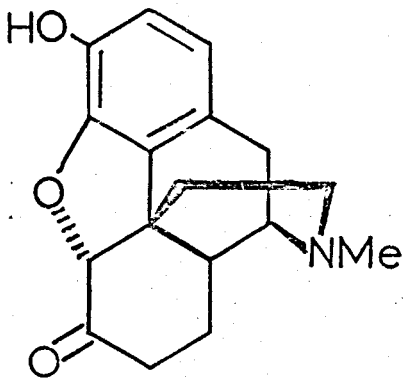
ie.



a) Morphine derivatives

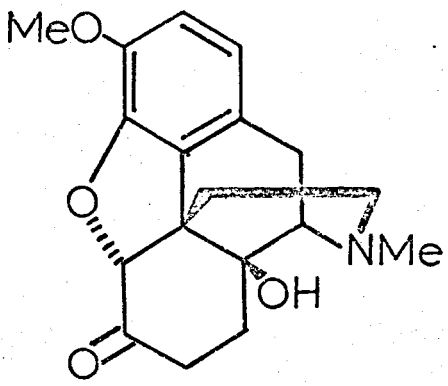
Amongst the opium alkaloids only morphine (1), codeine (2), and papaverine (5) are of medicinal importance. Methylation of the phenolic hydroxyl group in morphine (1) produced codeine (2). Interestingly, alteration of this small nature within the parent alkaloid (1) gives rise to a significant lowering of both analgesic potency (one tenth that of morphine) and dependence liability.[17] Dextrorotatory (+)-morphine, the mirror image of the natural alkaloid, is devoid of morphinomimetic activity. Practically all other morphine-like pentacyclic structures that have been pharmacologically investigated in some detail are semi-synthetic alkaloids derived from (-)-morphine. The Committee on Drug Addiction of the National Research Council (U.S.A) initiated the first methodical examination of the structure-activity relationships in morphine-like compounds. This team, led by Small and Eddy, prepared in the region of 120 compounds and reported their findings in 1938.[17] The chemical anatomy of potent morphine-like analgesics has been reviewed.[18] Dihydromorphinone (14), which can be derived from morphine (1), is a potent analgesic with 3-5 times the potency of the equivalent 6-hydroxyl compound, it does however possess higher addiction liability. 14-Hydroxydi-hydrocodeinone (15) of limited clinical utility, is of interest because on controlled demethylation it affords the potent analgesic 14-hydroxydihydromorphinone (Numorphan,16).[19]

Although 6-8 times effective as morphine, Numorphan is more highly addicting and must be used with caution. 5-Methyl-dihydromorphinone (Metopon, 17)[20] is about three times as potent as morphine and shows lower addiction liability. Metopon, however, has not been promoted for general use - quite possibly because of inherent manufacturing difficulties.



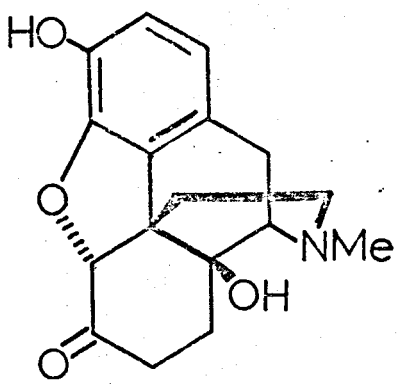
(14)

dihydromorphinone



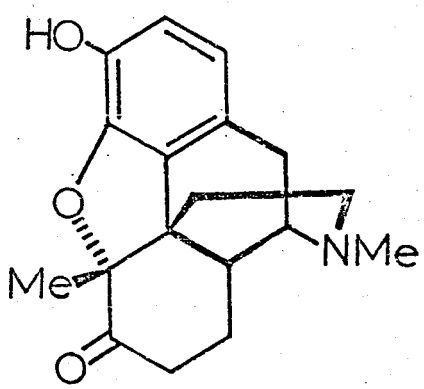
(15)

14-hydroxydihydro codeinone.



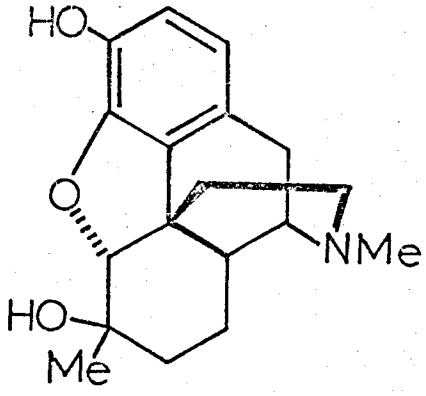
(16)

14-hydroxydihydro morphinone.

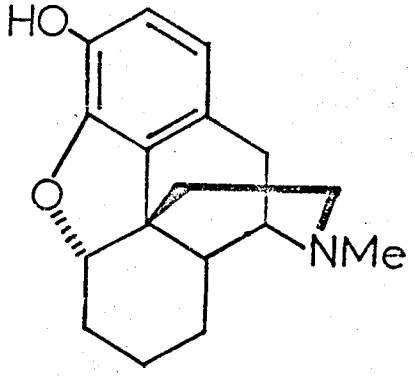


(17)

5-methyldihydro morphinone.



(18)



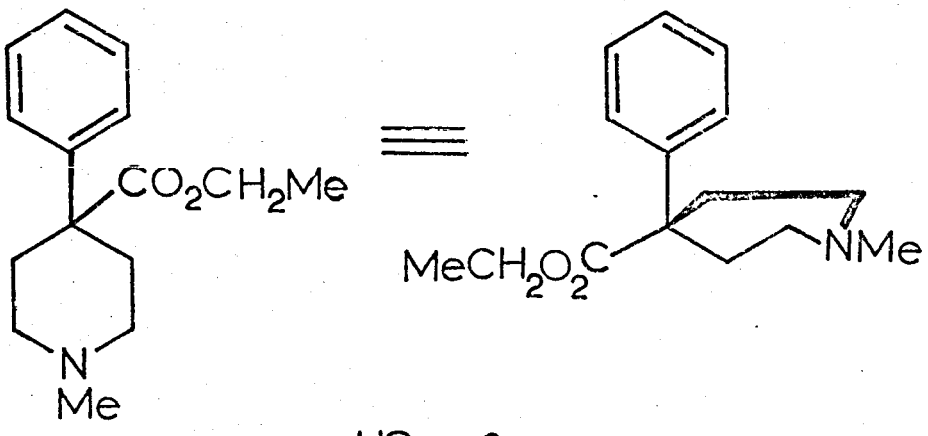
(19)

Treatment of dihydromorphinone (14) with methyl lithium affords 6-methyldihydromorphinone (18).[21] Like metopon, the latter derivative showed useful analgesic properties, it also proved to be longer acting than morphine and elicited less intense abstinence phenomena following withdrawal.[21] Dihydrodeoxymorphine-D (desomorphine, 19) is reputed to be three times as potent as morphine with little emetic or other untoward gastrointestinal effects. Ring-C bridged derivatives will be discussed later.

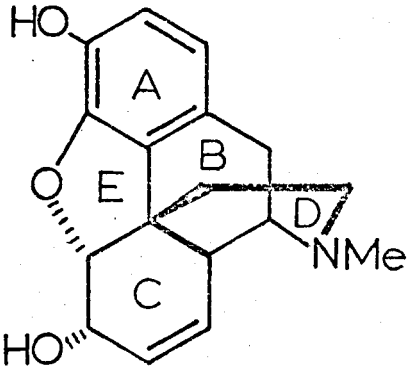
b) 4-Phenylpiperidines

In 1939 Eisleb and Schaumann[22] synthesised the first potent analgesic which did not depend upon opium for its prime source, viz pethidine (20), 1-methyl-4-carbethoxy-4-phenylpiperidine. It contains the elements of rings A and D of morphine.[23] Pethidine possesses one eigth the potency of morphine in man.[24] Unfortunately it is addictive and apart from being synthetic shows little improvement on morphine.

A structural alteration at the 4-position of the piperidine ring, giving the "reversed ester" series of pethidine[25] combined with the incorporation of a methyl group at C-3 produced a diastereoisomeric pair of compounds (±)-1,3-dimethyl-4-phenyl-4-propionoxypiperidine (alphaprodine, 21) and β-racemate (betaprodine, 22).[26]

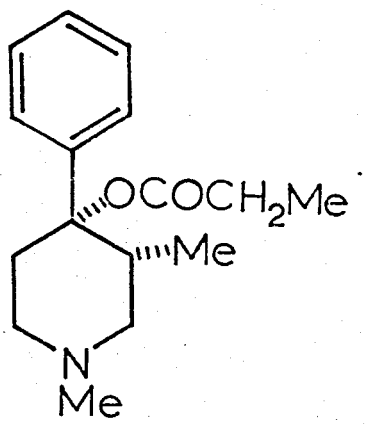


(20)



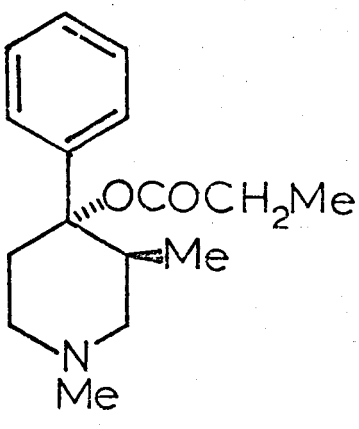
(1)

Alphaprodine is approximately equal to morphine in analgesic potency, and betaprodine is about 3 times more active than morphine. Both compounds show addiction potential of the same order as pethidine.



(21)

alphaprodine

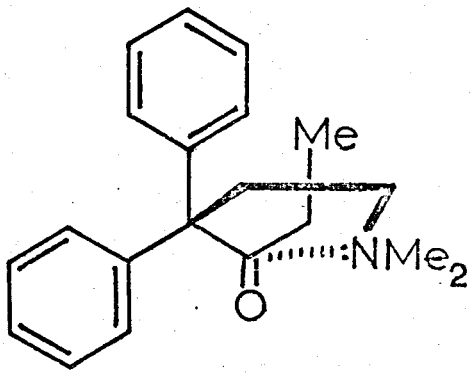


(22)

betaprodine

c) 3,3-Diphenylpropylamines

In 1948 the first member of an important new group of synthetic analgesics based upon the 3,3-diphenylpropylamine structure was introduced under the name of methadone[27] (23). Although methadone does not contain a piperidine ring it has been suggested by Beckett[28] that there is an interaction between the lone-pair of electrons on the nitrogen atom and the electron-deficient carbon of the carbonyl group thus presenting some steric resemblance to pethidine as depicted in (23).



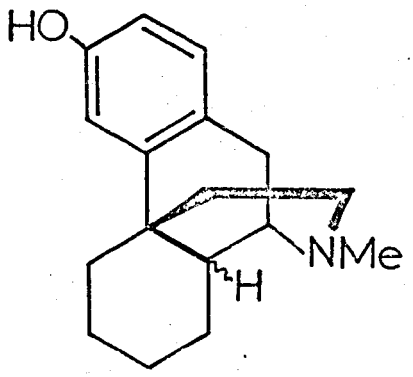
(23)

methadone

Methadone resembles morphine in its pharmacological properties including to a significant degree, its dependence liability.[28a] It is used in the stabilisation treatment of narcotic addicts.[29]

d) Morphinans

The morphinans[30] are bases representing the fundamental carbon skeleton of morphine without the 4,5-oxygen bridge. Schnider and Grussner[31] in 1949 and Grewe[32] soon after, described racemorphan; (±)-3-hydroxy-N-methylmorphinan (24), as an analgesic more potent than morphine and obtained by a totally synthetic route. The initial synthesis of these compounds led to a mixture of enantiomers. In 1951 Schnider and Grussner[33] accomplished the optical resolution of (24). The levo enantiomorph (levorphanol), which possesses the same absolute configuration as natural



(24)

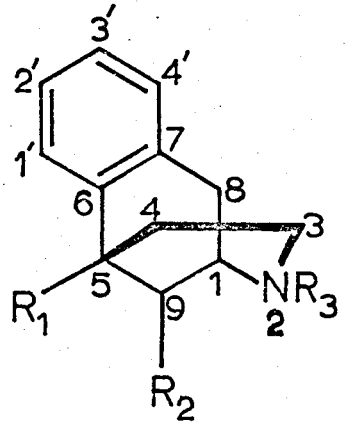
Racemorphan

(±)-3-hydroxy-N-methylmorphinan

morphine, was the form responsible for the analgesic activity. A review of the synthesis of morphinans has been published.[34] Although the side-effects in these compounds are not as severe as those found in morphine, all of them do show the deficiencies of the parent alkaloid (1), ie. its dependence liability and respiratory-depressant properties.

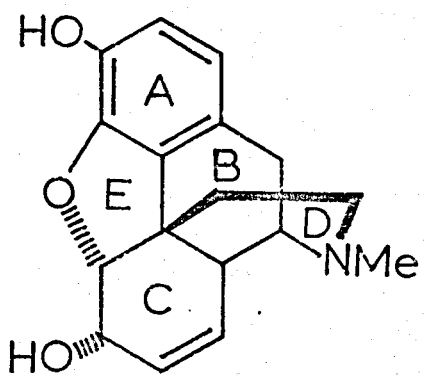
e) Benzomorphans

In 1954 E.L.May and associates[35] instituted their work on 6,7-benzomorphans (25);[36] these compounds retain the A, B and D rings of the morphine structure (1).



(25)

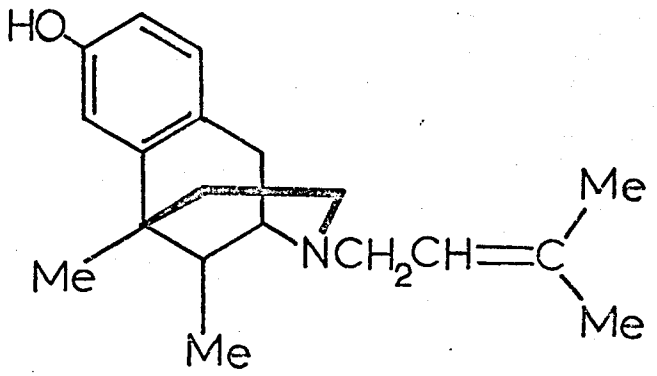
6,7-benzomorphan



(1)

morphine

The medicinally useful drugs in this series exhibit a clear separation of dependence liability and analgesic activity. Pentazocine (26), N-(3,3-dimethylallyl)benzomorphan, has been claimed to be a non-addictive analgesic[37] possessing weak antagonist activity.

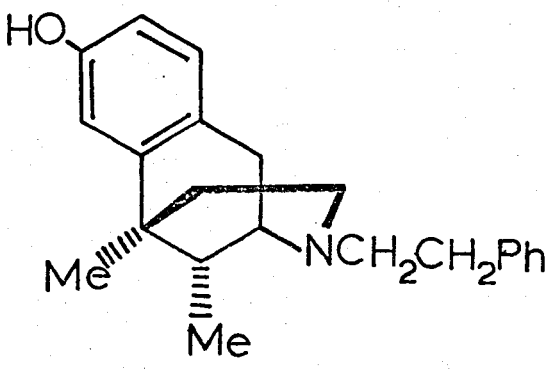


(26)
pentazocine

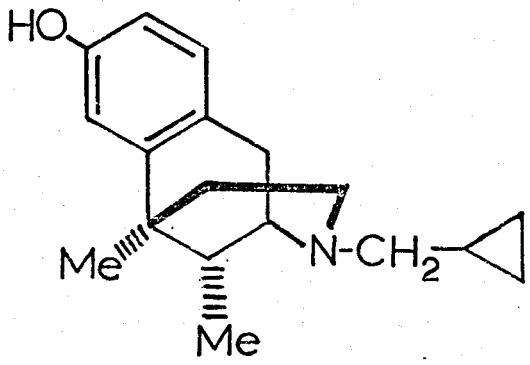
As mentioned above there are several structural features which seem to be frequently associated with the presence or absence of strong analgesic activity. These have been critically reviewed by Mellet and Woods.[38] Although there are exceptions, many strong analgesics contain an aromatic ring bonded to a saturated two- or three- carbon chain terminating with an amino nitrogen. Other restrictive generalisations have been made.[39] In the case of morphine analogues the presence of an appropriately positioned phenolic hydroxyl, tertiary amino functionality, and quaternary benzylic carbon (no bonds to hydrogen) all appear to enhance analgesic activity. Profound and consistent changes in activity ranging from narcotic agonist to antagonist, brought about merely by changing N-methyl to N-allyl in morphine and many of its simplified derivatives, provides startling evidence of the dramatic and structurally reproducible changes in activity which can occur.[40]

6,7-Benzomorphans are one of the most extensively investigated morphine analogues. Useful synthetic routes

to this ring system have been developed, and chemical modifications have provided valuable new narcotic analgesics and narcotic antagonists of practical and theoretical importance. Phenazocine (27) was the first potent benzomorphan to achieve widespread clinical use.[41] Phenazocine is four to five times as potent as morphine in man but it produces respiratory depression to the same degree.

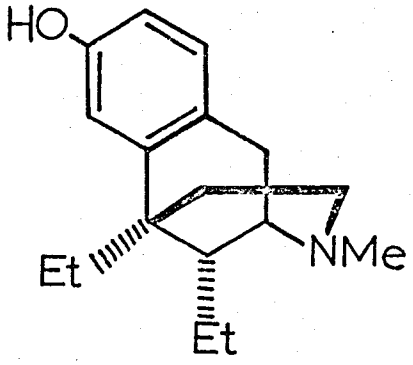


(27)
phenazocine



(28)
cyclazocine

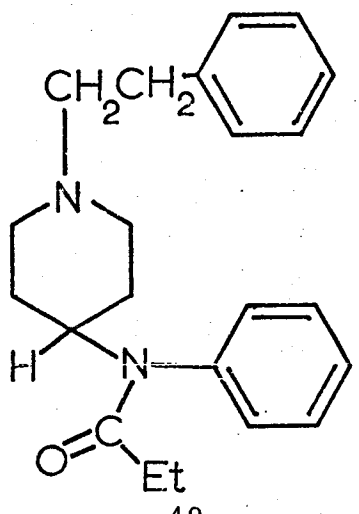
Replacement of the N-methyl group with cyclopropyl methyl e.g. cyclazocine[42] (28); 2-cyclopropylmethyl-2'-hydroxyl-5,9-dimethyl-6,7-benzomorphan, produces compounds which are more powerful antagonists than nalorphine or levallorphan. The (-) isomer of cis-5,9-diethylbenzomorphan (29) is as potent as (-) morphine (natural) as an analgesic but even though the nitrogen atom is substituted with a methyl group it possesses nalorphine-like antagonism.[43] This was the first example of an N-methyl compound possessing antagonist properties. There have been several short reviews of benzomorphan chemistry[44-47] and numerous reviews of analgesic structure-activity relationships which include benzomorphans.[38,40,44,48]



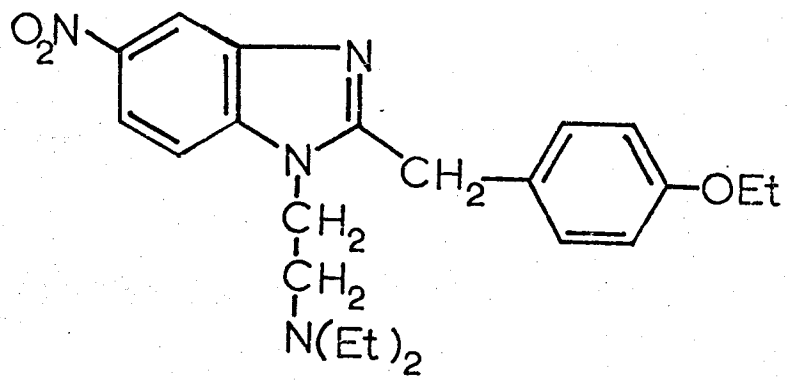
(29)

f) Miscellaneous

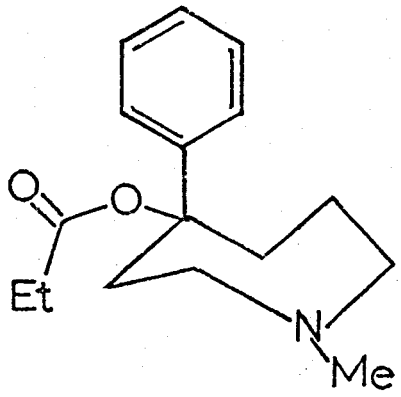
Various other potent analgesics have been described some of which have only limited similarity to the morphine skeleton. We produce below a selection.



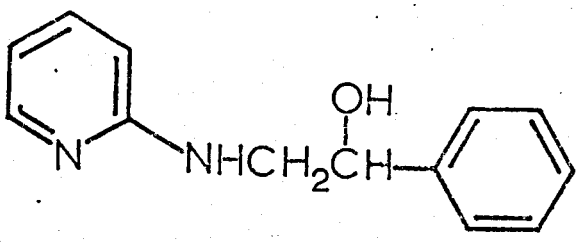
fentanyl[49]
(150 x morphine)



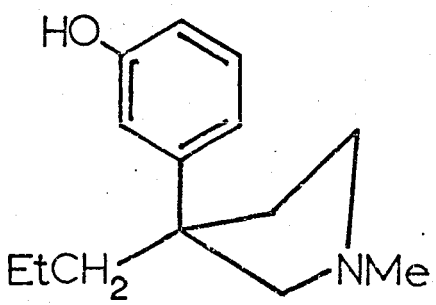
etonitazine[50]
(1000 x morphine)



ethoheptazine[51,52]
(similar in activity to codeine)



phenyramidol[53]
(codeine-like)



m-(1-methyl-3-propyl-3-pyrrolidinyl)phenol[54,55]
(equipotent with pethidine)

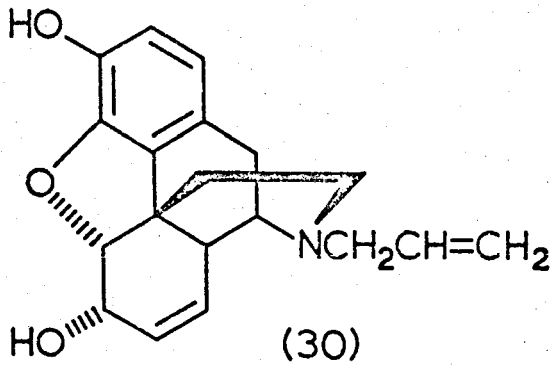
Narcotic Antagonists

Derivatives of morphine that induce some or all of the actions of morphine are known as opiate agonists, and those that block (nullify) these actions are termed antagonists. The opiate antagonists have the remarkable property of specifically reversing the major pharmacodynamic actions of the narcotics. The more potent ones are capable of inducing an immediate and intense withdrawal syndrome when administered to narcotic addicts.[56]

This group of compounds is produced by the replacement of the N-methyl group of the morphine, morphinan and the 6,7-benzomorphan series of analgesics with varying substituents. Since 1943 N-allylnormorphine (nalorphine) (30) has been known to antagonise the effects of morphine.[57] For this reason it is avaluable antidote in cases of narcotic overdosage when the effects are dramatically rapid.

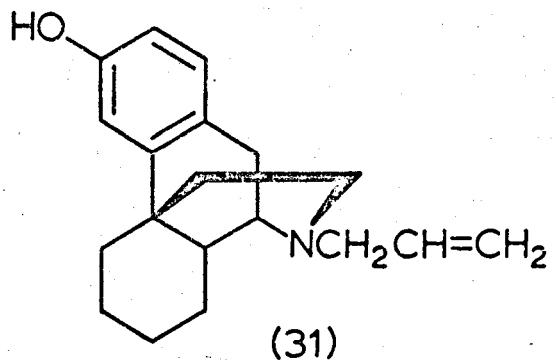
The mode of action of antagonists is not fully understood, possibly they compete successfully with morphine and similar drugs for occupation of the receptor surface. The replacement of the N-methyl group in the morphinans; e.g. levallorphan (31)(the N-allyl analogue of 3-hydroxy-N-methylmorphinan), in the benzomorphans and in bases represented by the series of bridged oripavines (32) and thebaines (33) also leads to morphine antagonists, some of which are more potent than nalorphine itself. Pentazocine (26) and diprenorphine (34) are representative. Nalorphine (30) and pentazocine (26) are examples of 'partial' agonists since they show both agonist and antagonist properties. It has been found that nalorphine is a potent analgesic in man devoid of addiction liability.[58,59] However, nalorphine is not acceptable for clinical use as an analgesic because of a high incidence of undesirable, sometimes bizarre, psychotic effects attending it use.[57]

Gates and Montzka introduced the cyclopropylmethyl group as an N-substituent which conferred morphine antagonism in potent analgesics.[42] (-)-3-Hydroxy-N-cyclopropylmethylmorphan (35) and N-cyclopropylmethylnormorphine (36) were found to be potent morphine antagonists capable of precipitating withdrawal symptoms of maximum intensity in addicted monkeys. It has been found since that in general



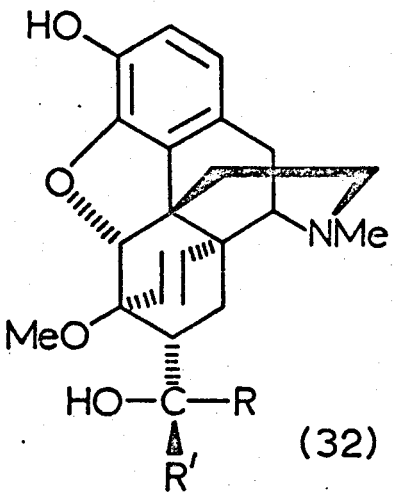
(30)

nalorphine



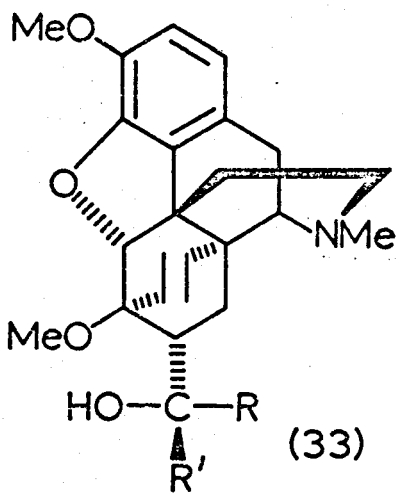
(31)

levallorphan



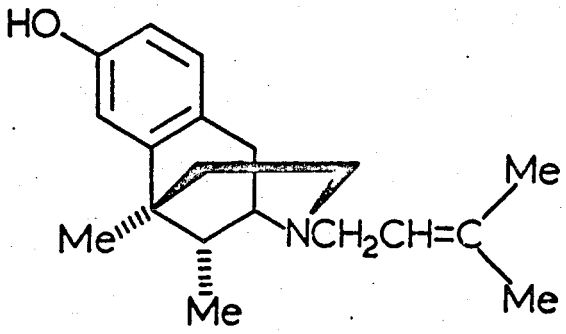
(32)

bridged oripavine derivatives



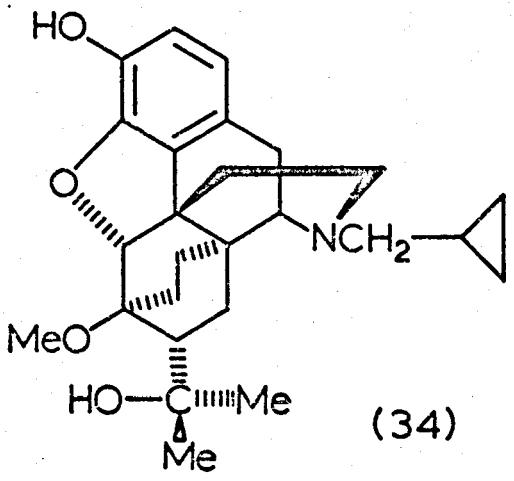
(33)

bridged thebaine derivatives



(26)

pentazocine

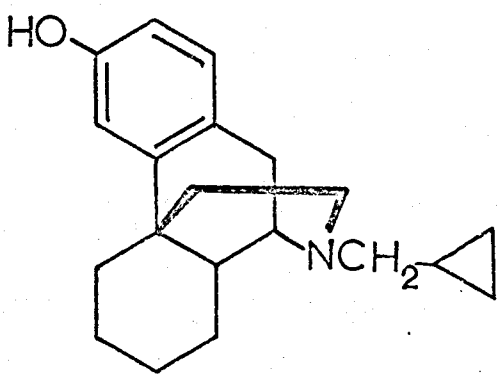


(34)

diprenorphine

the cyclopropylmethyl group gives the most potent antagonists in a particular series.

In 1965 Blumberg et al[60] described a compound which antagonised the analgesia produced by both morphine and nalorphine. No analgesic properties have been found for this



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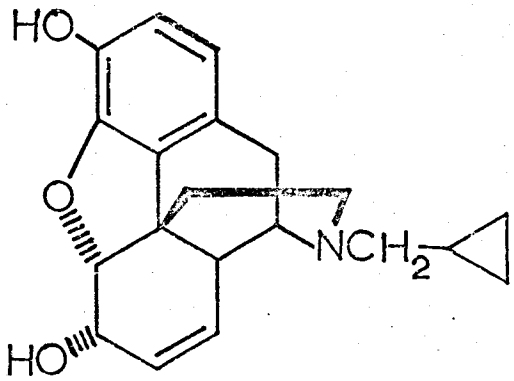

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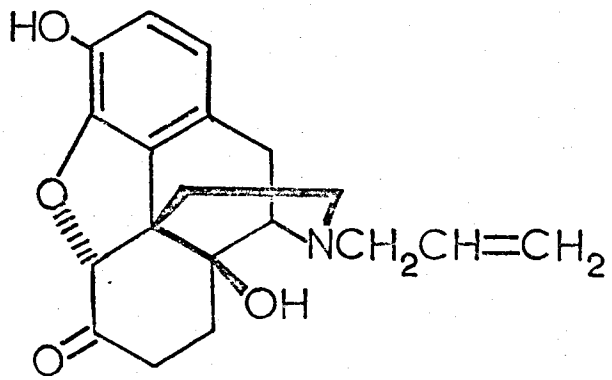


(37)

naloxone

compound in animals or in man. The compound (37), naloxone, first reported as an antagonist in 1961,[61] is termed a 'pure' antagonist, so completing the spectrum of activity of morphine-like agonists and antagonists. It is now generally accepted that to obtain a compound suitable for clinical use as a strong analgesic it needs to be a partial agonist; an agonist component for analgesia and an antagonist component so that the compound lacks dependence liability.

The Analgesic Receptor and Structure-Activity Relationships.

Since analgesia is controlled by subtle stereochemical factors[62,63] it was postulated that analgesia results from the interaction of the drug molecules with a special receptor located in the central nervous system. These receptors must be a framework of biochemical substances, probably a portion of a macromolecule, found naturally in living organisms and especially the higher mammalian species. Since the isomers of many potent analgesics show remarkably different analgesic potency, the analgesic receptor can best be regarded as a three-dimensional structure composed of units of naturally occurring optically active substances providing for stereospecificity. The chemical configuration of atoms of the receptor must be complementary to the analgesic drug molecule.[38]

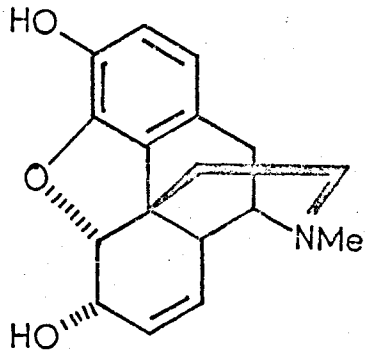
Beckett and Casey in 1954 postulated the nature of the analgesic receptor based on the evidence available on the stereochemistry and structural features common to analgesics and their antagonists at that time.[64] They envisaged a "three-point" interaction between a drug molecule and the receptor surface. These three essential binding sites were:

(a) a flat surface which associates with the aromatic ring of the drug molecule through van der Waals forces;

(b) an anionic site which interacts with the basic amine function, (which will be appreciably protonated at physiological pH), and

(c) a cavity which accommodates the ethano portion of the piperidine ring containing the aromatic ring and the nitrogen atom [carbons 15 and 16 in structure (1)].

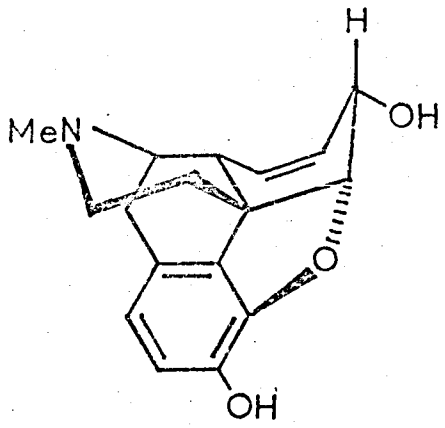
Although the Beckett and Casey hypothesis appeared to fit the facts quite well and was a useful hypothesis for a number of years certain anomalies exist which cannot be accommodated by it. The carbethoxy analogues of methadone depicted in structure (38) and diampromide (39) are both potent analgesics yet they do not possess the configurational relationships required to fit the Beckett receptor, also the

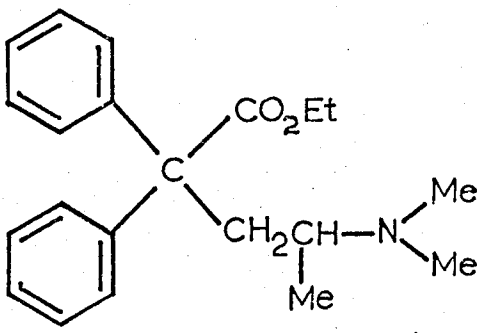


(1)

(-)-morphine

≡





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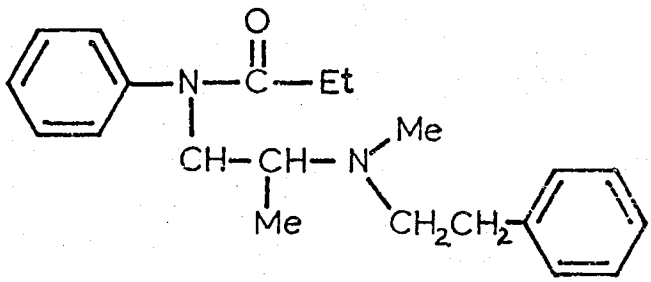

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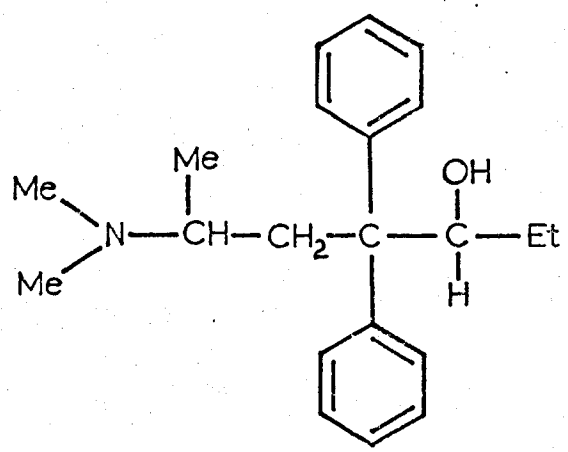
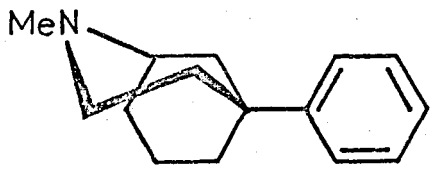


(40)

active isomers of the methadols (40) do not possess the required configurational relationships. Another factor that was implicit in considering a proper receptor fit for the morphine molecule and its congeners was that the phenyl ring in the 4- position of the piperidine moeity should be in the axial orientation for maximum activity. The fact that structure (41) has only an equatorial phenyl group, yet is found to possess activity equal to that of morphine would seem to cast doubt on the necessity for axial orientation as a receptor fit requirement.[65]

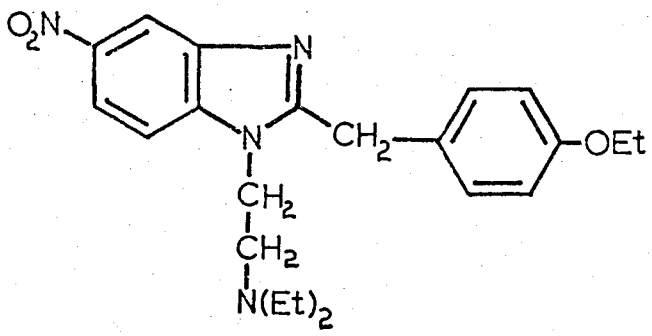


(41)

In view of the difficulty of accepting Beckett and Casy's hypothesis as a complete picture of analgesic-receptor interaction, Portoghese in 1965[66] published his work on the mode of interaction of narcotic analgesics and receptors. The Portoghese hypothesis is based in part on the established ability of enzymes and other types of macromolecules to undergo conformational changes on interaction with small molecules. The fact that configurationally unrelated analgesics can bind and exert activity is interpreted as meaning that more than one mode of binding may be possible at the same receptor.[67] Recent work derived from studies on enzymes, has led to the idea that there can be mutual perturbation of receptor and drug during their interaction.[68]

The remarkable potencies of the 6,14-endoetheno-tetrahydrothebaine and oripavine series of analgesics (discussed later) cannot be explained purely on the basis of the Beckett and Casy hypothesis discussed above. Only a few other analgesics have exhibited such high potencies,

notably etonitazine (42).[50] These remarkable potencies



(42)

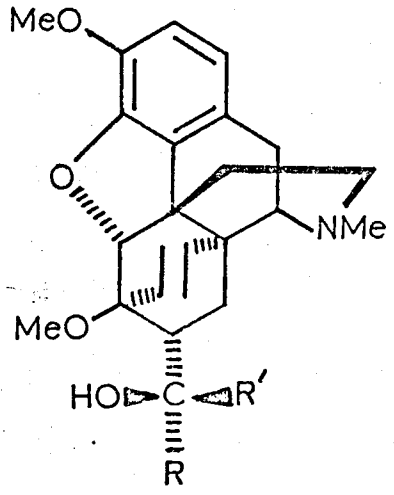
could be partly due to the compounds ability to penetrate the CNS rapidly and to concentrate on the receptor surface. This conclusion is based on data obtained from partition studies in polar/non-polar systems and peak effect times determined after the intravenous administration of these drugs.[69] Obviously, this cannot be the only explanation for such high potency differences, and it seems quite likely that the thebaine derivatives like etorphine are more acceptable to the analgesic receptor than morphine. Evidence for this inference is derived from

(a) the "receptor-activity" evaluations of Kutter et al[70], which take into consideration distribution factors; and

(b) the significant influence of the structure and stereochemistry of the tertiary alcohol group at C-7 on the activity of these compounds; e.g. as the R' chain length in (43, R=Me) is increased potency reaches a maximum at n-Pr and then falls sharply,[71] while the diastereoisomeric alcohols (43, R=Me, R'=n-Pr; configurations at C-19 are opposite) show a 100-fold difference in activity.[72] Neither of these alterations should lead to significant differences in physical properties.

With a view to accommodating these novel structures Bentley and Lewis[73] proposed the extension of the receptor to include a lipophilic site, such as is required by the phenethyl

moeity of the 7-substituent of 6,14-endoethenotetrahydrothebaine (44). The suggested orientation of the molecule towards the modified receptor is shown in Fig.1.



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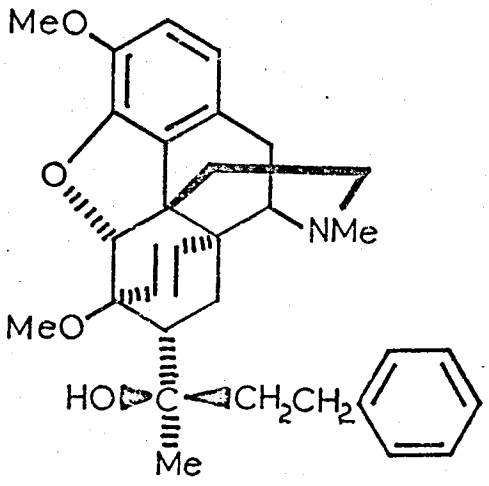

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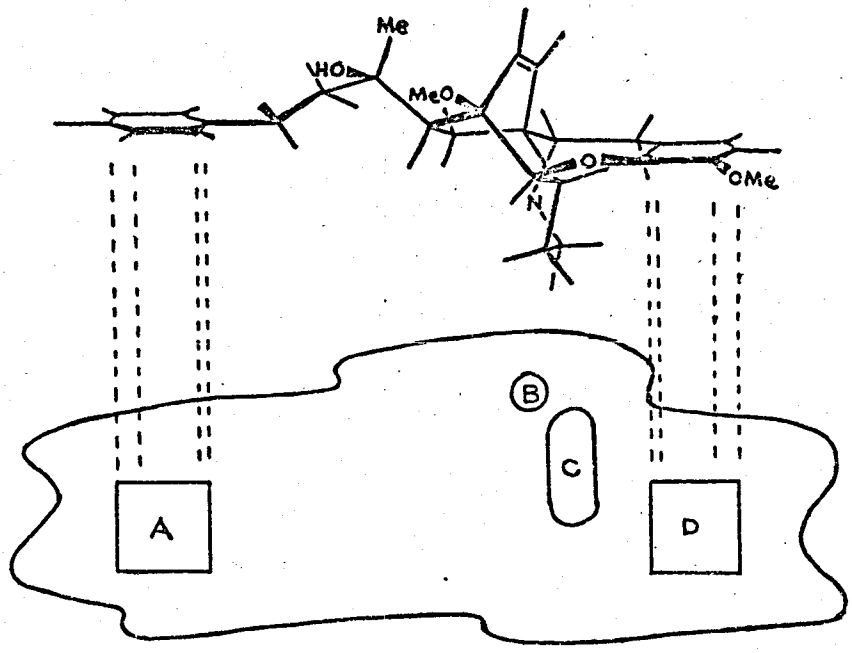
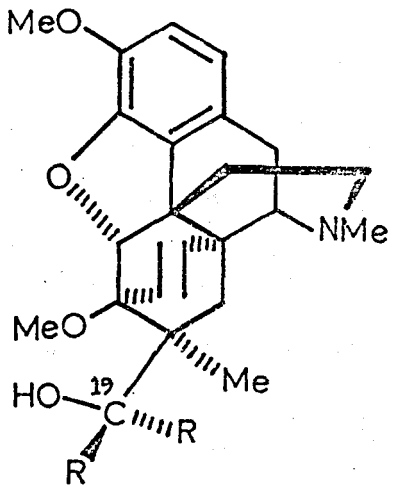


A. Lipophylic site
B. Anionic site
C. Cavity for C-15 and C-16
D. Flat surface for aromatic ring

Receptor site for 6,14-endo-ethenotetrahydrothebaine series.

Fig. 1.

The existence of a lipophilic area on the analgesic receptor provides a reasonable explanation for the unusually large difference in activity between the secondary alcohol (45a) 40 x morphine; and the related tertiary alcohol (45b) 0.4 x morphine.[74] The alcohols belong to a different stereochemical series (45a = 19R; 45b = 19S) and it has been suggested that only the secondary alcohol can achieve considerable association of the side chain aromatic function with the proposed lipophilic area on the receptor surface.



(45)

a) R = Ph, R' = H
b) R = Me, R' = Ph

Within the brain it has been shown that stereospecific opiate receptor binding is localised to the synaptic membranes.[75] The midbrain periaqueductal gray matter (PAG) seems to be a major site of opiate analgesic action. It has been shown that sodium ions are important in mediating the specific binding.[76] Sodium ions considerably enhance the binding of antagonists such as naloxone whereas the binding of agonists such as morphine is markedly decreased. Mixed agonist-antagonist drugs, e.g. pentazocine, are affected by sodium ions in an intermediate fashion. The increase in antagonist binding found on the addition of sodium ions has

been shown to be caused not by change in the receptor affinity but by an increase in the number of receptor sites available.

Iodoacetamide,[77] a protein-modifying reagent, has been shown to markedly reduce the receptor binding of a series of agonists, but does not affect the binding of antagonists. Proteolytic enzymes have also been shown to inhibit agonist binding more than antagonist binding,[78] whereas bivalent cations, especially manganese ions, have been shown to have the opposite effect.[79] It has therefore been suggested by Snyder[80] that the opiate receptor can assume two different conformations, one favouring antagonists, the other favouring agonists ("mutual perturbation"). The two conformations can be allosterically transformed by sodium ions and it would appear that the agonist conformation is the more labile. Snyder has proposed a model of the opiate receptor[81] explaining the structure-activity relationship of opiates and suggesting molecular mechanisms for the interconversion of the receptor between the agonist binding state and the antagonist binding state.

As the opiate analgesics have been shown to interact with stereospecific receptors in certain discrete regions of the brain, and it has been shown that none of the established neurotransmitter substances appeared to interact with the opiate receptors, it was suggested that the mode of action of the opiates might well involve an unknown mechanism in the brain. As many neurotransmitters are derived from amino-acids it was suggested that the endogeneous ligand of the opiate receptor might be a peptide. This theory was substantiated in 1975.[82] Kosterlitz and co-workers isolated this peptide; named 'enkephalin'[83] from pig brains. Enkephalin was found to be composed of the pentapeptides

H-Tyr-Gly-Gly-Phe-Met-OH (methionine enkephalin) and H-Tyr-Gly-Gly-Phe-Ley-OH (leucine enkephalin) in the ratio of methionine enkephalin to leucine enkephalin of 3 or 4 to 1.[83] Biological activity was found to be very rapidly destroyed if the substance was exposed to proteolytic enzymes and a similar substance was shown to be present in extracts of cat, rabbit, guinea-pig and cow brains. An important similarity between

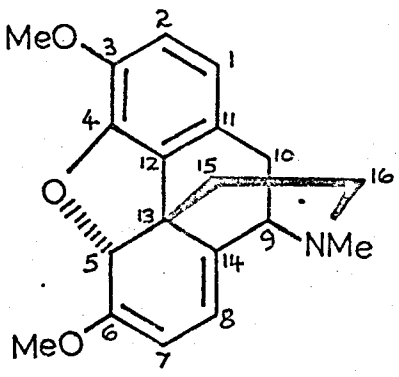
morphine and enkephalin was that the effects of both substances in blocking electrically evoked contractions in either the guinea-pig ileum or mouse vas deferens could be reversed by low concentrations of specific morphine antagonists such as naloxone.

The discovery of the endogeneous opiate peptide 'enkephalin' invoked an evaluation of a large number of synthetic peptides for opiate activity and some important structure-activity relationships have been found.[84] It has also become apparent that there are other large peptides present in the brain which are also potent opiate agonists and the generic title 'endorphin' has been proposed for them.[85]

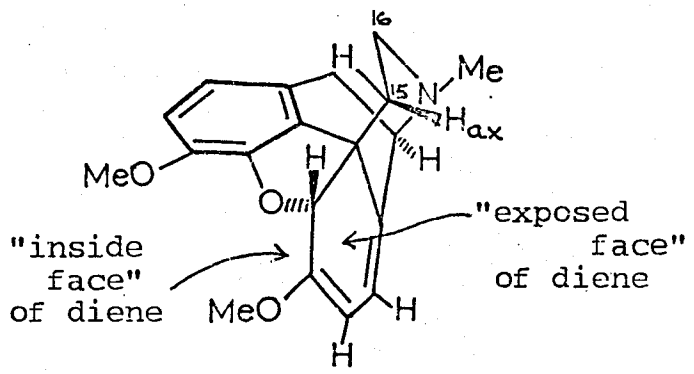
Ring-C-Bridged Morphine Derivatives. The 6,14-Endo-ethenotetrahydrothebaines and Oripavines.

Bentley and Hardy[86] considered that the compounds studied which were simpler than morphine, being more flexible, would probably be at least as acceptable as morphine itself at the presumably closely similar receptors associated with analgesia, respiratory depression and addiction liability etc. It seemed reasonable, therefore to make compounds more complex than morphine, which by virtue of their greater complexity, rigidity, and substantially different peripheral shape would be unacceptable at some of the receptor surfaces and thus give rise to a separation of the various effects. Such derivatives can be obtained by Diels-Alder addition to thebaine (3).[86-92] The introduction of a new two-carbon bridge across ring C confers rigidity on the resultant adduct molecules. It has been claimed that addition of dienophiles to thebaine occurs readily only on the 'exposed face' of the diene system, see structure (46). This gives the 6,14-endo-ethenotetrahydro-thebaines in which the etheno bridge is disposed "inside" the tetrahydrothebaine skeleton, as in structure (47). On studying models of the thebaine molecule we consider there is little difference in steric interference with dienophile approach from either face. Indeed the axial C-15 hydrogen in (46) would provide some interference; matched only on the "inside" face by the π-electron cloud of ring A and lone pair

on ring E oxygen. However, a factor which may promote attack of dienophiles such as α,β-unsaturated ketones to the exposed face is charge transfer complex formation (or its equivalent) between the ring D nitrogen lone pair and the δ-positive enone carbon β to the carbonyl.

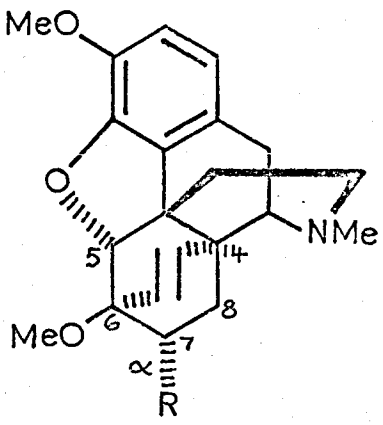


(3)



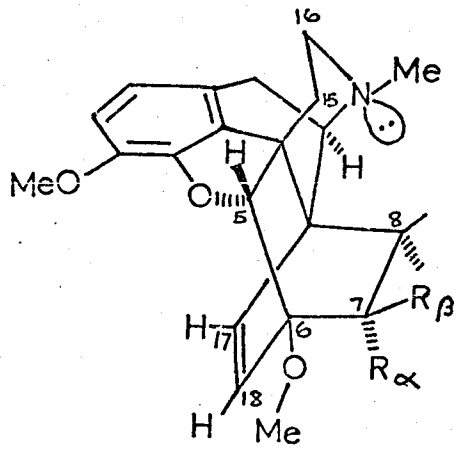
(46)

CH_2=CHR



(47)

CH_2=CHR



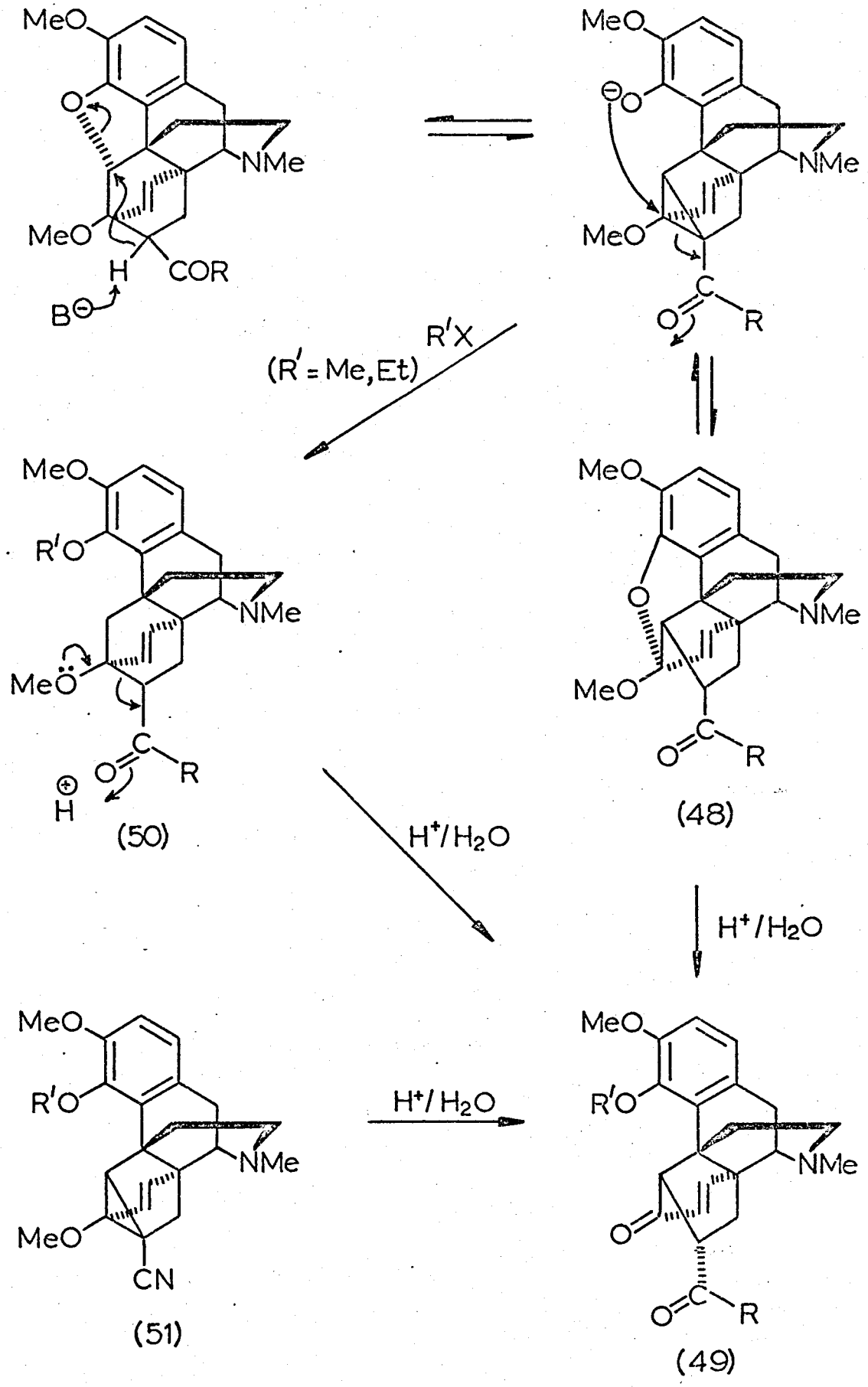
(47)

Thebaine methiodide does not undergo Diels-Alder condensation with methyl and phenyl vinyl ketones, ethyl acrylate, acrylonitrile, and maleic anhydride.[93] With p-benzoquinone[94] and 1,4-naphthoquinone[90] crystalline charge-transfer complexes are formed which are stabilised by resonance.[86] The larger effective size of the quaternary nitrogen system, compared with the tertiary nitrogen in thebaine, presumably prevents a sufficient close approach of the diene and dienophile systems to permit the establishment of new carbon-carbon bonds. Quaternisation of the nitrogen atom would also prevent nitrogen lone pair-dienophile interactions from occurring. No examples of adducts derived from the approach of the dienophile from the "inside" face of the diene system ie. giving exo-etheno-tetrahydrothebaine derivatives have been reported.

The Diels-Alder reaction benefits in this case by the electronic releasing character of the 6-methoxy group such that with enones regiospecific cycloaddition is observed, the ketonic function appearing at C-7 in the adduct (and not C-8). Normally the substituent is found in the 7α-configuration[86]; since this avoids the non-bonded interactions between a 7β-substituent and the C-5 hydrogen and axial C-15 hydrogen.

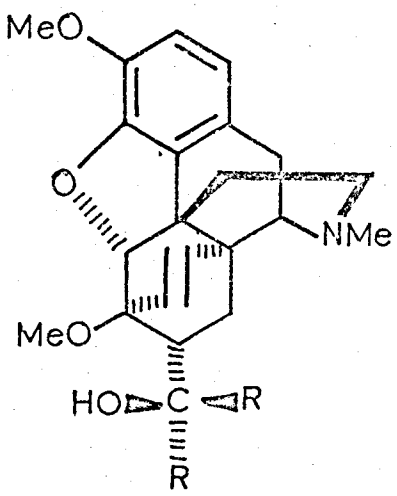
The addition of alkyl vinyl ketones and alkyl acrylates to thebaine results in almost entirely the 7α-epimers (47, R=COR; or 47, R=CO.OR). (This would also be expected from a consideration of the normal mode of addition in Diels-Alder reactions.[95-100]) A mixture of 7α (47; R=CN) and 7β nitriles is obtained in approximately equal amounts when acrylonitrile adds to thebaine.[86] It has been demonstrated that the Diels-Alder adducts are C-7 substituted rather than C-8 by base-catalysed rearrangement of both isomers (7α and 7β) of the methyl vinyl ketone adduct (47; R=COMe) to give the same ketone (48, R=Me)[86] which may undergo further rearrangement in the presence of acid to the diketone (49; R=Me, R'=H)[101] as shown in scheme 2.

Chemical confirmation that the alkyl acrylate adducts have the keto-substituent at C-7 has also been achieved by conversion of both adducts (7α and 7β) to the



Scheme 2

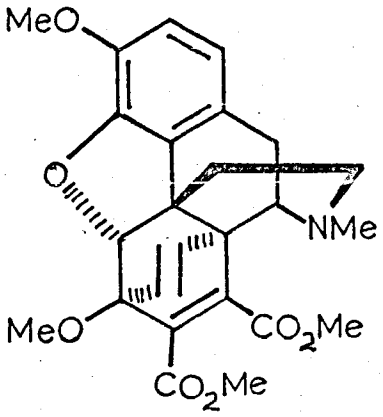
Base catalysed rearrangement of thebaine adducts



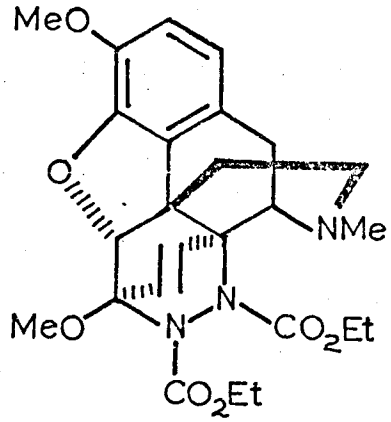
(52)

tertiary carbinol (52; R=R'=Me) with methyl magnesium iodide.[86] The 7α and 7β esters undergo base-catalysed rearrangement in the presence of an alkyl halide (R'X) to give the same product (50; R=OEt) which can also rearrange under acid catalysis to the keto-ester (49; R=OEt).[101] Similarly base-catalysed rearrangement in the presence of alkyl halide of the epimeric C-7 nitrile adducts affords the nitrile (51) which may further rearrange in acid to the keto nitrile (49; COR=CN).[101] Confirmation of the configuration at C-7 has been achieved for the epimeric 7α and 7β nitriles and ketones (47; R = CN or COMe) by application of n.m.r. spectroscopy, using spin decoupling techniques.[102]

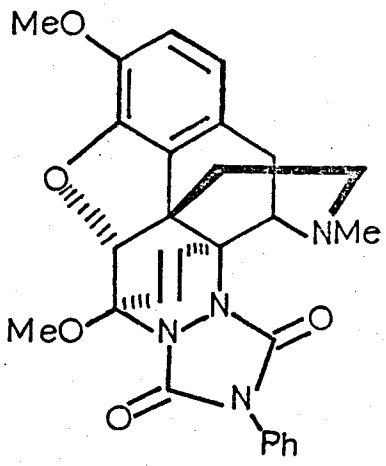
Other Diels-Alder adducts of thebaine have been reported in recent years and various chemical transformations carried out on them. Adducts have been obtained with dimethyl acetylene dicarboxylate (53)[103,104]; diethylazodicarboxylate (54)[105]; and 4-phenyl-1,2,4-triazoline-3,5-dione (55).[106,107] With the latter three symmetrical dienophiles the possibility of isomeric products is precluded.



(53)



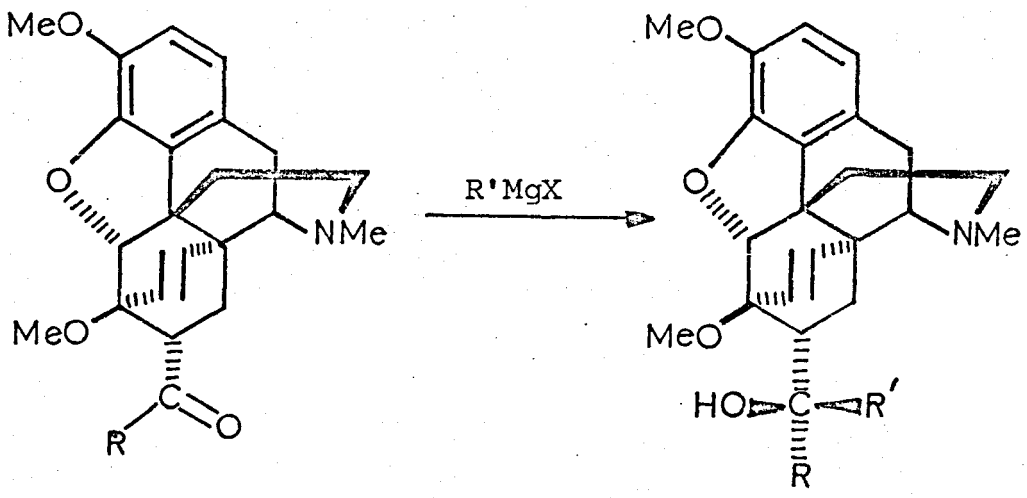
(54)



(55)

The most extensively studied Diels-Alder adducts obtained from thebaine are those derived from alkyl vinyl ketones (47; R = COR) and alkyl acryiates (47; R = CO.OR). The Grignard reaction of the ketone adducts (56; R = Me) in this series showed a remarkably high degree of stereoselectivity.[108]

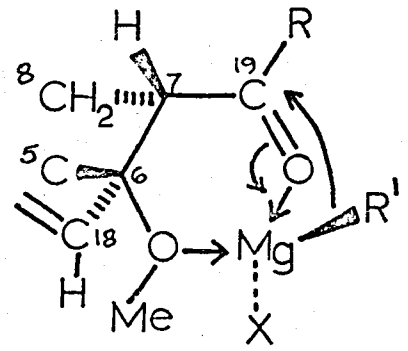
Normal Grignard reaction, which in most cases is accompanied by competing reduction of the ketone and base-catalysed rearrangement, gave tertiary carbinols of structure (57) with uniform stereochemistry.



(56) (57)

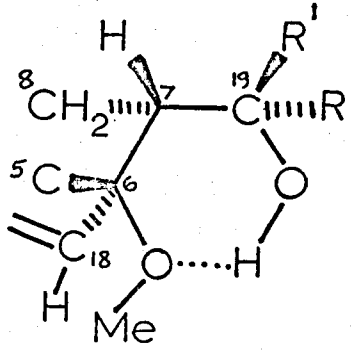
The asymmetric induction encountered in these Grignard reactions has been explained by regarding the Grignard complex as a six-membered intermediate in which the magnesium atom of the Grignard reagent is co-ordinated with the oxygen atoms of both the C-7 carbonyl group and the C-6 methoxyl group as depicted in Fig. 2. From Dreiding models of the transition state involved it can be seen that "top side" attack of the group R' to the carbonyl carbon of (58) leading to (59) is much less hindered than attack from below; due to the 6,14-etheno-bridge. When the group R' contains a β-hydrogen atom, Grignard reduction can occur via a similar transition state (to give secondary carbinols e.g. (59; R' = H)).

The alcohols of structure (57) provided a series of bases of high analgesic potency, highest activity was found in the alcohols R' = n-Pr, Ch_2Ph and CH_2CH_2Ph, which were found to be 90, 150, and 500 times, respectively, as potent as morphine in the rat tail pressure test.[108] A series of substantially more potent analgesics were obtained by demethylation of the C-3 methoxyl group of these alcohols. The resulting phenols (60), derivatives of oripavine, contained several bases whose activity was about 1000-80,000 times that of morphine in the animal test employed. The most potent being (60) (R' = n-Pr, n-Bu, n-Am, i-Am and CH_2CH_2Ph).[109]

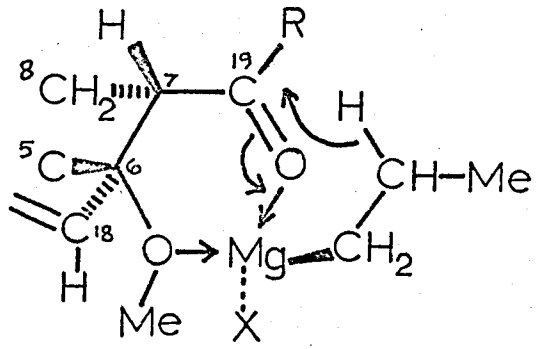


(58)

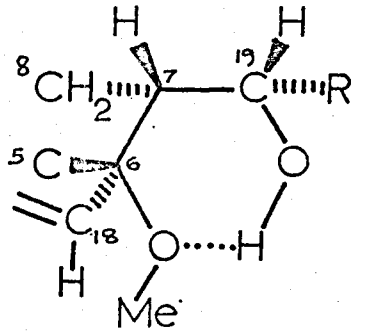
Grignard reaction



(59)

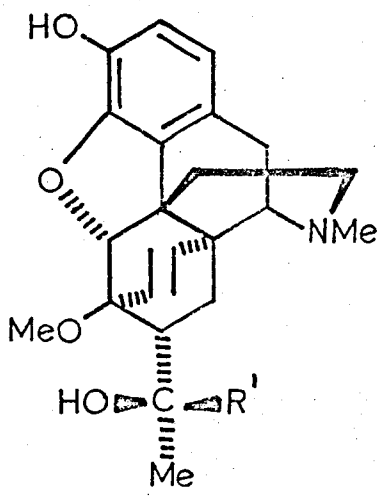


Grignard reduction



(59, R'=H)

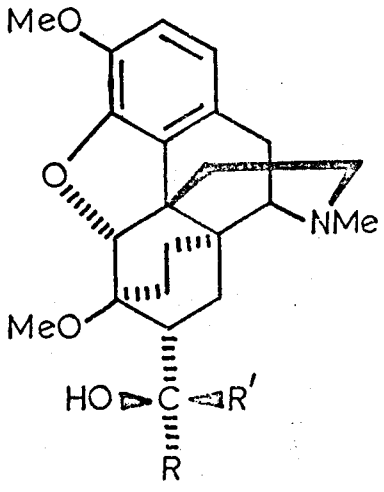
Fig.2.



(60)

Etorphine (60; R' = n-Pr) has been used in the immobilisation of wild game.

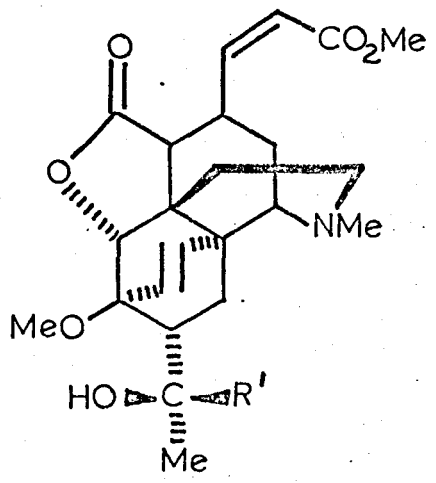
Catalytic reduction of the 6,14-endo double bond in the tertiary alcohols (57) can only be effected at elevated temperature and pressure.[108] Hydrogen bonding between the hydroxyl and 6-methoxyl groups gives rise to conformations where either R or R' hinders the approach of the etheno double bond to the catalyst surface. The ketone adduct (56; R = Me) can be reduced under milder conditions and its 7β-epimer, in which there is no obstruction to the etheno-bridge, is readily hydrogenated at room temperature and pressure. The 6,14-ethano-ketones thus obtained can then be converted by Grignard reaction to carbinols (61) which are generally found to be more potent than their 6,14-etheno-analogues.



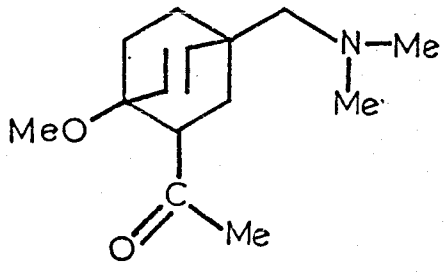
(61)

The 6,14-endo-ethenotetrahydrothebaines and oripavine derivatives discussed above may be regarded as derivatives of (-)-morphine in which the 6 and 14 carbon atoms of ring C are linked by an ethylene chain that carries a tertiary alcohol group. Furthermore, crystallographic study of etorphine (60; R' = n-Pr) has established that these derivatives bear a close resemblance both in structure and stereochemistry, to morphine.[110]

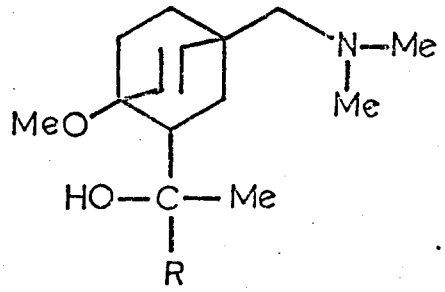
The high potency of the carbinols (60) and (61) and the influence of C-7 substituents on activity in the series led to the postulate that the analgesic receptor is more extensive than originally proposed (as discussed earlier) and contains an area capable of independently mediating analgesic effects through suitable C-7 groups.[111] Thus, destruction of the aromatic nucleus in certain derivatives might not lead to complete loss of analgesic activity. This prediction has been verified by fission of the aromatic nucleus between C-3 and C-4 in the alcohols (57; R = Me) by ozonolysis to give lactonic esters (62; R' = n-Pr, n-Bu and n-Am) having activities comparable with that of morphine.[112] Steric factors would prevent the unsaturated lactonic ester system from adopting an arrangement isosteric with the aromatic nucleus of the precursors in relation to the analgesic receptor. Isomeric mixtures of simpler fragments of the carbinols (57) and (62)(64; R = Me, n-Pr and $Me_2CH.CH_2CH_2$) have been synthesised by treating a mixture of the epimeric Diels-Alder Adducts (63) with lithium alkyls, however, none of these products showed analgesic activity.[112]



(62)



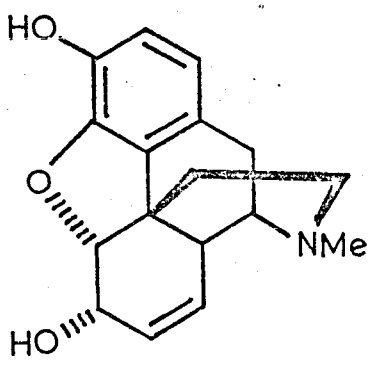
(63)



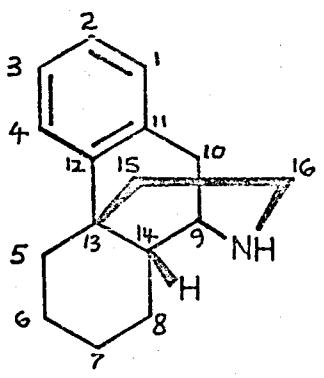
(64)

The Synthesis of Morphinans

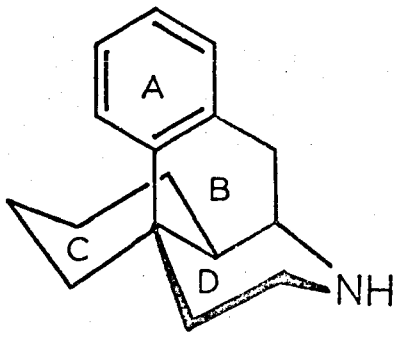
Our studies of the synthesis of isoquinolines containing a reduced carbocyclic ring-A were designed in part to permit subsequent extension to the formation of the morphinan system. We summarise here previous routes to this system. As mentioned earlier (p.12) the morphinans (65) contain the complete carbon-nitrogen skeleton of morphine(1).



(1)

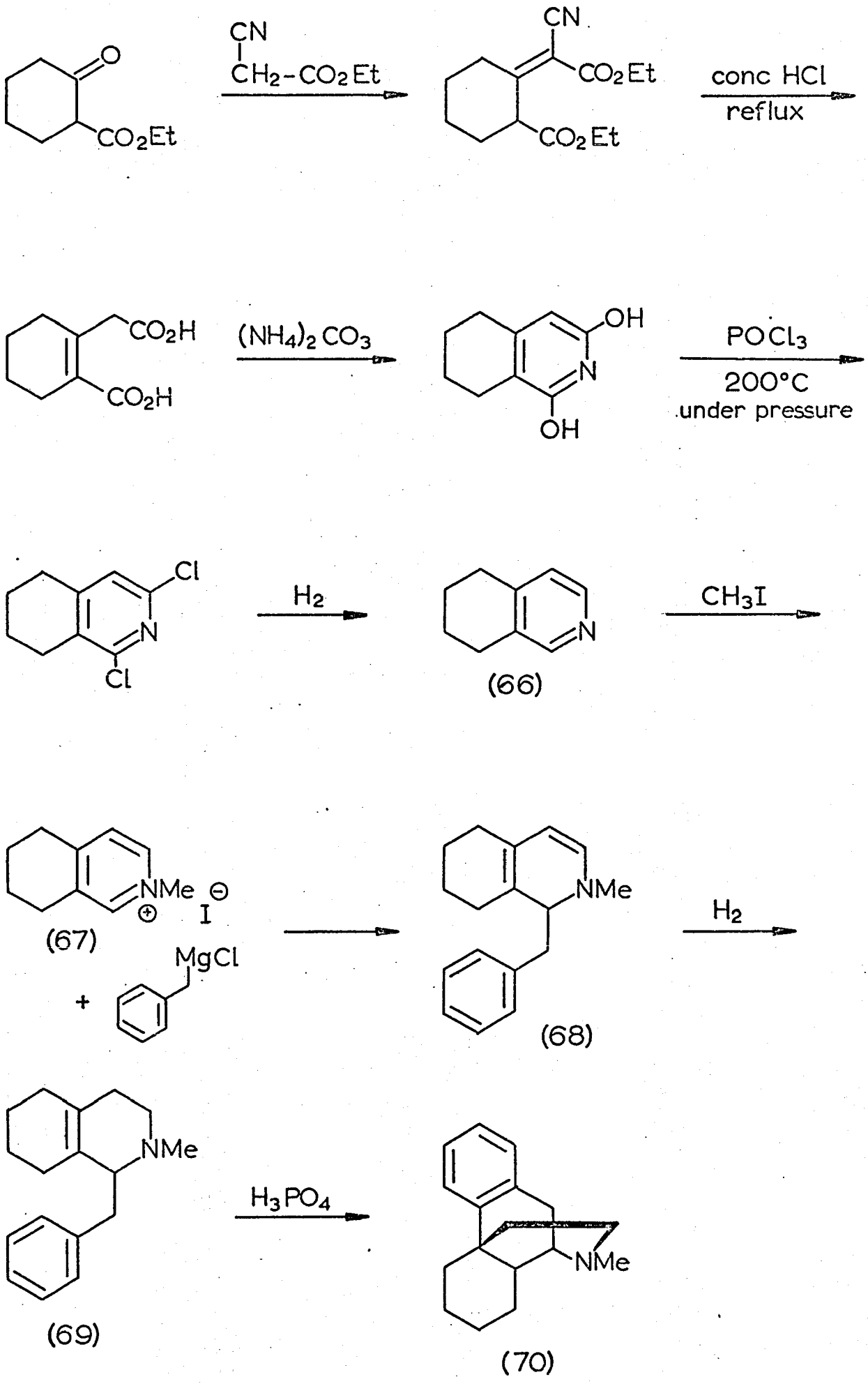


(65)

(65) ≡ 

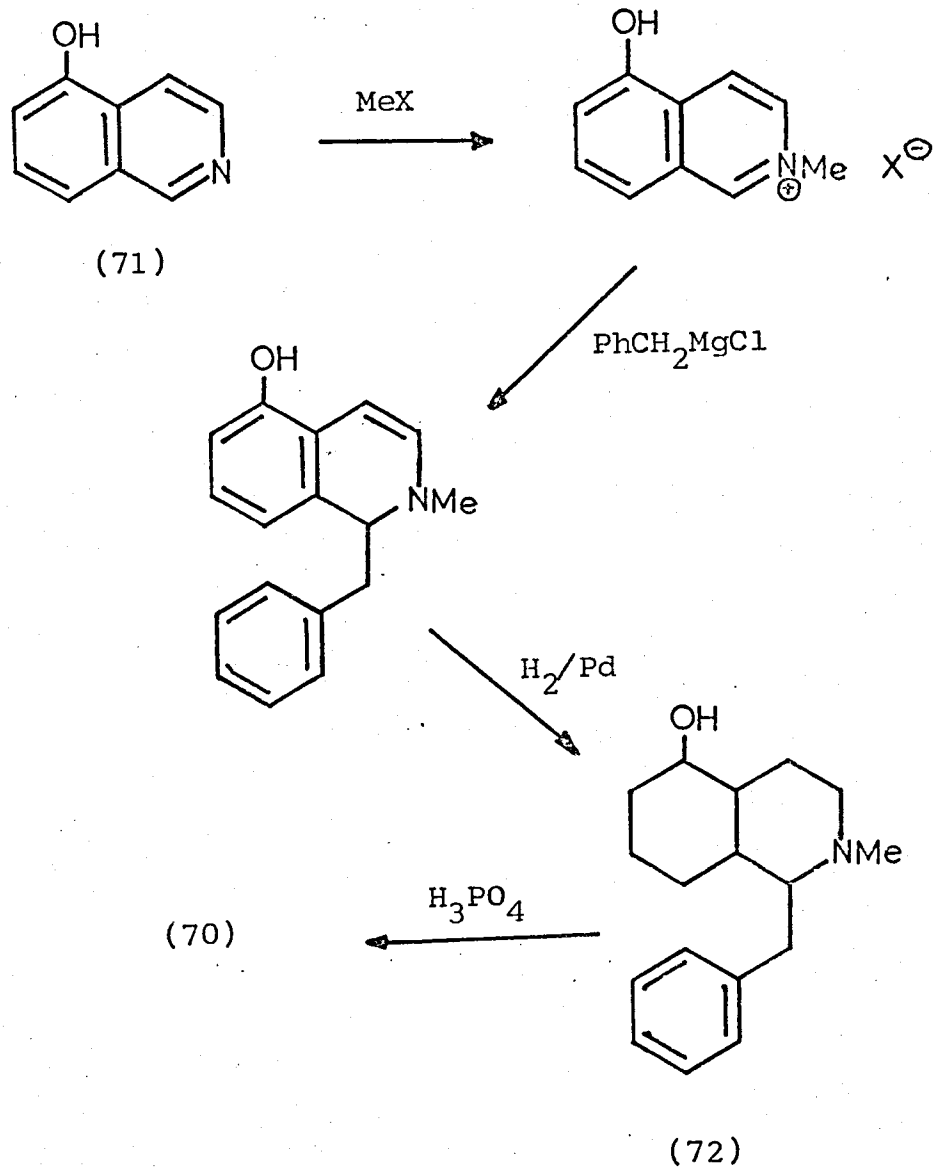
B/C cis, C/D trans

In 1946 Grewe[113] synthesised N-methylmorphinan and found it to have one-fifth the potency of morphine. This marked the era of research on "simplified morphines". The Grewe synthesis of N-methylmorphinan (70) is outlined in scheme 3. Thus 1-benzyl-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (69) [prepared by the reaction of benzylmagnesium chloride with 2-methyl-5,6,7,8-tetrahydroisoquinolinium iodide (67) and catalytic reduction of the resultant unstable hexahydro base (68)] could be cyclised with concentrated phosphoric acid to the octahydrophenanthrene derivative, N-methylmorphinan in 50% yield.


CN
CH2-CO2Et
CO2Et
CO2Et
CO2Et
conc HCl
reflux
CO2H
CO2H
(NH4)2CO3
OH
N
OH
POCl3
200°C
under pressure
Cl
N
Cl
H2
N
(66)
CH3I
NMe
I
(67)
MgCl
+
NMe
(68)
H2
NMe
H3PO4
NMe
(69)
(70)

Scheme 3

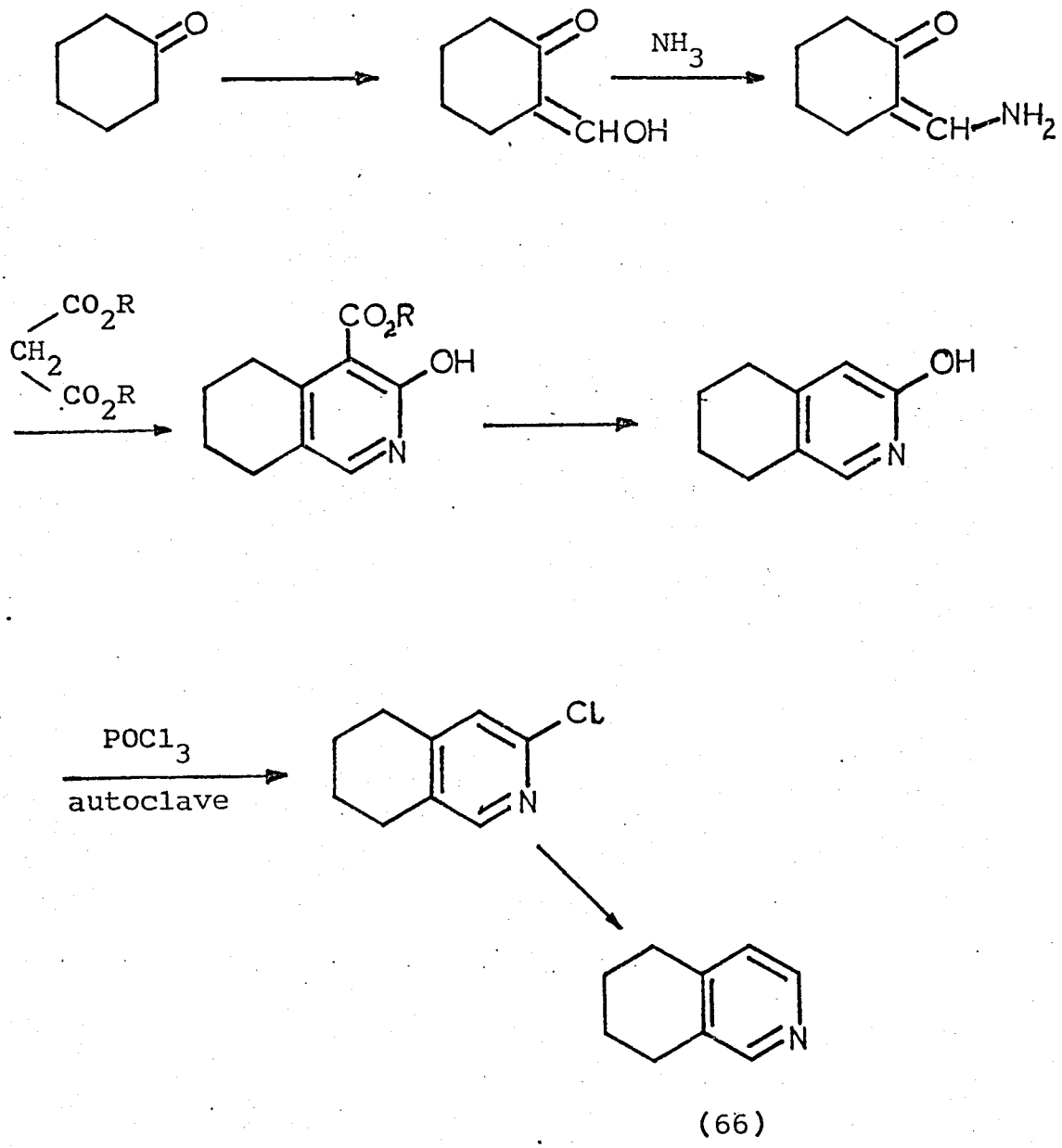
A modification of this synthesis starting with 5-hydroxyisoquinoline (71) was described some years later by Koelsch and Albertson[114] who obtained N-methylmorphinan by the route outlined in scheme 4 , via the 5-hydroxydecahydro-isoquinoline (72), the cyclisation step proceeded in 10% yield.



Scheme 4

Interest was mainly focused on 3-hydroxymorphinan derivatives in which the hydroxy group is in an analogous position to that in morphine since Eddy et.al. had already shown that 3-hydroxy-phenanthrene, unlike other hydroxy-phenanthrene compounds, possesses some analgesic activity.[17,115]

Schnider et.al.[30] and independently, Schlittler and Merian[116] prepared 5,6,7,8-tetrahydroisoquinoline (66) as shown in scheme 5 ; an improvement on Grewes route.[113]

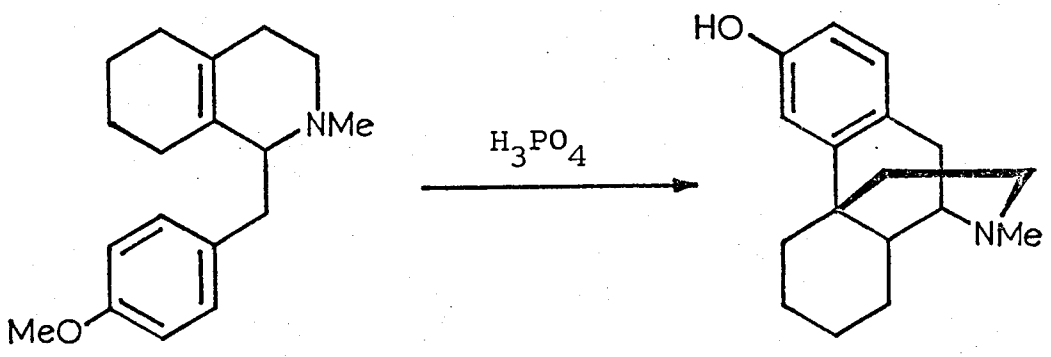


(66)

Scheme 5

Schnider and Grussner[31] synthesised 3-hydroxy-N-methylmorphinan (24) utilising the Grewe method and p-methoxy-

benzylmagnesium chloride in place of benzylmagnesium chloride; the morphinan cyclisation proceeding in 60% yield.

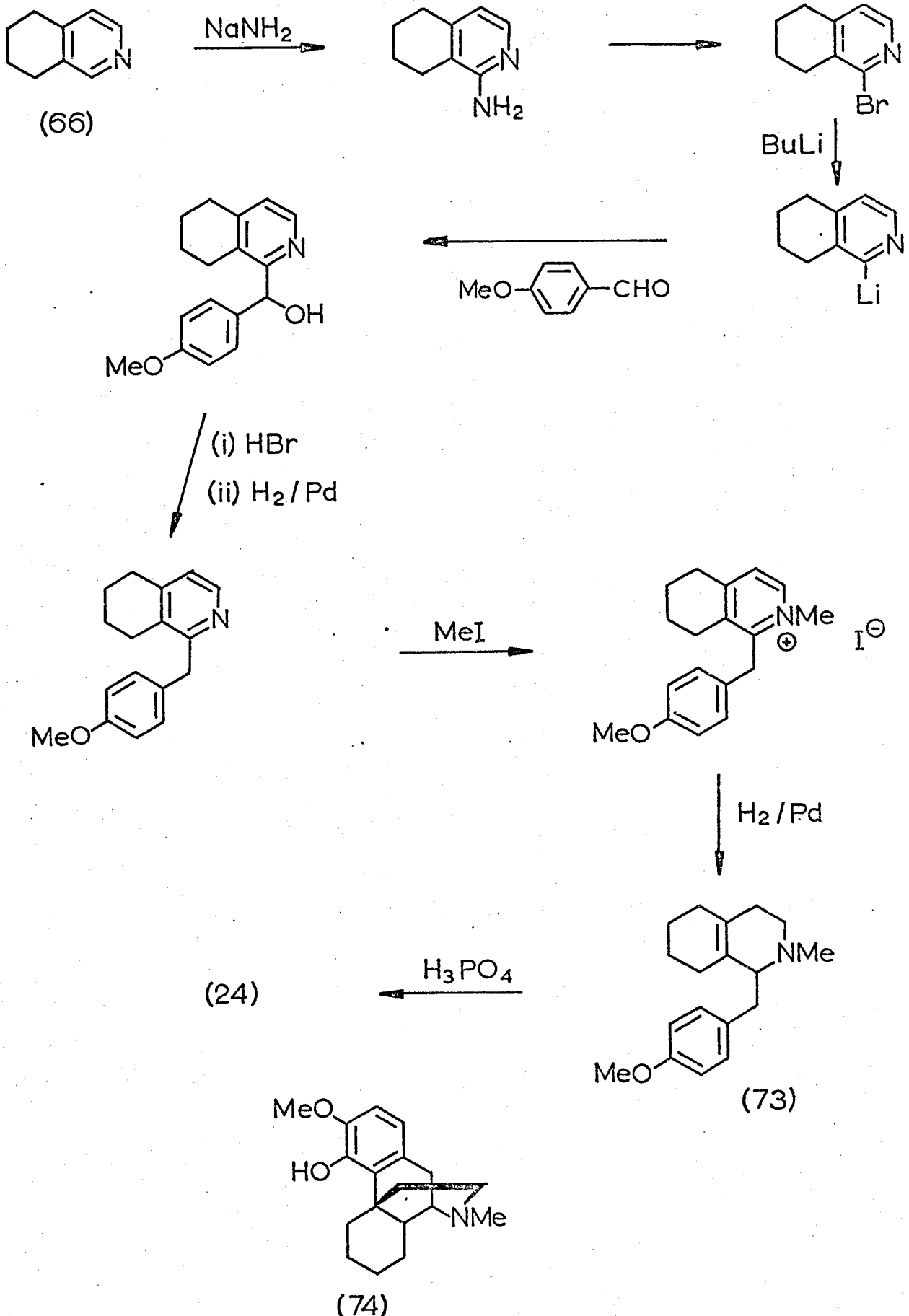


(73) (24)

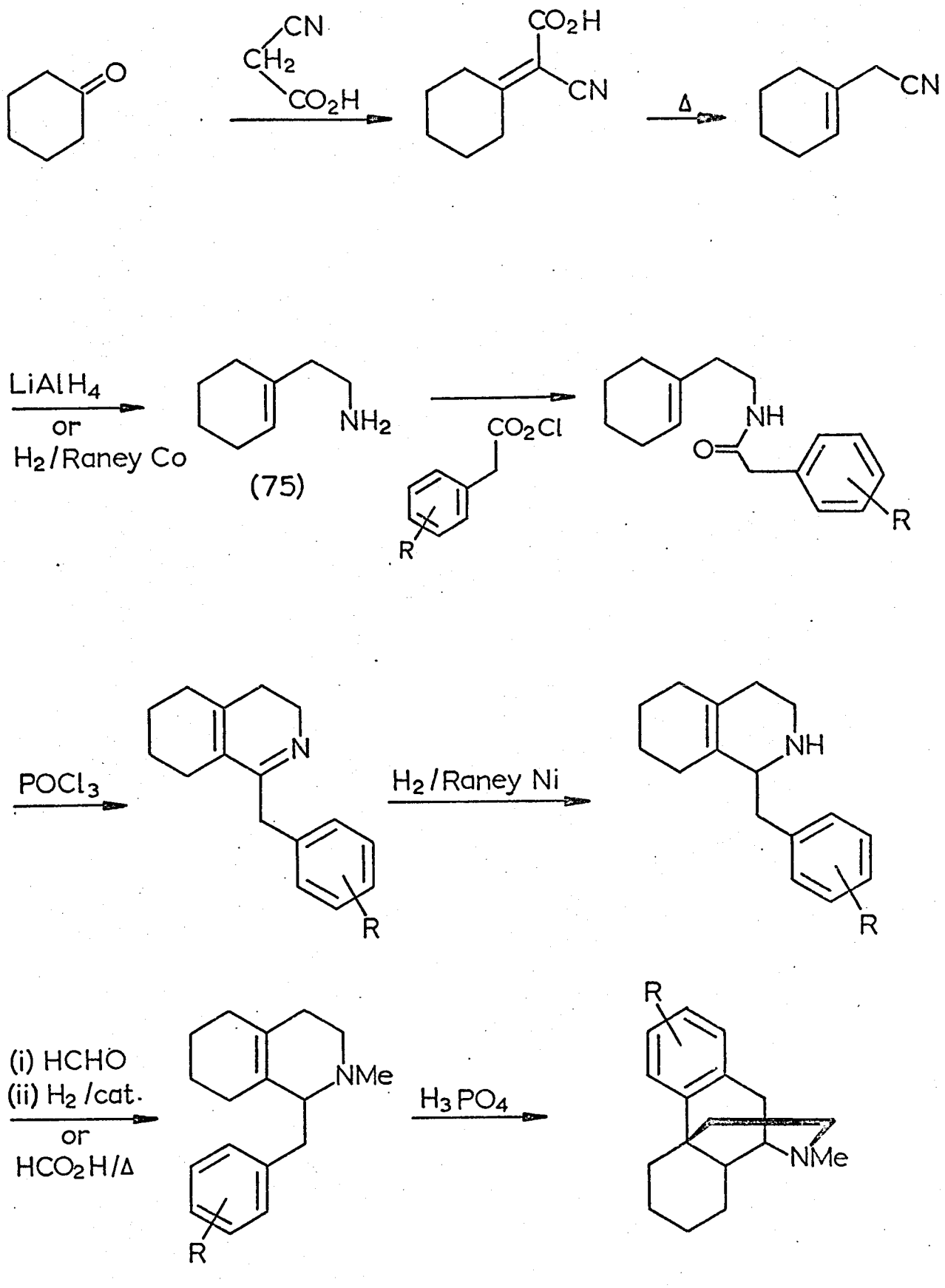
Almost simultaneously (24) and tetrahydrodeoxycodeine (74), with 30% and 2.6% yields for the morphinan cyclisations, respectively, were obtained by Grewe[32] by a different route, although (66) was used as starting material (scheme 6). When 3,4-dimethoxybenzaldehyde was used by Grewe in lieu of anisaldehyde, a small yield (2.6%) of (±)-3-methoxy-4-hydroxy-N-methylmorphinan [tetrahydrodeoxycodeine (74)] was obtained, a result which established the stereochemical equivalence of the morphinans and morphine (1) at the B/C cis- ring junction and iminoethano system.

Schnider and Hellerbach[117] using the cyclohexenylethylamine (75) as starting material synthesised morphinans by the method outlined in scheme 7, including 3-hydroxy-N-methylmorphinan (24) which has superior analgesic action to morphine and longer duration of action.[118-120] The method was put to technical use.[121]

The amine (75) was used subsequently to obtain several morphinans by Grewe,[122] Henecka[123] and Sasamoto.[124] Several extensions and modifications of this useful synthesis have been made.[123-126] All have in common the morphinan precursor, a 1-benzyl-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline such as (73) and appear to offer no particular advantage over the original synthesis by Schnider and Hellerbach.[117]


NaNH2
(66)
NH2
Br
BuLi
Li
MeO
CHO
OH
MeO
(i) HBr
(ii) H2 / Pd
MeI
NMe
I⊖
MeO
H2 / Pd
NMe
MeO
(73)
H3PO4
(24)
MeO
HO
NMe
(74)

Scheme 6

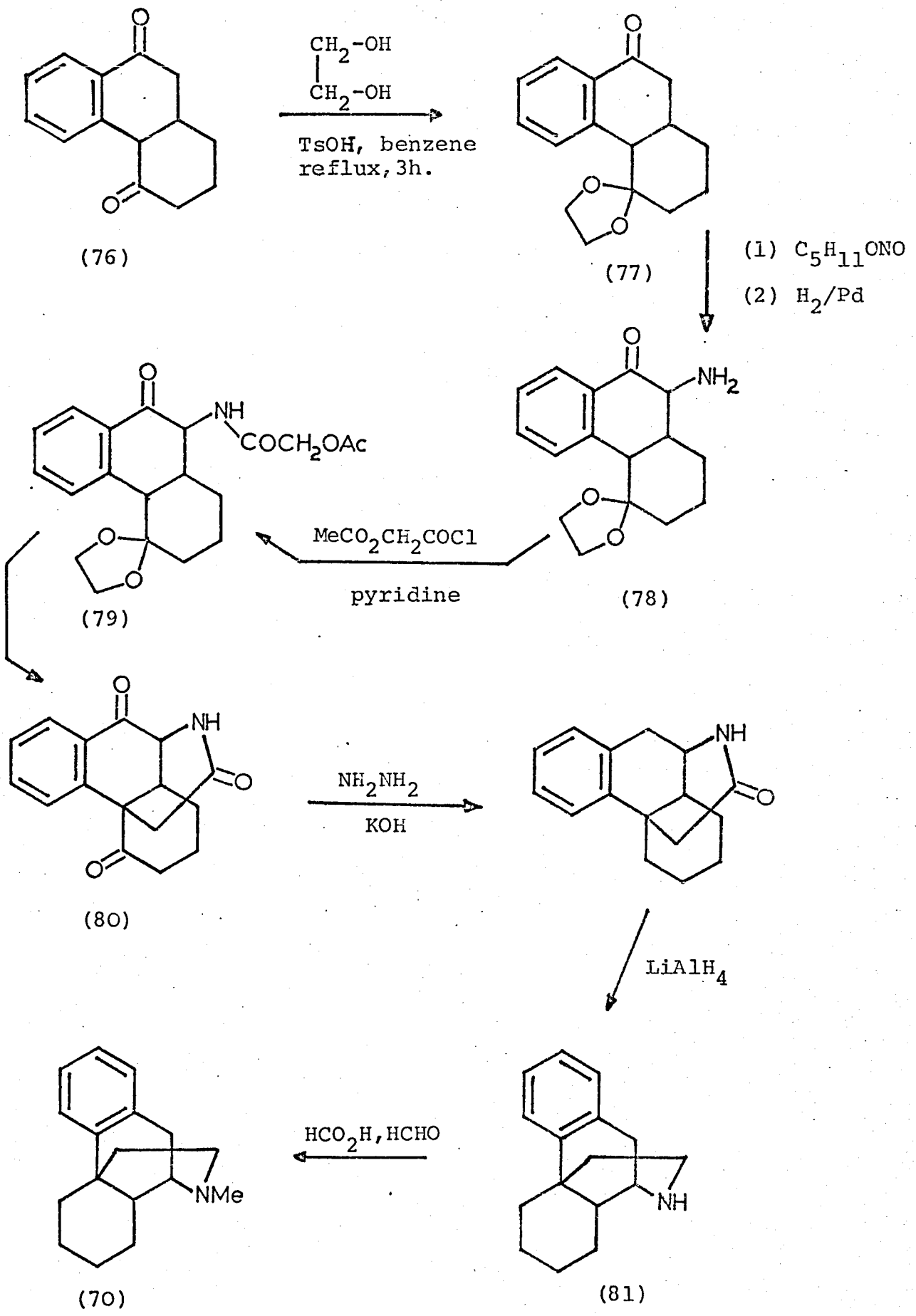

CN
CH2
CO2H
CO2H
CN
Δ
CN
LiAlH4
or
H2/Raney Co
NH2
(75)
CO2Cl
R
NH
O
R
POCl3
N
R
H2/Raney Ni
NH
R
(i) HCHO
(ii) H2/cat.
or
HCO2H/Δ
NMe
R
H3PO4
R
NMe

Scheme 7

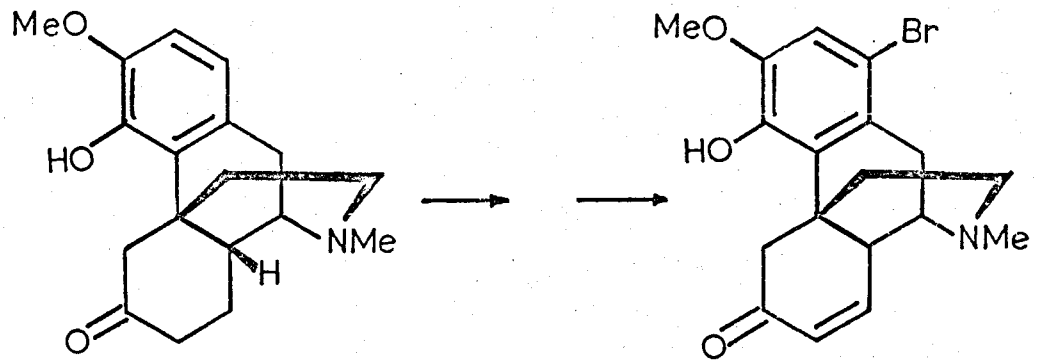
In 1951 Ginsburg and Pappo[127] synthesised morphinan derivatives by a novel route starting from the octahydrophenanthrene derivative (76) as depicted in scheme 8. Diketo-octahydrophenanthrene (76) was converted to the monoketal (77) which yielded the 9-amino derivative (78) when treated with amyl nitrite followed by hydrogenation. The latter was reacted with acetoxyacetyl chloride to yield (79). An attempt to make the diketal of this compound resulted in an unexpected cyclisation to a tetracyclic compound, which was assigned structure (80). Wolf-Kishner reduction of (80) followed by lithium aluminium hydride reduction and subsequent N-methylation of the tetracyclic amine (81) afforded N-methylmorphinan (70). Utilising this new method of cyclisation Ginsburg et.al. synthesised dihydrothebainone (82) from the appropriate starting materials. This was subsequently transformed into morphine via 1-bromocodeinone (83) by the method of Gates and Tschudi[4,5] as shown in scheme 9.[128] Another synthesis of the morphinan ring system was reported in 1952 by Barltrop and Saxton[129] starting from β-tetralone (84) by the reaction sequence shown in scheme 10. This synthesis gave, in small yield, a compound to which Barltrop assigned the structure of 7-oxo-N-ethyl-$\Delta^{8,14}$-dehydromorphinanbromoethylate (85). This assumption was based on the similarity of the synthesis to the series of reactions used for preparing benzomorphans also carried out by Barltrop.[130] However, no rigorous structural conformation was reported.

In 1971 Weisner and co-workers[131] synthesised a 4,5-deoxythebaine analogue (86), in which the nitrogen atom is trans-located from C-17 to the 16-position as outlined in scheme 11. It was subsequently converted into the endoetheno-adduct (87) by successive Diels-Alder and Grignard reactions, a route discovered by K.W.Bentley et.al.[86,108]

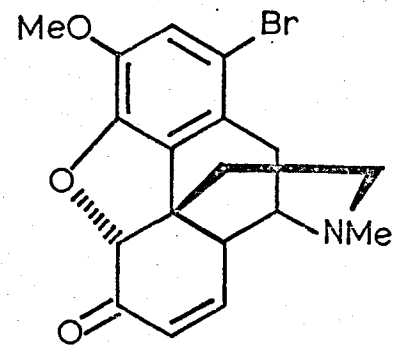
In 1967 Grewe et.al.[132] and Morrison et.al.[133] independently published the acid-catalysed cyclisation of 1,2,3,4,5,8-hexahydro-1-(3-hydroxy-4-methoxybenzyl)-6-methoxy-2-methylisoquinoline (88). Although they worked with different acids, viz. 85% phosphoric acid and 10% hydrochloric acid,


CH2-OH
CH2-OH
TsOH, benzene
reflux, 3h.
(76)
(77)
(1) C5H11ONO
(2) H2/Pd
NH2
NH
COCH2OAc
MeCO2CH2COCl
pyridine
(78)
(79)
NH
O
NH2NH2
KOH
(80)
LiAlH4
NMe
HCO2H, HCHO
(70)
(81)

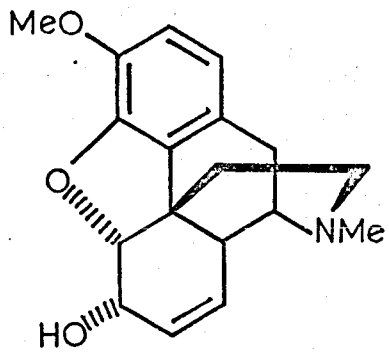
Scheme 8.



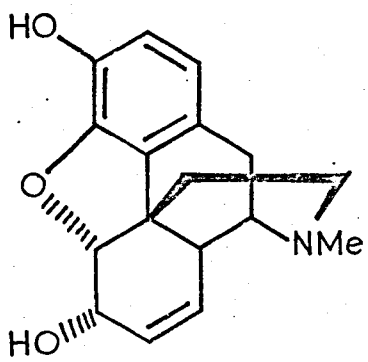
(82)



(83)

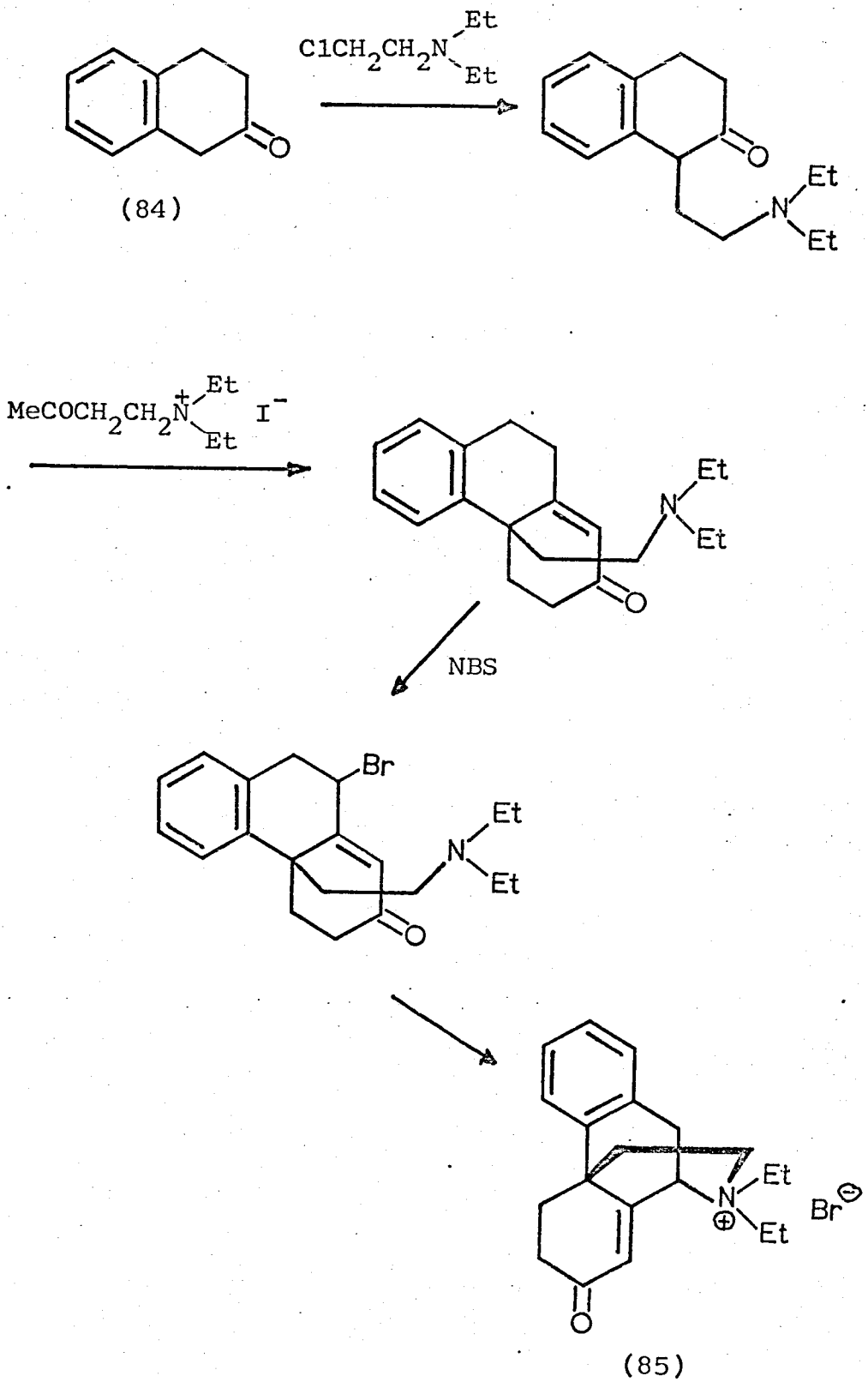


(2)
codeine

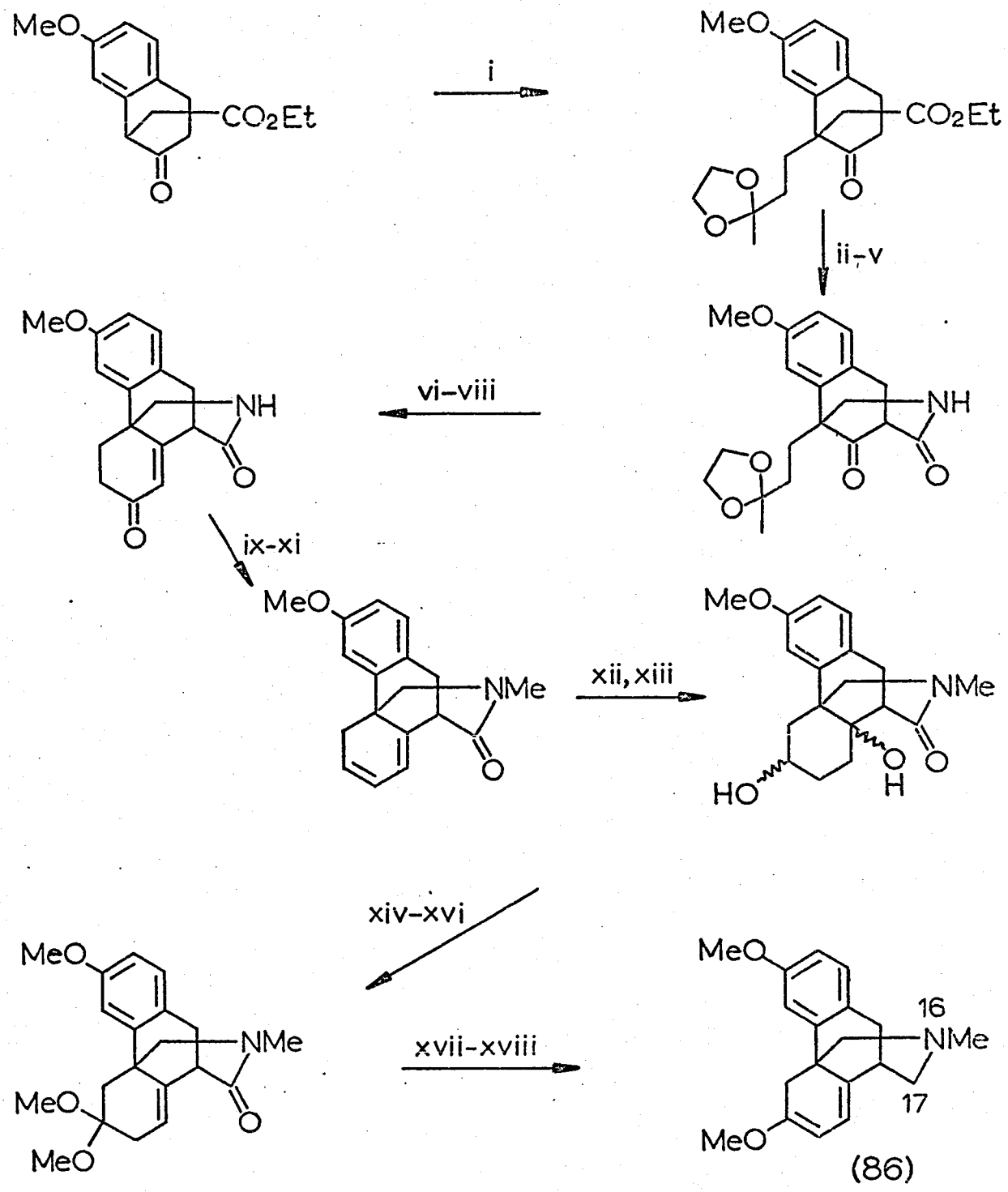


(1)
morphine

Scheme 9



Scheme 10

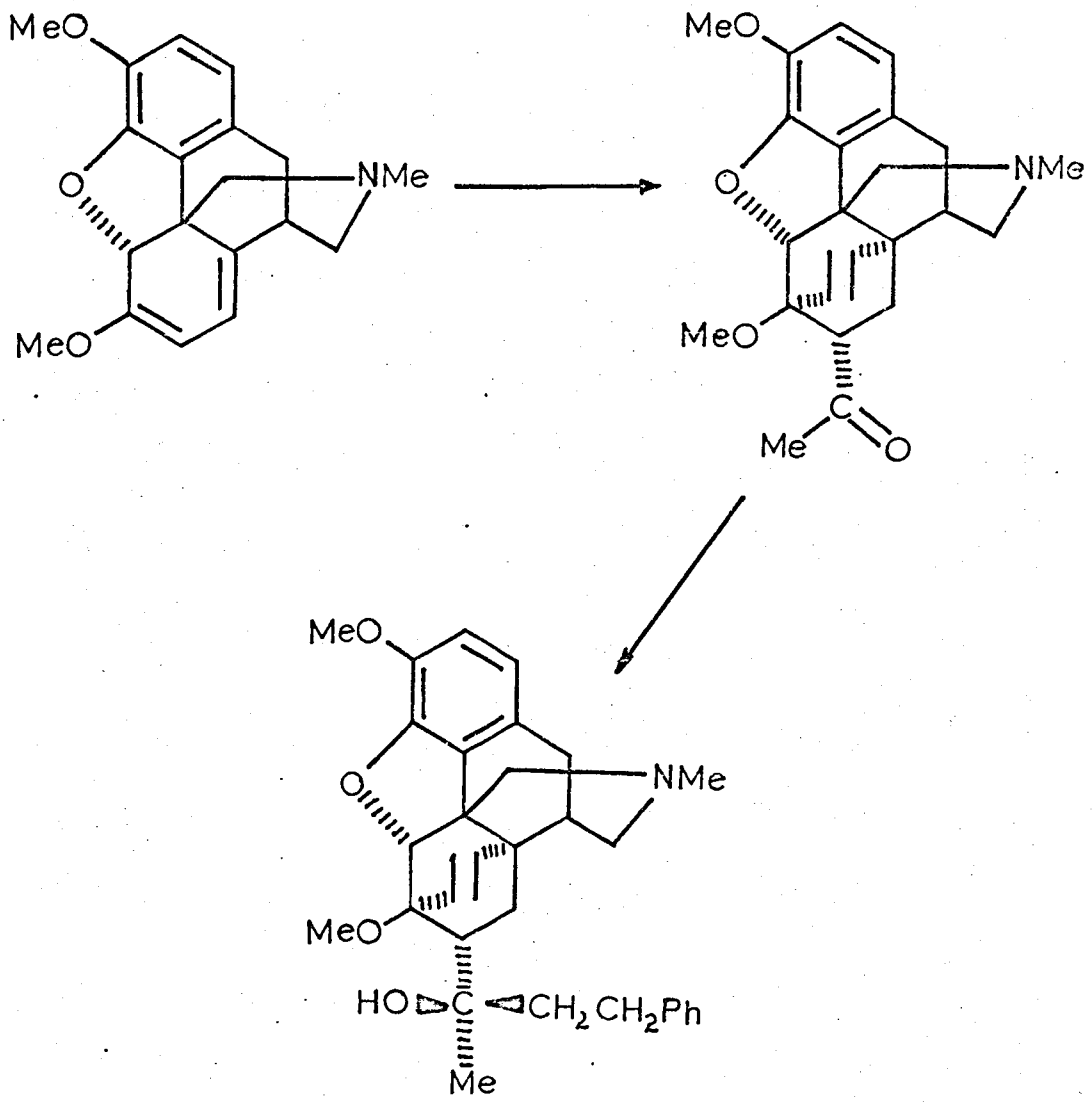


(86)

Reagents. i NaH,C_6H_6;$MeC(OCH_2CH_2O)CH_2CH_2OTs$; ii,5% NaOH; iii,$Et_3N$, $ClCO_2Et$,NaN_3; iv, 80°C, C_6H_5Me; v, NaH, MeI, C_6H_6; vii, TsOH, MeCOMe; viii, TsOH, C_6H_6; ix, $NaBH_4$; x, C_6H_5COCl, pyridine; xi, 200°C; xii, hν, O_2, eosin; xiii, H_2, PtO_2; xiv, CrO_3, HOAc; xv, $SOCl_2$, pyridine; xvi. TsOH, $HC(OMe)_3$, C_6H_6; xvii, Δ, xylene; xviii, $LiAlH_4$.

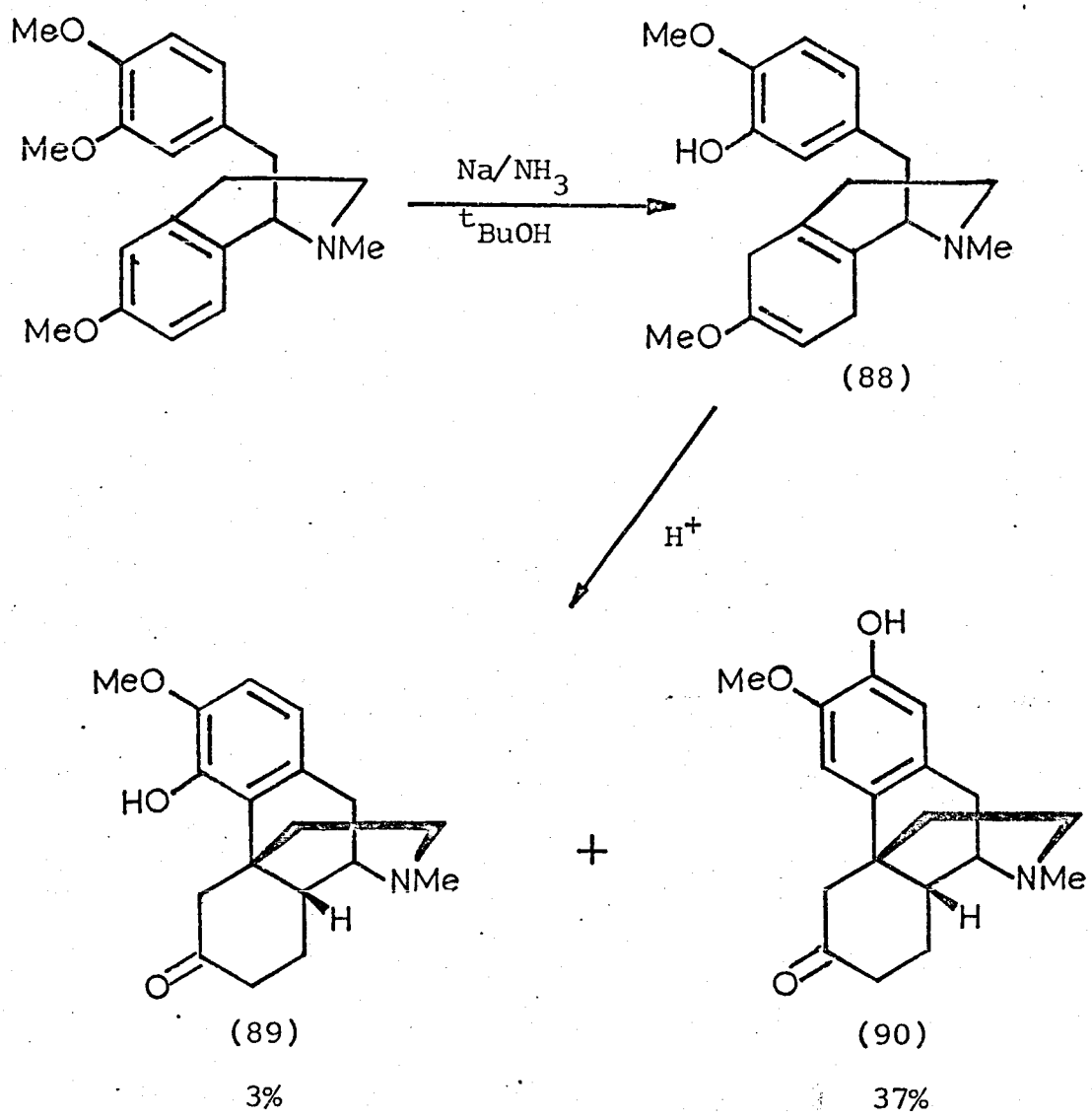
Scheme 11

respectively, both groups of workers obtained the 4-hydroxymorphinan (89) in a 3% yield and the isomeric 2-hydroxy compound (90) in a 37% yield. Both groups of

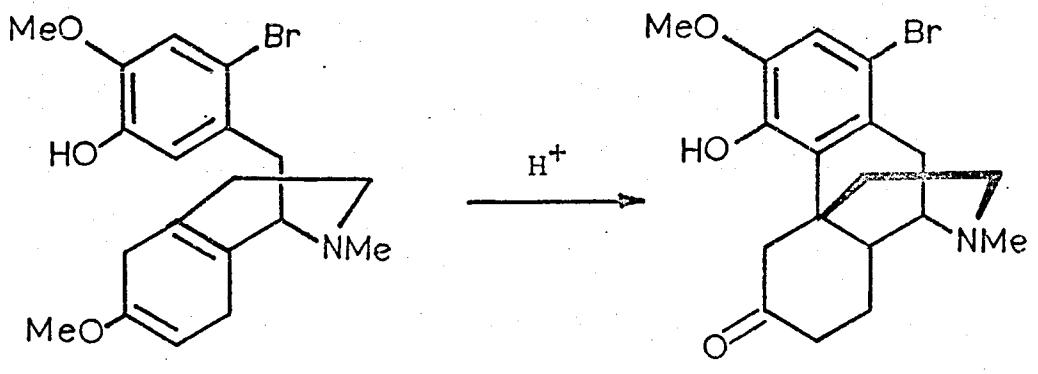


(87)

workers were searching for a precursor for the synthesis of codeine and morphine. In order to close the oxygen bridge between the carbon atoms 4 and 5 a hydroxyl function in position 4 is necessary. The isomer (90) (37% yield) is unsuitable for this purpose.



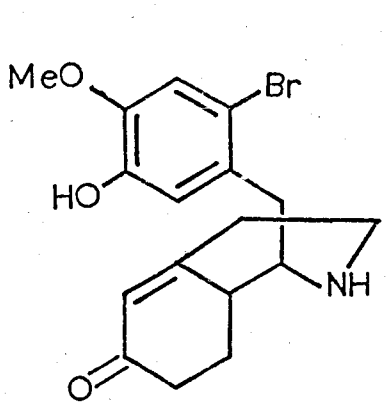
H.C.Beyerman and co-workers[134,135] reasoned that a blocking group para to the hydroxyl group in (88) would prevent formation of (90) and lead to the formation of (89) as the major product. A patent of Merck. Inc.[136] reported the successful cyclisation of the 1-benzyl-hexahydroisoquinoline (91) with a bromine substituent in position 2 of the benzyl group to give the morphinan (92).



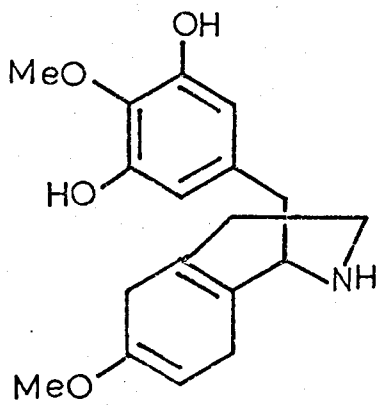
(91) (92)

However, the credibility of this cyclisation has been strongly criticised since Beyerman[134,135], and De Graw et.al.[137] could not repeat the synthesis. The p-bromophenol (93) and its N-methoxycarbonyl derivative failed to undergo acid-catalysed cyclisation to a morphinan.[137] Also, although 2-hydroxydihydronorthebainone (95) was readily obtained by cyclisation of (94), removal of the 2-hydroxyl group could not be achieved.[137]

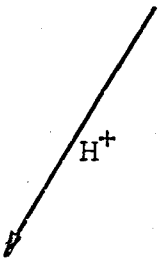
It has been shown that 1-benzyl-1,2,3,4,5,6,7,8-octahydroisoquinolines can be cyclised more effectively when an electron-withdrawing group is present on the nitrogen atom, the formyl group particularly has been found to markedly effect the rate of acid-catalysed cyclisation of such compounds.[138] H.C.Beyerman et.al. eliminated the undesired isomer of type (90) by use of (96, R_1 = CHO, R_2 = Me), to give 85% of (97; R_1 = CHO, R_2 = Me).[134,135] It was conceivable that if a suitable blocking function at R_2 could be introduced into (96), a synthesis of morphine paralleling the Gates approach would be possible. Utilising a symmetrically substituted 1-benzyl group in the 1,2,3,4,5,8-hexahydroisoquinoline (98; R_1 = R_2 = OH) H.C. Beyerman and co-workers have achieved a convenient and total synthesis of codeine and morphine by the Grewe method as depicted in scheme 12.

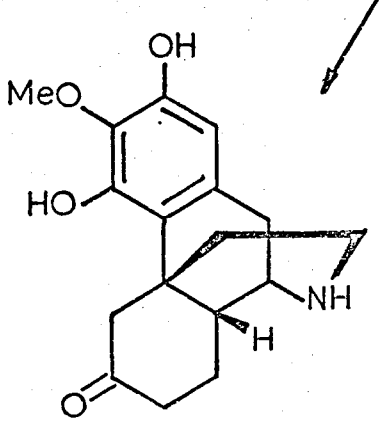


(93)



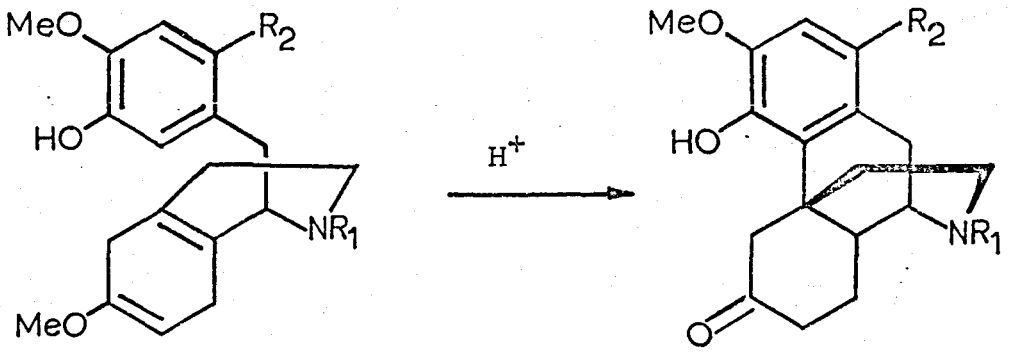
(94)





(95)

Acid-catalysed cyclisation of (98) gives the morphinan (99; $R_1 = R_2 = OH$). The phenolic hydroxyl group at C-2 was selectively removed by reduction of the 1-phenyl-tetrazol-5-yl ether derivative (99; $R_1 = O\text{-}CN_4\text{-}C_6H_5$; $R_2 = OH$) to afford (-)-N-formylnordihydrothebainone (100),[139] removal of the hydroxyl group at C-4 in the morphinan (101) was also accomplished by slightly different conditions.[140] Reduction of (-)-N-formylnor-dihydrothebainone (100) to (-)-dihydrothebainone (102) was possible with palladium on carbon as catalyst.[140]

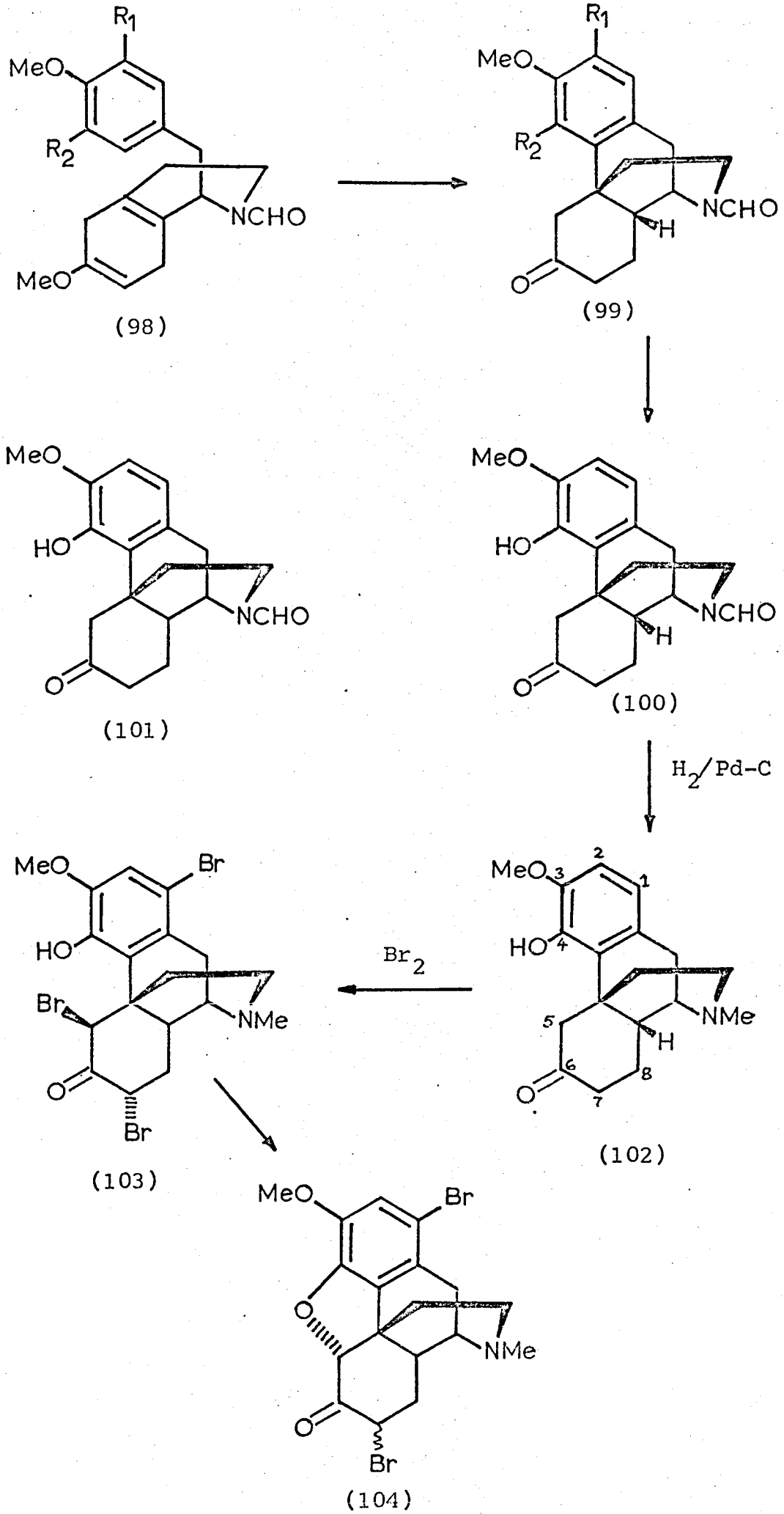


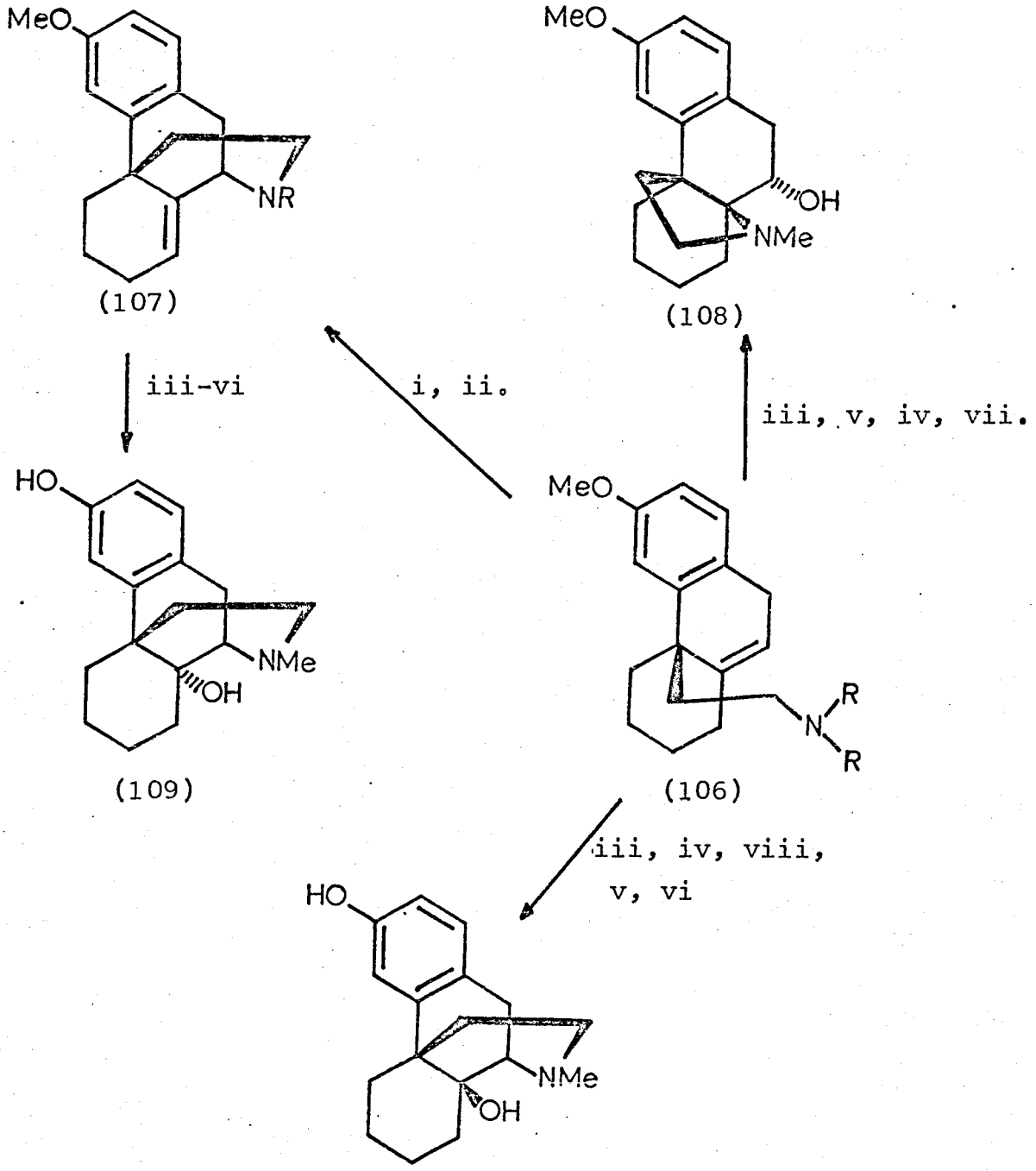
(96) (97)

Bromination of (102) yielded successively 1-bromo, 1,7α-dibromo-, and 1,5β,7α-tribromo-dihydrothebainone (103).[141] Closure of the oxygen bridge in (103) in boiling ethanol, yields an equilibrium mixture of 1,7α and 1,7β-dibromodihydrothebainone (104): scheme 12.

The original Grewe synthesis of morphinans[113,31] which involved the acid-catalysed cyclisation of 1-benzyl-octahydroisoquinolines, normally yields mostly morphinans (B/C cis) rather than isomorphinans (B/C trans). Fry and May have shown that by using aluminium halides as cyclisation catalysts substantial amounts of trans-benzomorphans were produced during the cyclisation of benzyltetrahydropyridines.[142] Gates and co-workers[143] found that similar use of aluminium bromides in the morphinan cyclisation of 1-benzyloctahydroisoquinolines (105) yields substantial quantities of isomorphinans (106).

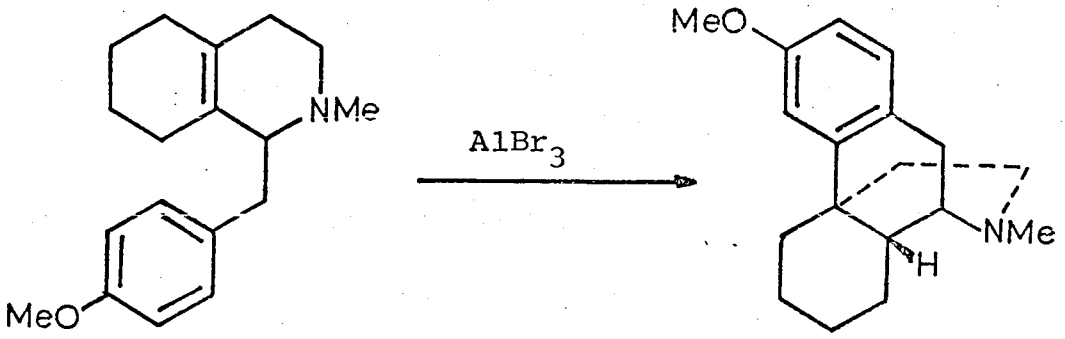
In 1973 Monkovic and Belleau and co-workers developed a new synthesis of the morphinan ring system. The amine (106; R = H) is utilised as the key intermediate not only of 3,14-dihydroxymorphinans[144] e.g. (110), (Scheme 13) and 9α-hydroxy-3-methoxyhasubanans[145] (108) but also of the first 3,14-dihydroxyisomorphinans[145] (109), via the 3-methoxy-$\Delta^{8,14}$-morphinan (107; R = H).


R1
MeO
R2
NCHO
MeO
(98)
(99)
(100)
(101)
H2/Pd-C
Br2
Br
NMe
(102)
(103)
(104)
Scheme 12.

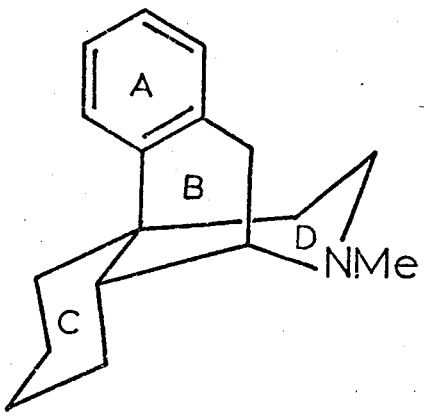


Reagents : i, Br_2, $CHCl_3$; ii, $NaHCO_3$, DMF, 130-135°C;
iii, $ClCO_2Et$, Et_3N; iv, m-$ClC_6H_4CO_3H$; v, $LiAlH_4$;
vi, BBr_3, CH_2Cl_2; vii, K_2CO_3, aq.MeOH;
viii, sodium t-pentyl oxide.

Scheme 13.

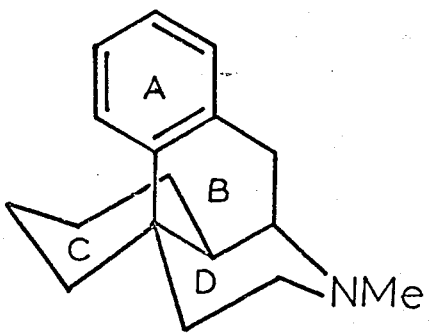


(105) (106)



B/C trans

cf:

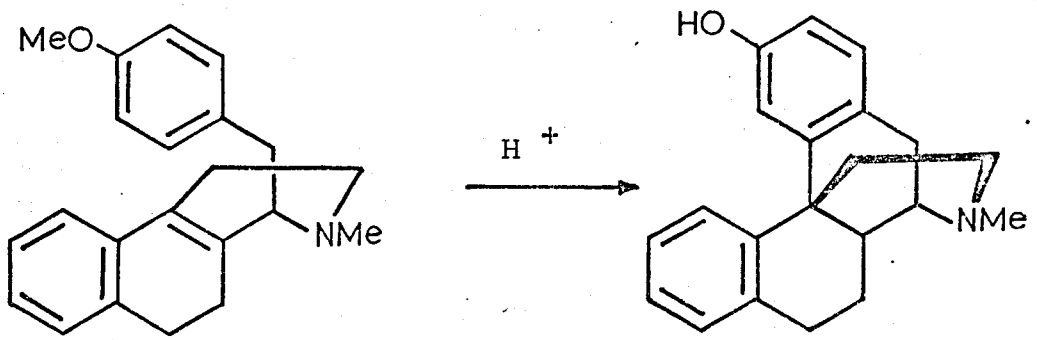


B/C cis

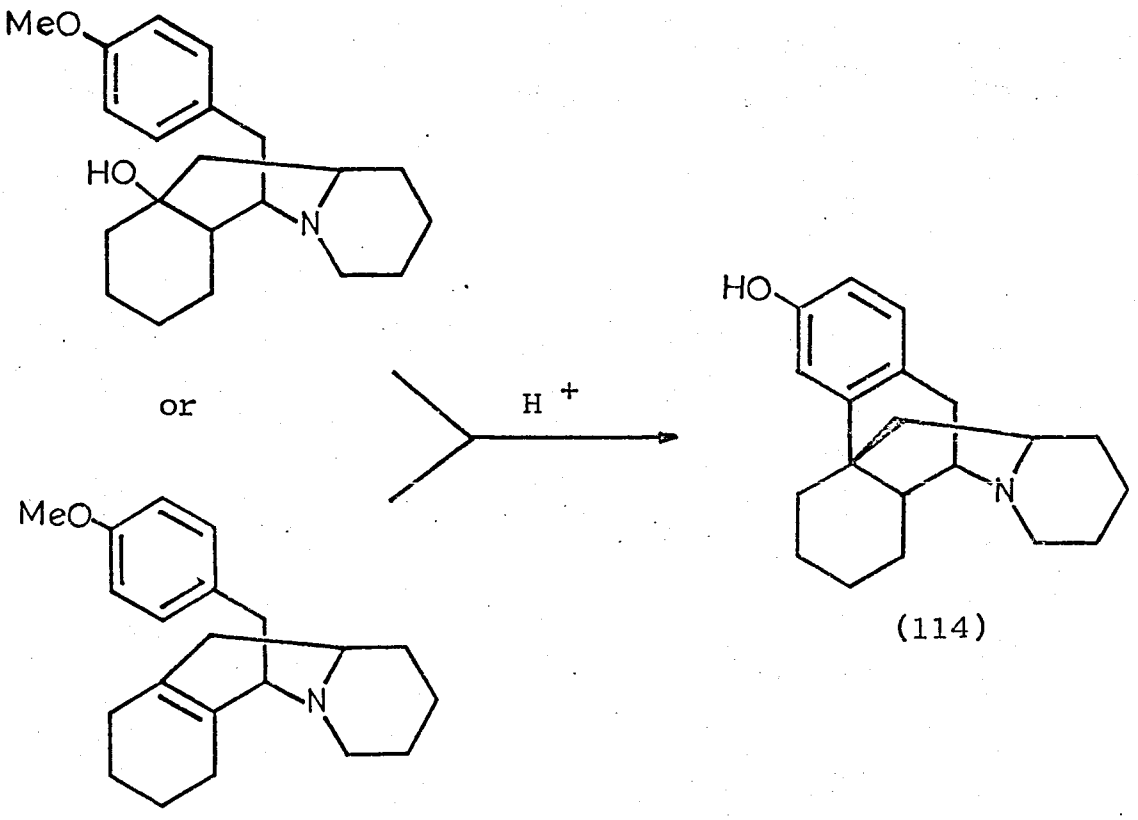
Some of the 3,14-dihydroxymorphinans synthesised by this group have been found to possess valuable pharmacological properties as analgesics and narcotic antagonists.[144,146]

Douglas and Meunier[147] in 1975 synthesised a series of morphinans with an additional aromatic or alicyclic

ring fused to the 5,6 positions e.g. (112) or an alicyclic ring fused to the 16,17 positions e.g. (114). The synthetic



(111) (112)

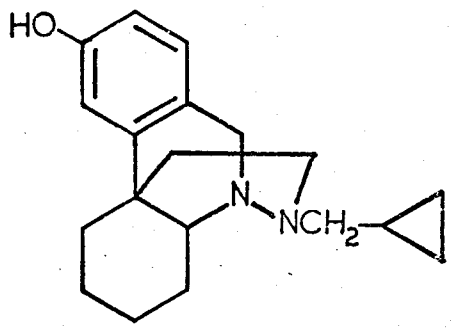


(113) (114)

sequence involved elaboration of the required benzylisoquinoline (111) or quinolizidine (113) for Grewe cyclisation

to the morphinans, and modification of the functional groups of the morphinan. These morphinans showed poor to moderate analgesic and narcotic antagonist activity.[147]

T.Kametani and co-workers[148] have synthesised the azamorphinan (115) the (-)-form of which is reported to be five times as active as pentazocine.[148]



(115)

DISCUSSION

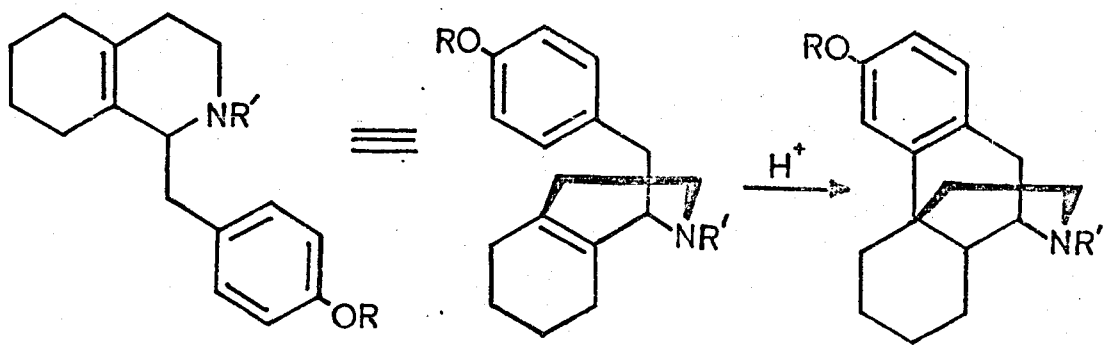
PART 1

Synthetic Approaches to Certain Partially Hydrogenated 8-Ketoisoquinolines.

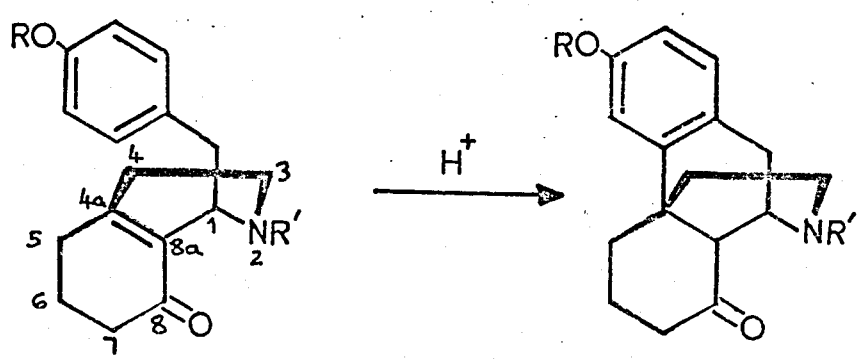
Preamble

No compounds in the series of morphine-like analgesics possessing substituents at C-8 alone have been studied. How suitably substituted C-8 morphinans would interact with the analgesic receptor and the lipophilic site suggested by Bentley and Lewis is of evident interest.

The Grewe[113] and Schnider[117] syntheses of the morphinan ring system (117) involve an acid-catalysed cyclisation on to an unactivated double bond in 1-benzyl-octahydroisoquinolines of type (116). The incorporation of an 8-substituent in the starting octahydroisoquinoline such as (118) would lead to an 8-functionalised morphinan (119)



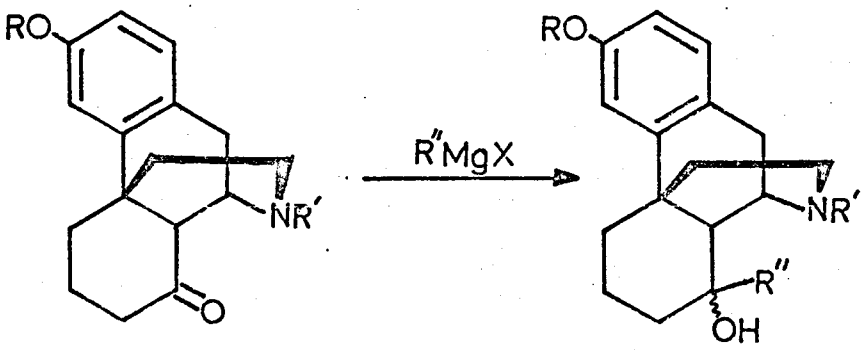
(116) (117)



(118) (119)

The 8-keto-group in (118) should greatly facilitate electrophilic attack by C-4a on the aromatic ring, ready protonation of the carbonyl oxygen of the enone providing the electrophile.

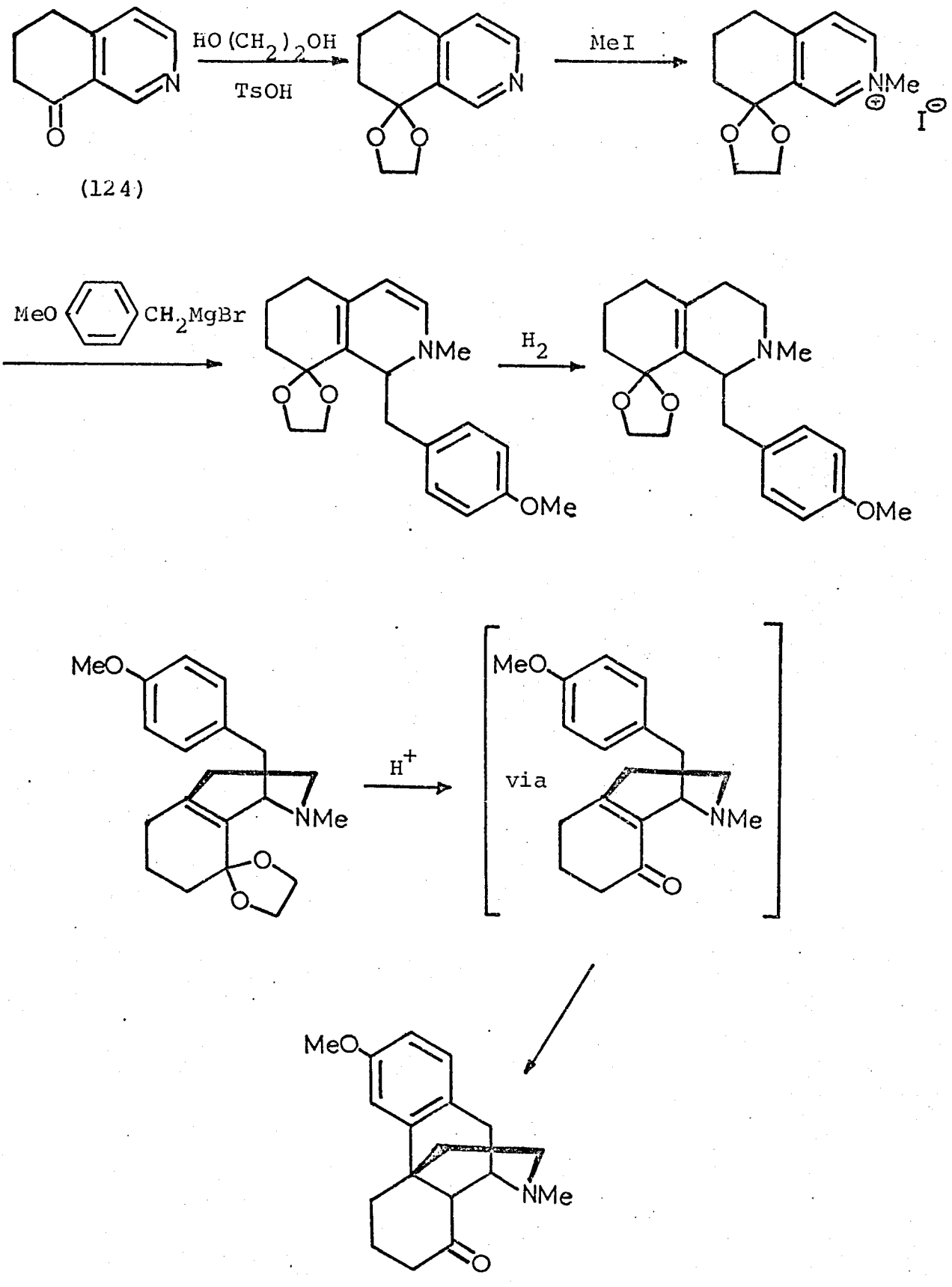
If morphinans of type (119) could be elaborated by this route they would permit many modifications of ring-C to be examined utilising the carbonyl functionality as starting point. Grignard reaction of (119) would produce novel carbinols (120),and other carbanion or nitrogen condensations at C-8 could be effected, so to permit structure-activity relationships to be studied in detail.



(119) (120)

Reduction of (119) and dehydration could provide access to the Δ-8,14-system (121). Allylic bromination and dehydrobromination could lead to dienes of type (122) and so permit Diels-Alder adducts of type (123) to be approached with suitable dienophiles.

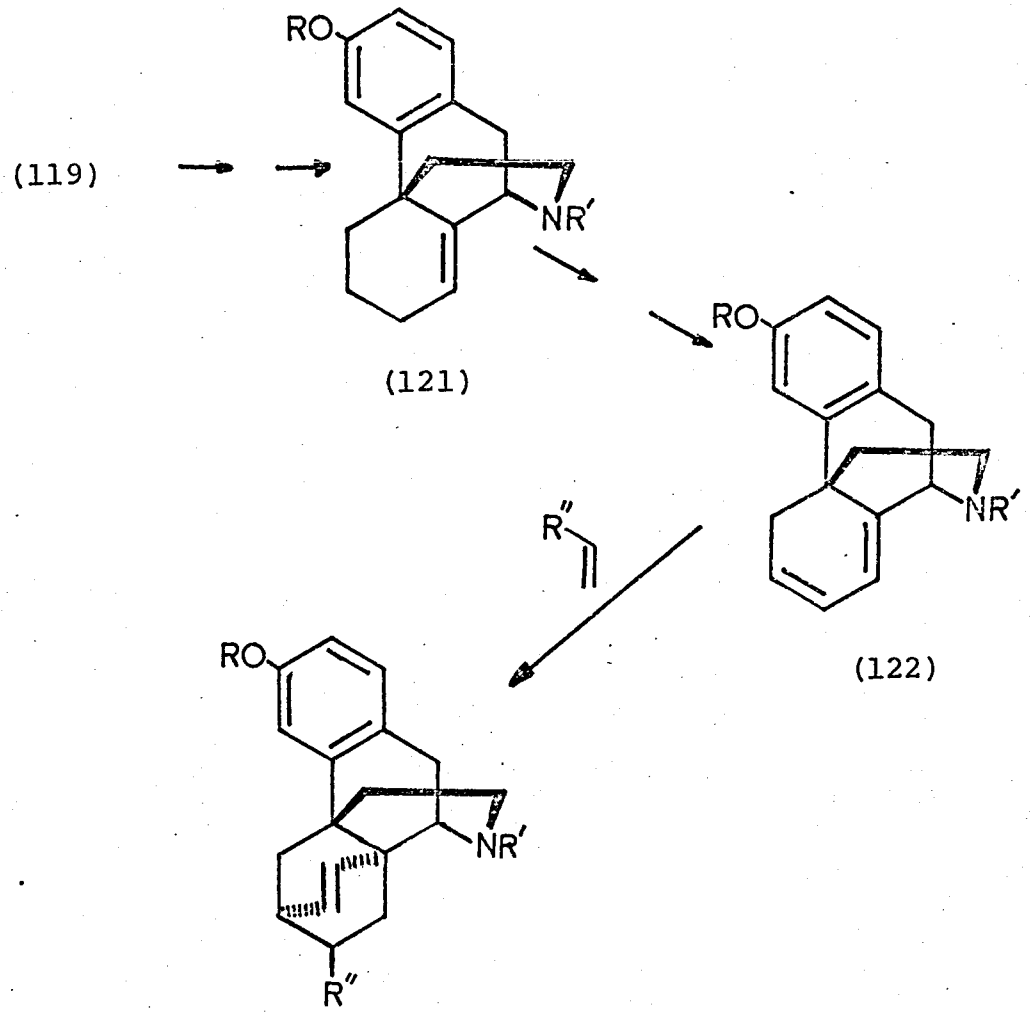
We therefore studied the synthesis of certain 8-keto-1,2,3,4,5,6,7,8-octahydroisoquinolines. If a reasonably high yield synthesis of 8-keto-5,6,7,8-tetrahydroisoquinoline (124) could be developed then scheme 14 provides a possible route for its conversion into the 8-ketomorphinan (119; R = Me, R' = Me) utilising the classical Grewe[113] cyclisation step.



(124)

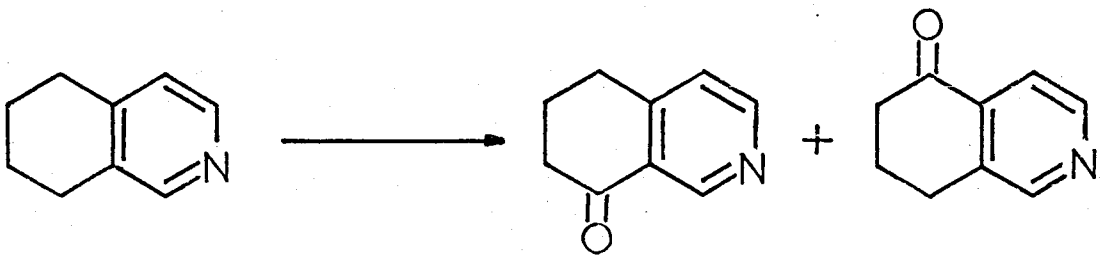
(119)

Scheme 14



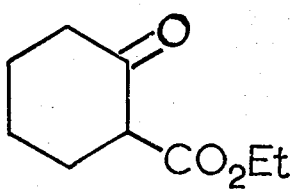
A Approaches to 8-Keto-5,6,7,8-tetrahydroisoquinolines via 5,6,7,8-tetrahydroisoquinoline.

8-Keto-5,6,7,8-isoquinoline (124) is reported[149] to be obtained from 5,6,7,8-isoquinoline (66) by chromium trioxide oxidation; it is formed together with the 5-oxo-5,6,7,8-tetrahydroisoquinoline (125); (in a ratio of 2:1 respectively) in 10% yield of (124). It was hoped we could improve this step by careful examination of the conditions. As discussed earlier (cf. Introduction p.39) 5,6,7,8-tetrahydroisoquinoline (66) has been synthesised from ethyl cyclohexanone-2-carboxylate (126) by Grewe et. al.[113] and from α-amino-methylene cyclohexanone (126a) by Schnider et.al.[30] and Schlittler and Merian.[116]

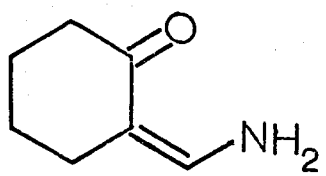


(66) (124) (125)

Murakami and co-workers[150] reported an improved synthesis of 3-substituted derivatives of N-methylmorphinan via 5,6,7,8-tetrahydroisoquinoline (66). The improved method



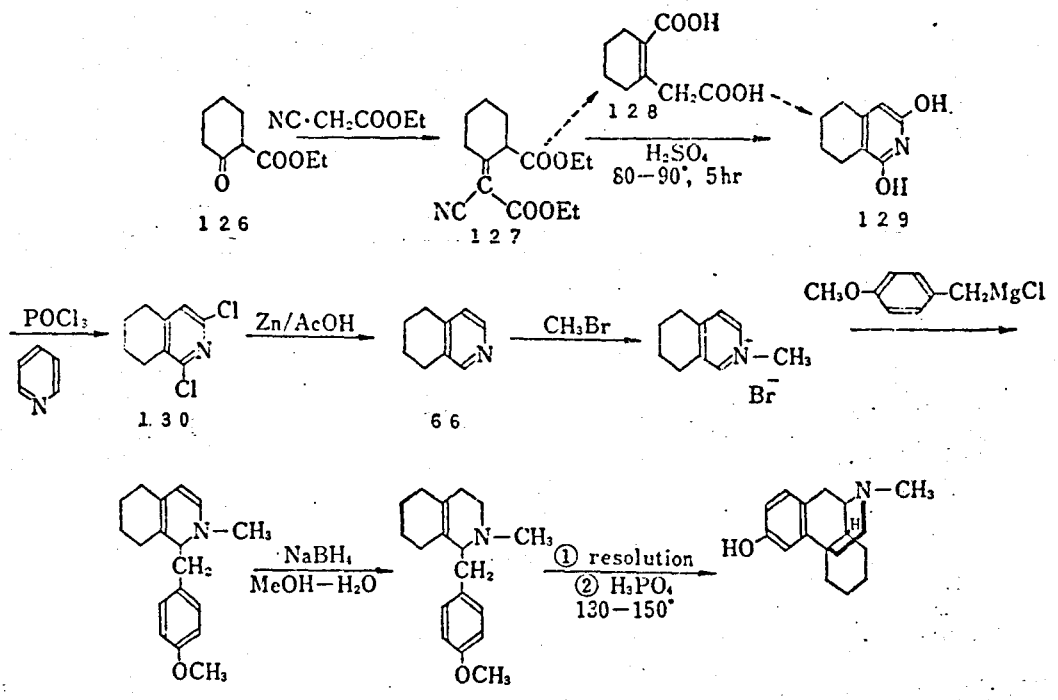
(126)



(126a)

is shown in scheme 15. (66) was the most important intermediate at the time (1972) for the synthesis of morphinan derivatives. Of the several known methods of synthesis the Grewe method already discussed seems to be the most useful one. Murakami et.al.[150] found that (129) could be directly obtained from (127) without proceeding via the dicarboxylic acid (128) as Grewe's route[113] (cf. scheme 3, p.40) : (129) was obtained in quantitative yield when (127) was heated in concentrated sulphuric acid at 80-90°C for five hours.

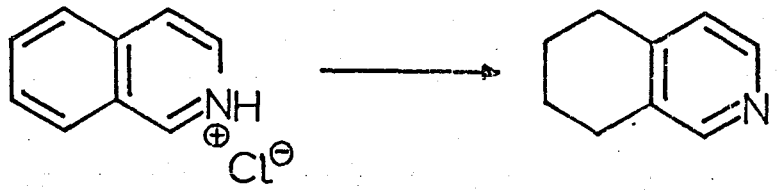
Following Murakami's synthesis we synthesised 1,3-dihydroxyisoquinoline (129) from ethyl cyclohexanone-2-carboxylate (126) in good yield. The next step in the synthesis involved the chlorination of the 1,3-dihydroxy



Scheme 15

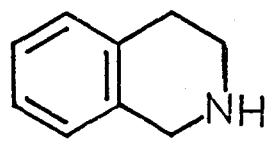
compound (129) with phosphorus oxychloride. Murakami et.al. report that the chlorination proceeded smoothly by heating a mixture of the 1,3-dihydroxy compound, phosphorus oxychloride and pyridine in a sealed tube at 200°C for 2h. We repeated the synthesis using sealed glass carius tubes but experienced difficulty with explosions occurring before the reaction time was completed. Only when the reaction was carried out on a very small scale could a reasonable yield of the 1,3-dichloro compound (130) be isolated. Even then the reaction would sometimes fail completely for no apparent reason. Substituting quinoline for pyridine prevented any further explosions but gave none of the desired product. In view of these difficulties we did not investigate the route further.

Several months later two papers appeared regarding the synthesis of the required 5,6,7,8-tetrahydroisoquinoline (66). J.Z.Ginos[151] reported the hydrogenation of isoquinoline hydrochloride (131) in 4N-HCl-MeOH at atmospheric pressure and room temperature over Adams catalyst (Pt) to yield 5,6,7,8-tetrahydroisoquinoline in 92% yield.



(131) (66)

Vierhapper and Eliel[152] reported the hydrogenation of quinoline, isoquinoline and substituted quinolines in strong acid media at 50psi and room temperature with Pt catalyst. 5,6,7,8-Tetrahydroisoquinoline was claimed in 95% yield when the hydrogenation was carried out in 12N hydrochloric and sulphuric acid. Following the procedure reported by Ginos[151] we only obtained 1,2,3,4-tetrahydroisoquinoline (132) as the sole product of the hydrogenation of isoquinoline hydrochloride (131) in 4N HCl-MeOH, characterised as its picrate salt.



(132)

When we repeated the reported work of Vierhapper and Eliel[152] we obtained the required 5,6,7,8-tetrahydroisoquinoline (66) in 95% yield, again as its picrate salt. We did note however that sometimes the reaction did not proceed to completion and hydrogen uptake ceased before reduction was fully completed. In these cases the product consisted of a mixture of isoquinoline and 5,6,7,8-tetrahydroisoquinoline which proved difficult to separate. Furthermore, very substantial quantities of platinum catalyst (0.75g for 6.45g isoquinoline) were required to ensure success and this was clearly a serious drawback to a large scale synthesis.

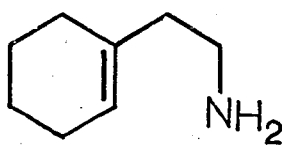
Since the introduction of the 8-keto-group by

chromium trioxide oxidation by the method of Sugimoto et. al.[149] only reported yields of 10% of the 8-oxo-compound (124) we abandoned further study of this approach.

B Approaches to 8-Keto-1,2,3,4,5,6,7,8-octahydroisoquinolines via heterocyclic ring closure.

(i) Syntheses starting from Cyclohex-2-enone.

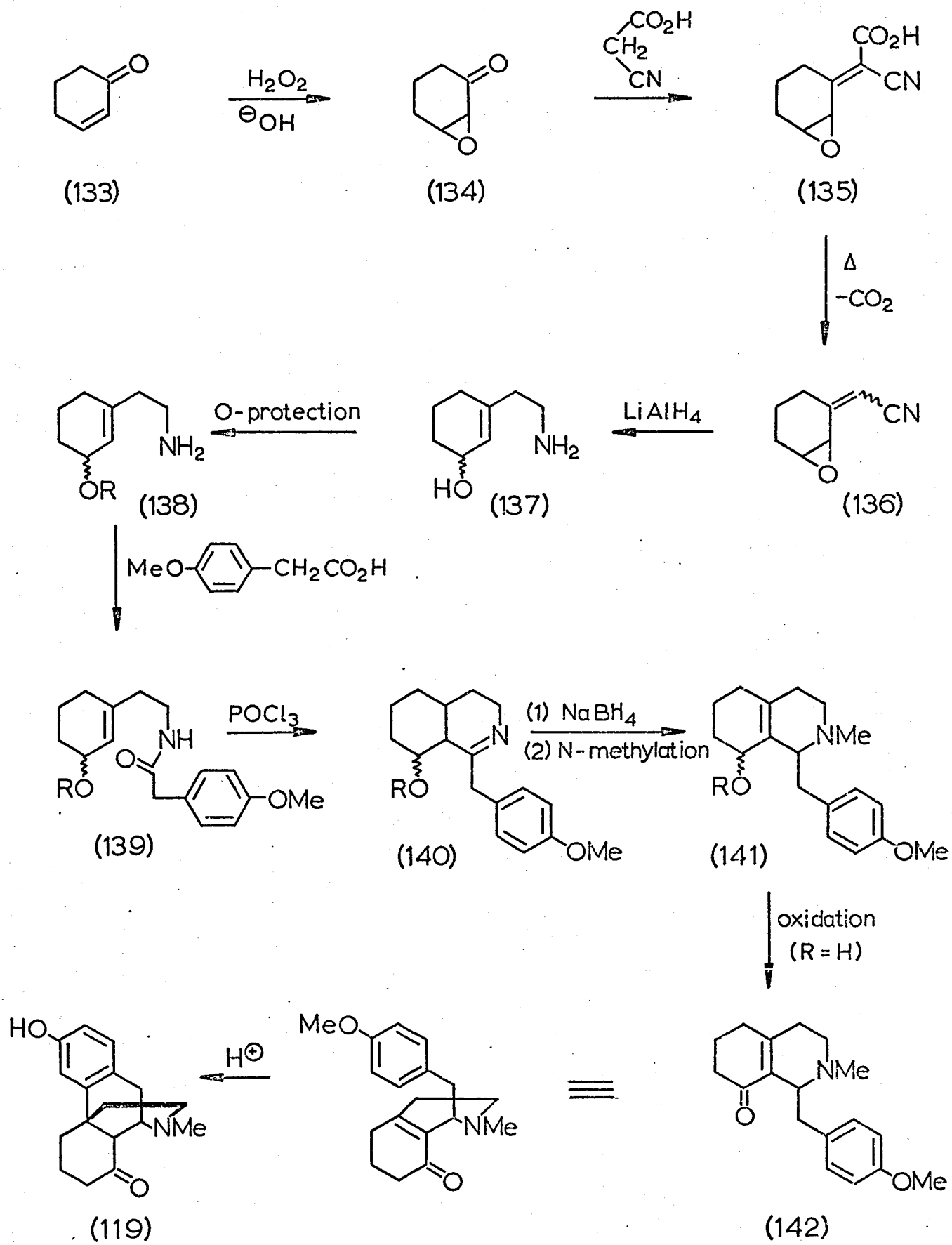
We turned our attention to the introduction of the keto-group (or its equivalent) prior to the formation of the heterocyclic ring of the isoquinoline. The Schnider and Hellerbach synthesis of N-methylmorphinan[117] discussed earlier (p. 43) utilises the β-cyclohex-1-enylethylamine(75) as a key intermediate.



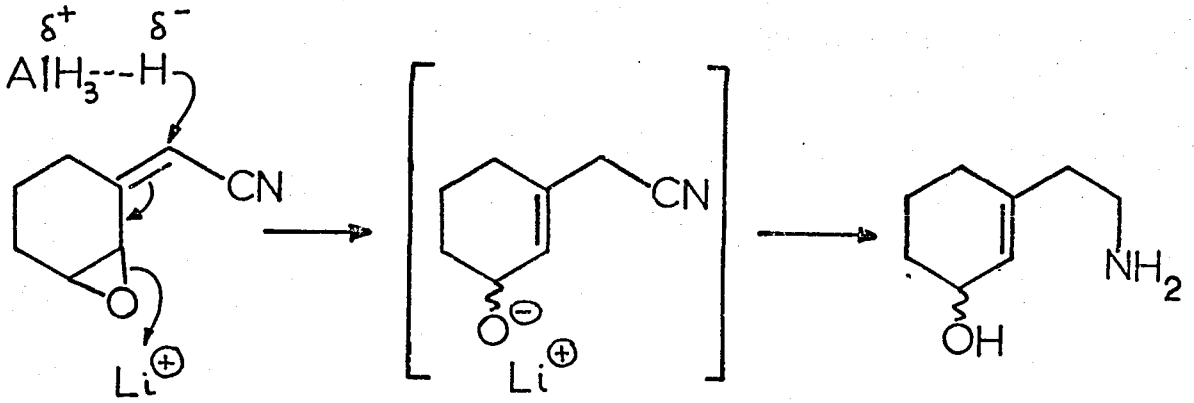
(75)

We reasoned that the incorporation of an oxygenated functionality in the starting amine (137) would allow the synthesis of an 8-functionalised-1-benzylisoquinoline such as (142) which upon acid-catalysed ring closure could provide access to an 8-ketomorphinan (119) as outlined in scheme 16.

Knoevenagel condensation[153-156] of the epoxide (134); obtained by alkaline peroxidation of cyclohex-2-enone (133), with cyanoacetic acid could afford the cyanocarboxylic acid (135) which upon subsequent decarboxylation could afford the α,β unsaturated nitrile (136). We anticipated that lithium aluminium hydride reduction of this compound would produce the amine (137) by the following mechanistic rationale:


H2O2
⊖OH
CO2H
CH2
CN
CO2H
CN
(133)
(134)
(135)
Δ
-CO2
O-protection
LiAlH4
NH2
OR
HO
CN
(138)
(137)
(136)
MeO
CH2CO2H
POCl3
NH
RO
OMe
(1) NaBH4
(2) N-methylation
N
NMe
(139)
(140)
(141)
oxidation
(R = H)
HO
H⊕
MeO
NMe
O
(119)
(142)

Scheme 16

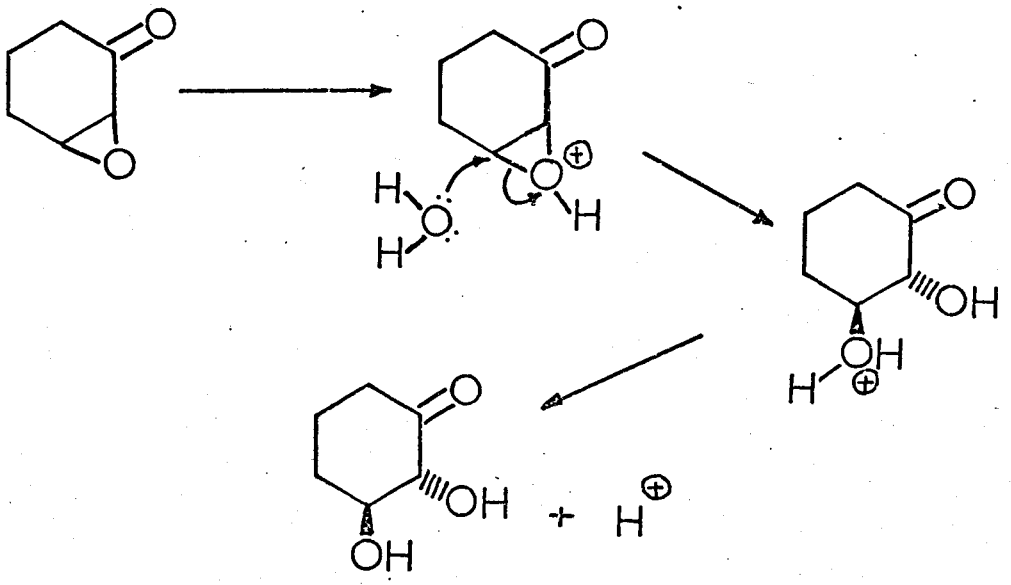


(136) (137)

Epoxide ring opening being facilitated by attack of hydride anion on the α-carbon to the nitrile function; followed by normal hydride reduction of the nitrile group to afford the required amine (137). Subsequent protection of the alcoholic moeity to provide the O-protected analogue (138) followed by condensation with the phenylacetic acid could provide the amide (139). Bischler-Napieralski cyclisation could afford the 3,4-dihydro compound (140) which could be progressed to the morphinan (119) as shown.

We treated cyclohex-2-enone (133) with hydrogen peroxide in alkaline media as reported by House and Wasson[157] and obtained the epoxide (134) as a colourless liquid. Knoevenagel condensation of the epoxy-ketone (134) in benzene with cyanoacetic acid and ammonium acetate as catalyst gave 3 components, separated by chromatography on silica gel. The first component to be eluted was shown to be the starting epoxy-ketone (134). Further development of the chromatogram with the addition of increasing amounts of ether afforded a crystalline compound m.pt. 87-88°C. This showed a broad hydroxyl peak in the infrared together with carbonyl absorption at 1705cm^{-1}. Mass spectral analysis showed a molecular ion at m/e = 130. On the basis of the data we assigned the diol structure (143) to this compound and its melting point is in good agreement with that reported in the literature.[158] Presumably the glycol (143) arises either during the condensation itself or in the aqueous work-up by hydrolytic cleavage of the epoxide. The facile cleavage of the epoxide ring is well known[159] and Russian

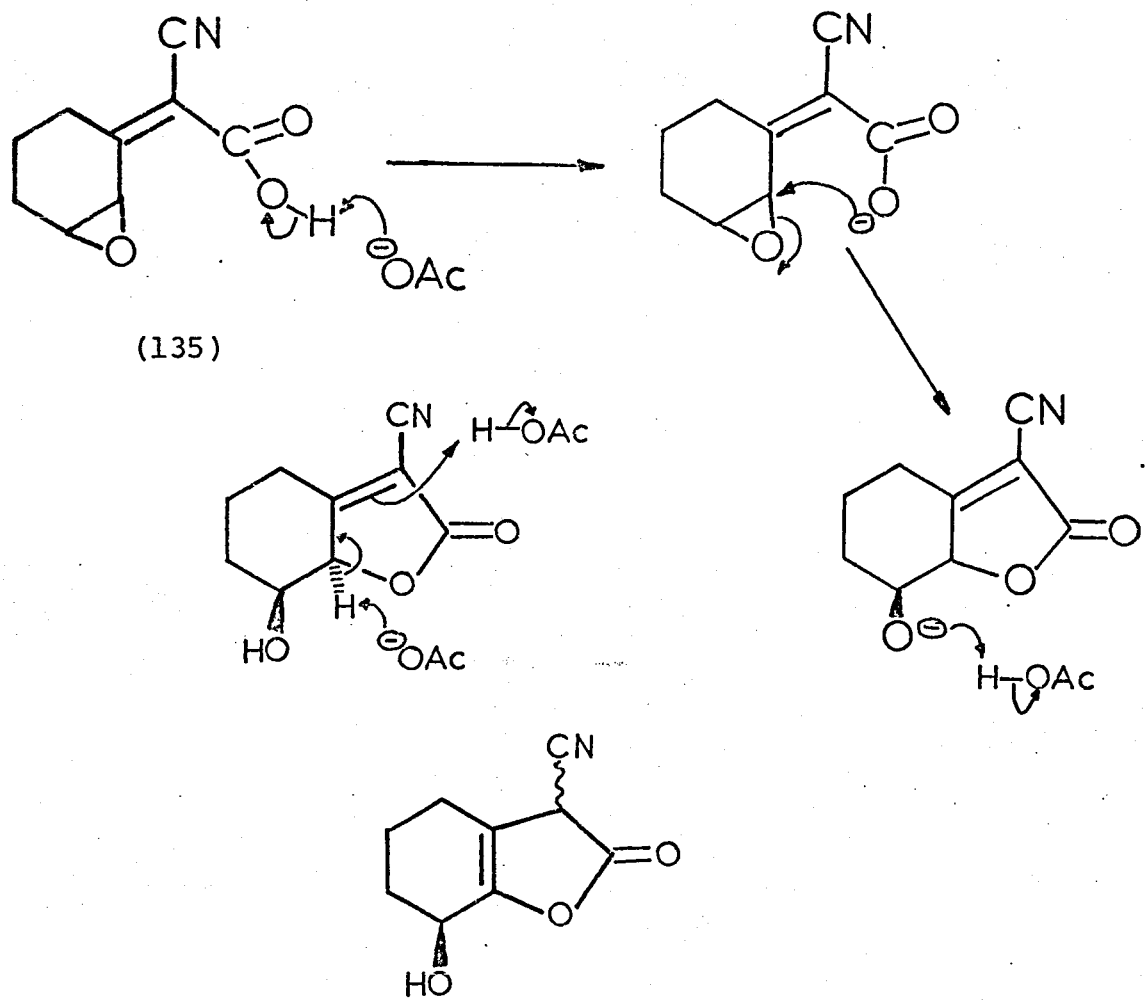
workers have reported[158] that the epoxy-ketone (134) gives rise to the glycol (143) upon standing in the presence of water at room temperature.



(143)

The final component eluted from the column was obtained in extremely small quantity as an oil which proved difficult to crystallise. The infrared spectrum contained an extremely high carbonyl absorption at 1785 cm^{-1} typical of a β,γ-unsaturated lactone[160], a stronger peak at 1715cm^{-1}, a nitrile function was evident at 2,200 cm^{-1} and a broad hydroxyl absorption centred at 3,500cm^{-1} together with a carbon-carbon double bond at 1660cm^{-1}. On this basis the unknown was assigned the β,γ-unsaturated lactone structure (144) which could arise from the expected condensation product (135) as outlined below. The compound (144) was not obtained analytically pure.

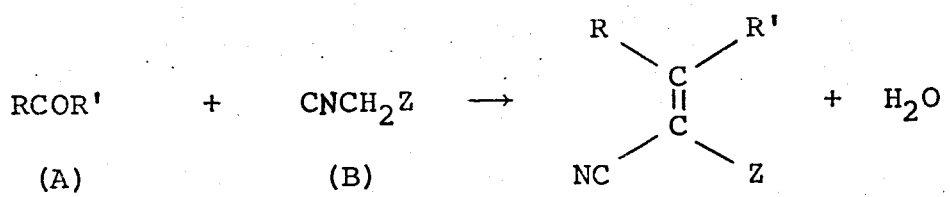
We next examined variation of the reaction conditions to effect condensation. The use of weakly-basic ion-exchange resins as catalysts for the condensation of aldehydes with various active methylene compounds has been studied by Astle and co-workers[161] and by Mastagli et.al.[162] It has also been reported by Hein, Astle and Shelton[163] that



(135)

(144)

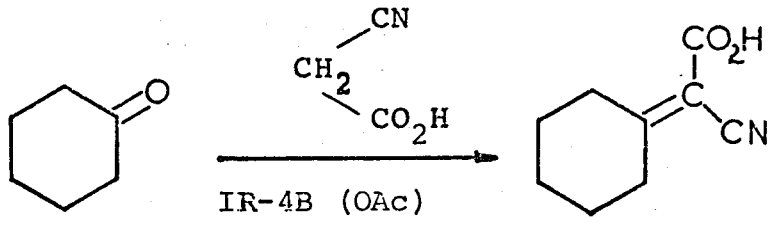
weakly basic ion-exchange resins and their organic salts are effective catalysts for the Knoevenagel condensation of unhindered ketones (A) with cyano active methylene compounds (B).



(A) (B)

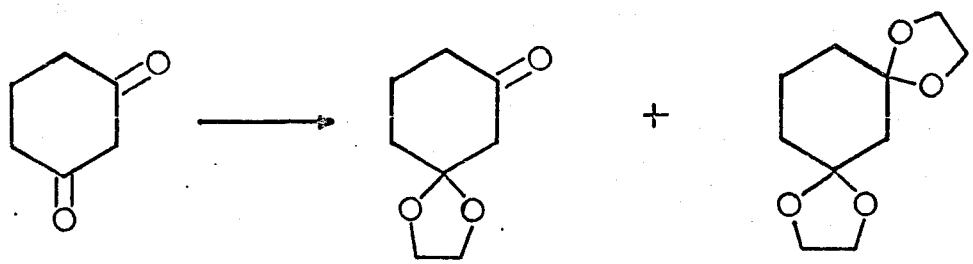
(R and R' = alkyl or aryl; Z = an electron-withdrawing group).

Condensation of cyclohexanone with cyanoacetic acid in the presence of the ion-exchange resin IR-4B acetate in benzene as a model reaction afforded us a good yield (70%) of the α-cyano-α,β-unsaturated acid (145).



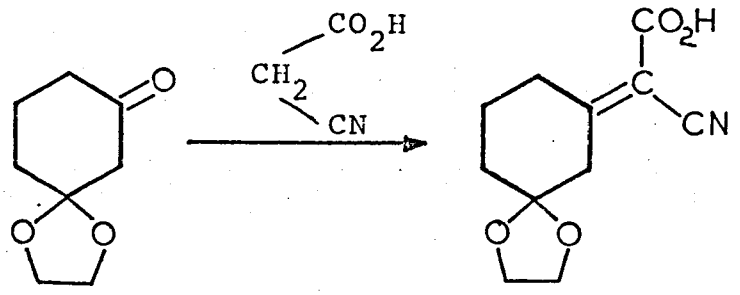
(145)

The melting point and spectral data of the product confirmed its structure as (145). Repetition of the reaction with the epoxide (134) of cyclohexanone in benzene, toluene and xylene as solvents produced only unchanged starting ketone, together with its glycol cleavage product (143). The facile cleavage of the epoxide ring under the conditions of the condensation indicated the need for an alternative starting material to initiate our synthetic scheme. The mono-ethylene ketal (147) of cyclohexan-1,3-dione (146) was considered in this respect. Mono-dioxolanation of cyclohexan-1,3-dione (146) by the literature procedure[164] with ethylene glycol and p-toluenesulphonic acid in benzene afforded (147) together with the diketal (148), easily separable by crystallisation of the latter and distillation of the monoketal.



(146) (147) (148)

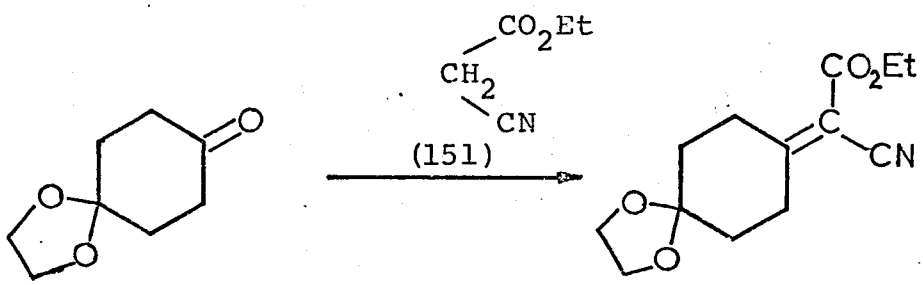
Knoevenagel condensation was investigated under the conditions previously discussed but none of the expected condensation product (149) was detected, only unchanged starting material (147) and cyclohexan-1,3-dione (146).



(147) (149)

This lack of success with the Knoevenagel condensation was disappointing. However, the literature indicates that the Knoevenagel condensation with cyanoacetic acid is by no means a clear cut reaction with all carbonyl compounds, yields of condensation products varying from 6-99%.[153] The reaction seems to be sensitive to a wide variety of conditions.

Since completing this section of our work a Japanese paper[165] has reported a successful synthesis of the α,β-unsaturated ester (152) by Knoevenagel condensation of the ketal (150) with ethyl cyanoacetate in refluxing benzene in the presence of ammonium acetate.



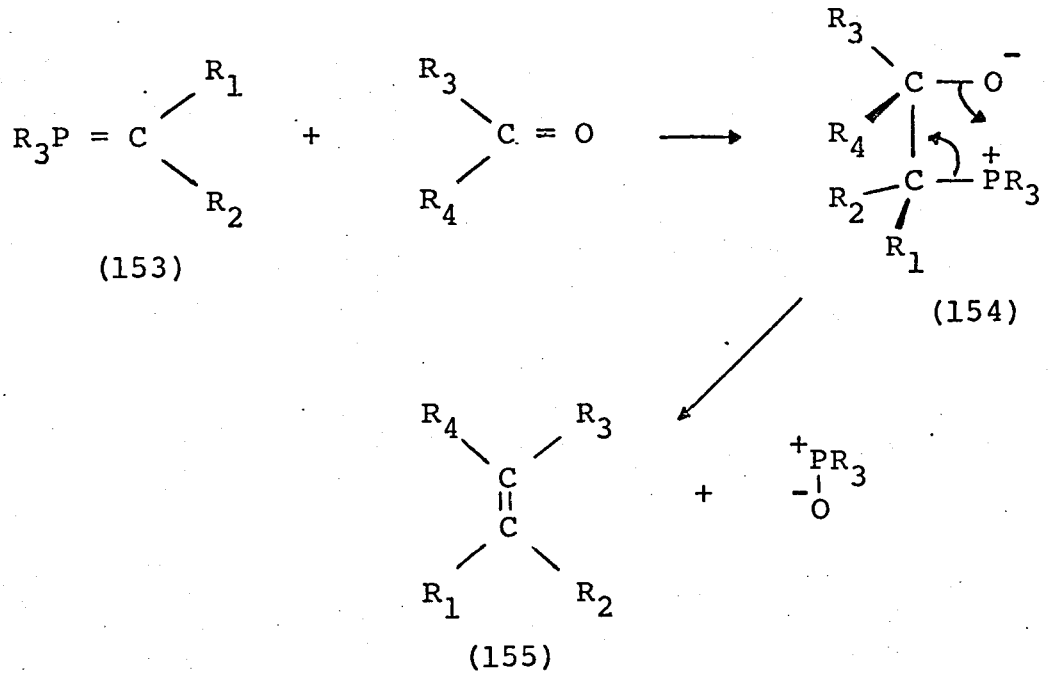
(150) (152)

Use of the ester (151) would probably minimise the oxygen ring opening which we experienced with cyanoacetic acid although the oxygen rings may present some steric interference, absent in (150).

In view of the difficulty experienced with the Knoevenagel condensation we examined alternative routes.

The Wittig olefin synthesis[166] involves the addition of an alkylidenephosphorane (153; R = alkyl, aryl) to a carbonyl compound, followed by elimination of phosphine

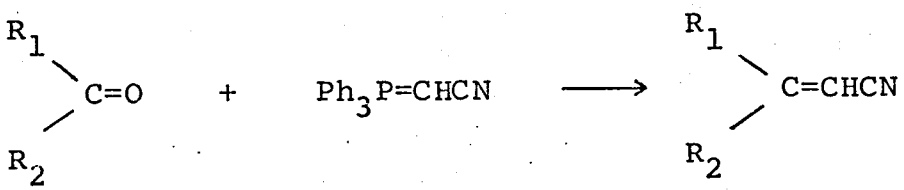
oxide from the intermediate betaine (154) to give the olefin (155).



(153) (154) (155)

The reaction proceeds via a four-membered transition state in the betaine intermediate (154). The synthesis has found a wide applicability in many fields and comprehensive reviews are available in the literature.[167]

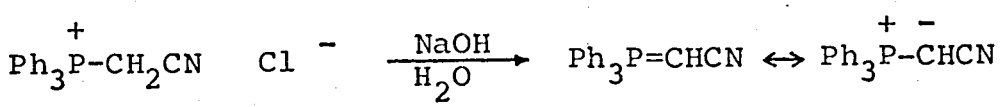
The use of α-cyanomethylenetriphenylphosphorane for the synthesis of α,β-unsaturated nitriles (157) from ketones is well documented.[167,168]



(156) (157)

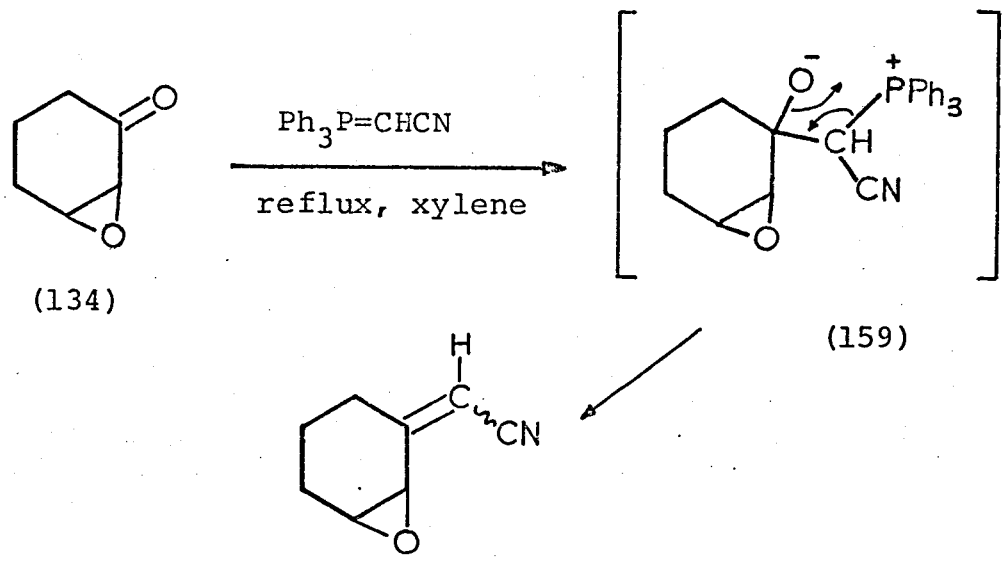
We wished to apply this method of synthesis to the epoxy ketone (134) and the dioxolan (147).

Cyanomethyltriphenylphosphonium chloride (158) was synthesised from triphenylphosphine and chloroacetonitrile by the known procedure.[168] α-Cyanomethylenetriphenylphosphorane (159) was obtained from the phosphonium salt (158) by treatment with ice-cold aqueous sodium hydroxide.



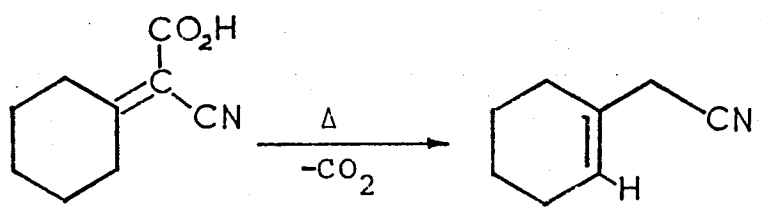
(158) (159)

Reaction of the epoxide (134) of cyclohex-2-enone with the phosphorane (159) in refluxing xylene afforded a modest yield (39%) of the α,β-unsaturated nitrile (136) as a colourless liquid.



(134) (159) (136)

Although the nitrile (136) was not obtained analytically pure, its structure was supported by the infrared and n.m.r. data, suggesting the exocyclic stereochemistry of the carbon-carbon double bond. In the infrared spectrum a sharp peak at 2220cm^{-1} was assigned to the α,β-unsaturated nitrile function and contrasts with 2250cm^{-1} for the non-conjugated nitrile (160) prepared as a model compound by decarboxylation of cyclohexenecyanoacetic acid (145).



(145) (160)

The vinyl proton resonance in the n.m.r. spectrum appeared as a broad singlet at δ5.55 which exhibited fine structure due to allylic coupling with the protons of the

cyclohexane ring (J ∿ 1.5Hz). The vinyl proton of (136) is slightly shielded (δ5.55) by the nitrile group (Fig. 3) as compared to δ5.8 in the nitrile (160). The edge of the

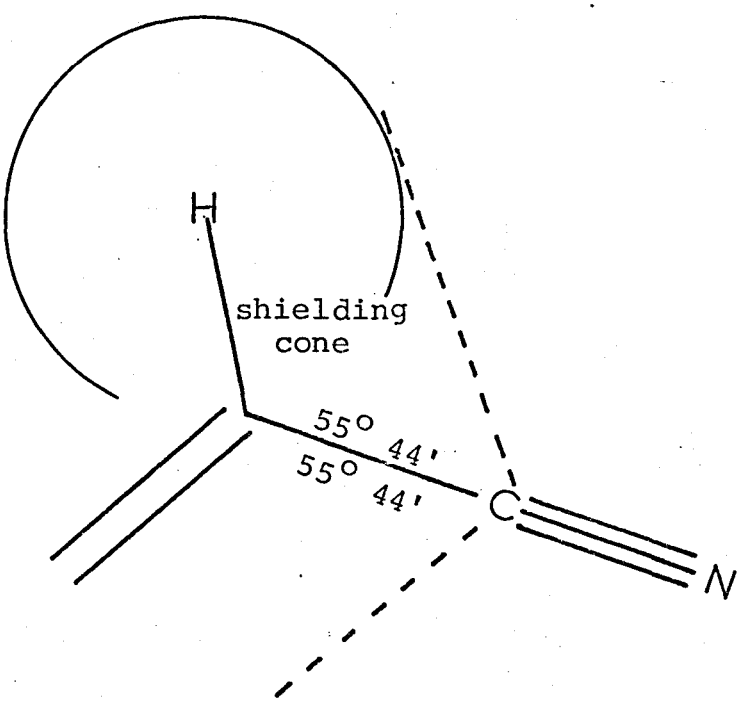
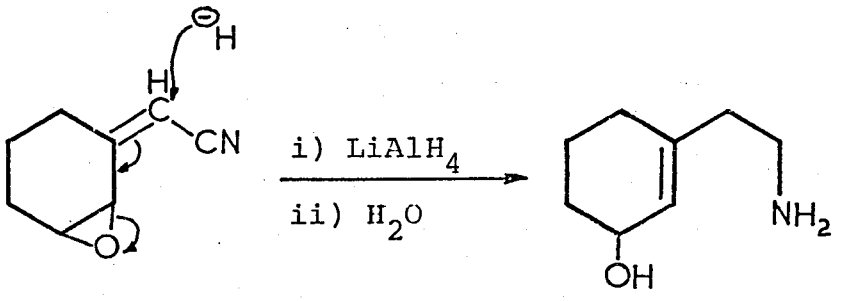


Fig.3

shielding cone is 55° 44' from the sp orbital axis[169] and the vinyl proton falls well within this. Also shielding is inversely proportional to the cube of the distance away.

It is of interest to note that it has been reported that phosphoranes can react with epoxides as well as ketones. Denney and Boskin[170] treated the epoxides of styrene and vinylcyclohexane with the phosphorane ester $Ph_3P{=}CHCO_2Et$ under vigorous conditions (200°C) and obtained cyclopropanes in moderate yields. We found no evidence of such a process with our epoxyketone (134). Lithium aluminium hydride reduction of the epoxynitrile (136) proved disappointing, yielding a mixture of non-basic products only, at 0°C, room temperature and ether reflux temperature (33°C).

We had hoped, in addition to nitrile reduction[171] to the primary amine, that hydride would cause reductive ring-opening of the epoxide by attack analogous to Michael fashion on the double bond as shown.

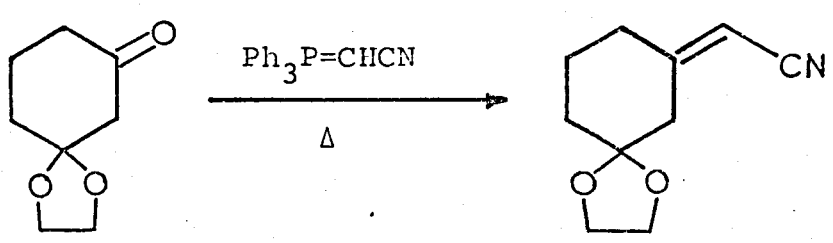


(136) (137)

This type of ring-opening reduction may have occurred, but probably accompanied by direct epoxide reduction and possibly allylic alcohol reduction to the saturated nitrile, since the mixture showed broad hydroxyl absorption (3300 - 3500cm^{-1}) in the infrared. It is not understood why the nitrile failed to reduce.

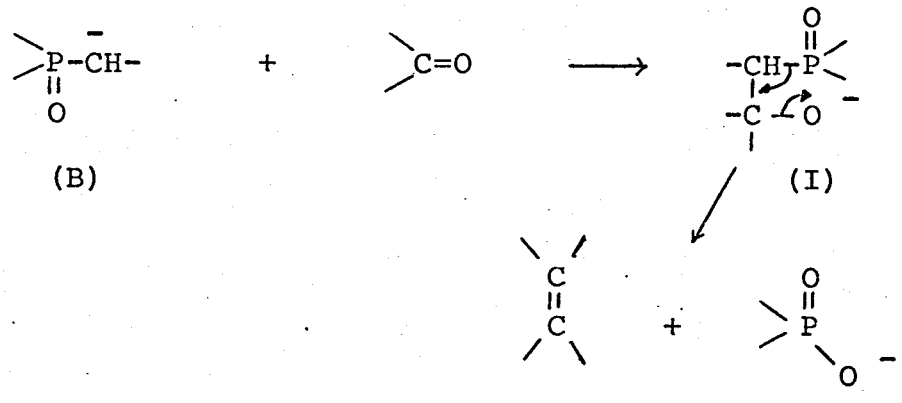
(ii) Syntheses starting from cyclohexan-1,3-dione.

The Wittig reaction of α-cyanomethylenetriphenylphosphorane with the monodioxolan protected cyclohexan-1,3-dione (147) was next examined but did not prove to be a viable method of synthesis of the α,β-unsaturated nitrile (161) even after extensive reflux times in xylene a large proportion of starting ketone remained unchanged.



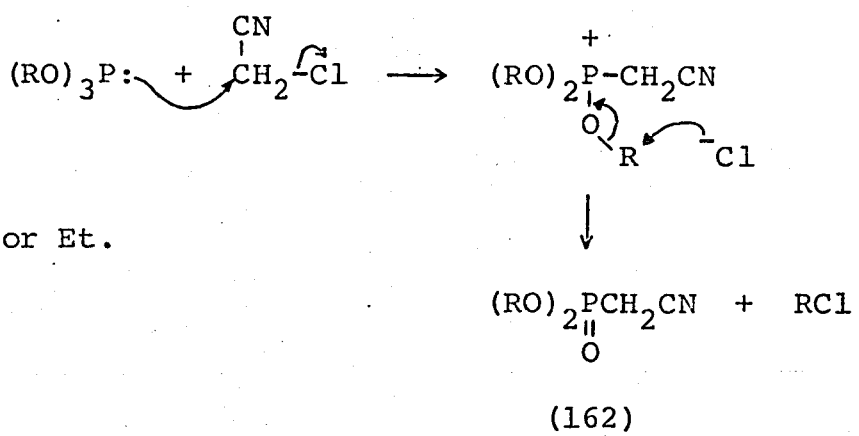
(147) (161)

The Wadsworth-Emmons-Horner modification of the Wittig reaction utilising phosphonate carbanions has found widespread use in olefin synthesis.[172] Horner et.al.[173] have shown that systems of the type $P(O)CH_2-$ give rise under basic conditions to conjugate bases (B) which can add to a carbonyl group to give a betaine like intermediate (I); this intermediate on heating breaks down in a Wittig fashion to form an olefin ie.



(B) (I)

The phosphonate is most readily obtained in the Arbusov reaction[174] between alkyl halides and trialkyl phosphites. We required diethyl (or dimethyl)cyanomethyl-phosphonate (162) which we synthesised from chloroaceto-nitrile and trialkyl phosphite

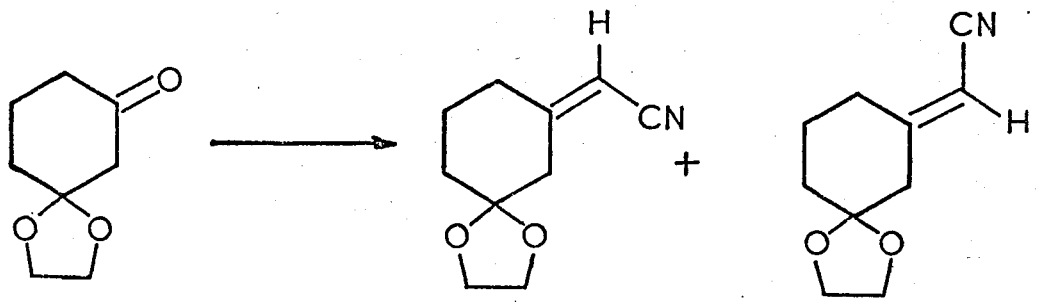


R = Me or Et.

(162)

The alkyl chloride is distilled from the reaction mixture at the reflux temperature of the reactants. The anion was generated from the phosphonate (162) by sodium hydride in 1,2-dimethoxyethane at room temperature. Elevated temperatures are detrimental to the anion as it is susceptible to self-condensation.[172(i)] The ketone (147)

was then added to the anion solution and reaction accomplished at room temperature. The product (161), which gave satisfactory analytical data, appeared to be a mixture of geometric isomers Z and E. The infrared spectrum with a peak at 2220cm^{-1} confirmed the conjugated nitrile[175] (in contrast to cyclohex-1-enylacetonitrile at 2250cm^{-1}), as did the ultraviolet maximum at 222nm.[176]

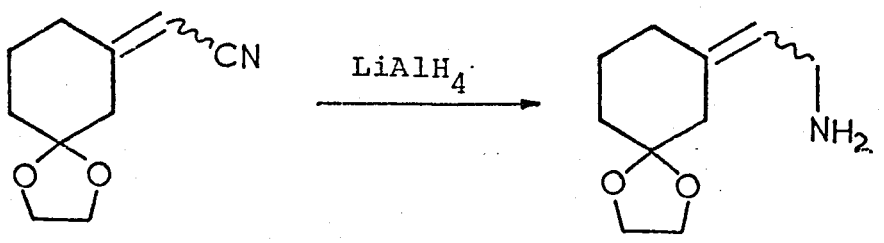


(147) Z E

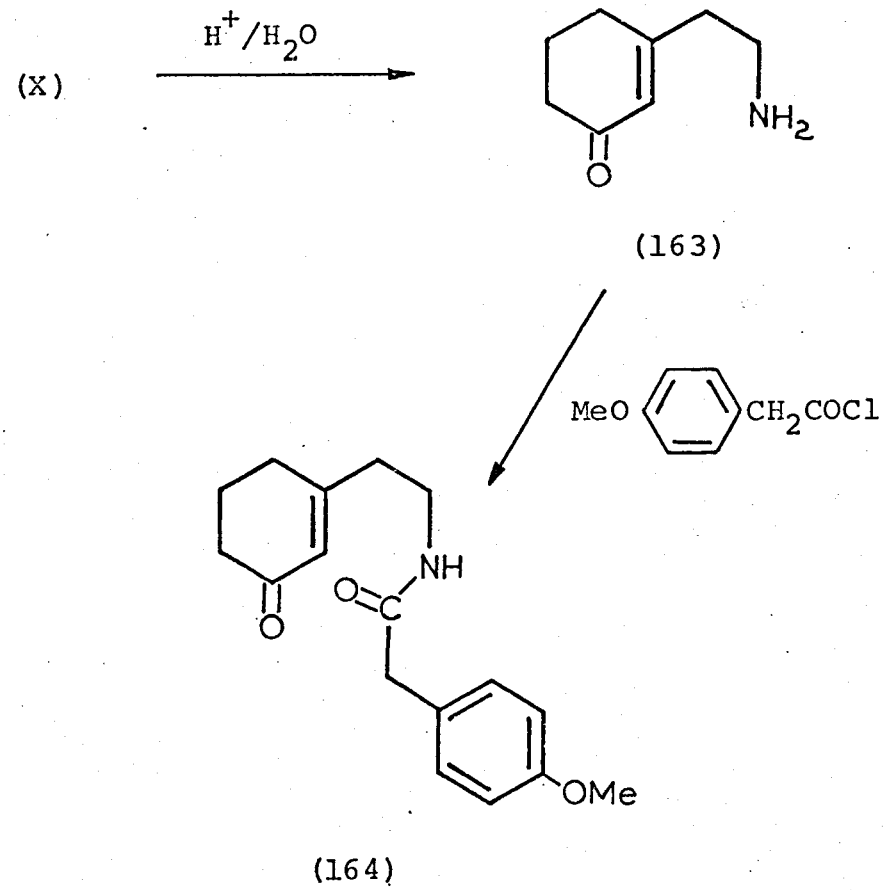
(161)

The n.m.r. spectrum showed two olefinic proton resonances (Z and E isomers) integrating in total for one proton at δ5.1 and δ5.2 ppm. The peak width at half height (5Hz) of each peak was consistent with allylic coupling (J = 1-2Hz) to four protons.

Unfortunately nitrile reduction with lithium aluminium hydride again proved unsatisfactory. The ketals (161) did yield some basic material but the mixture could not satisfactorily be separated. Acid hydrolysis to give the enone (163) was attempted on the mixture, in the hope of characterising the product as amide (164) but intractable mixtures resulted. Spectroscopic evidence suggested both endo and exocyclic double-bond material was present. In view of the difficulties this route was not further pursued.

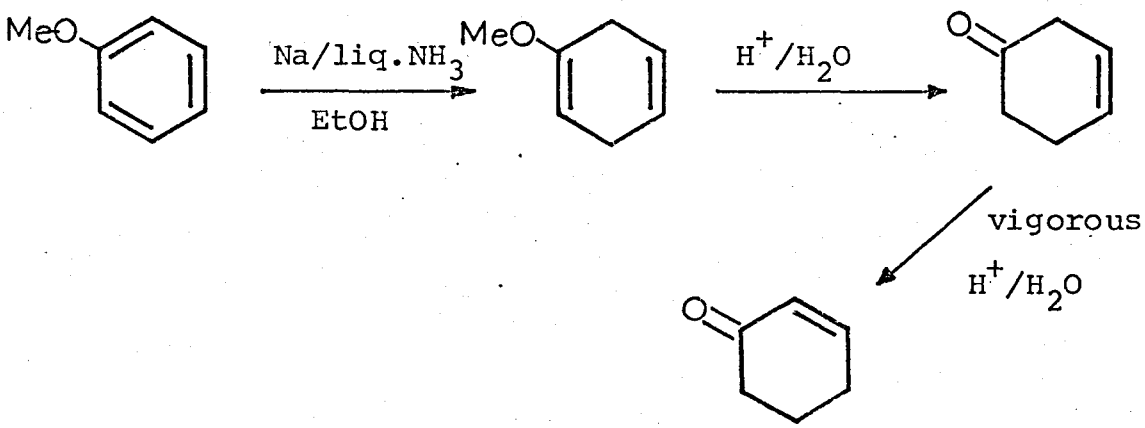


(161) (X)

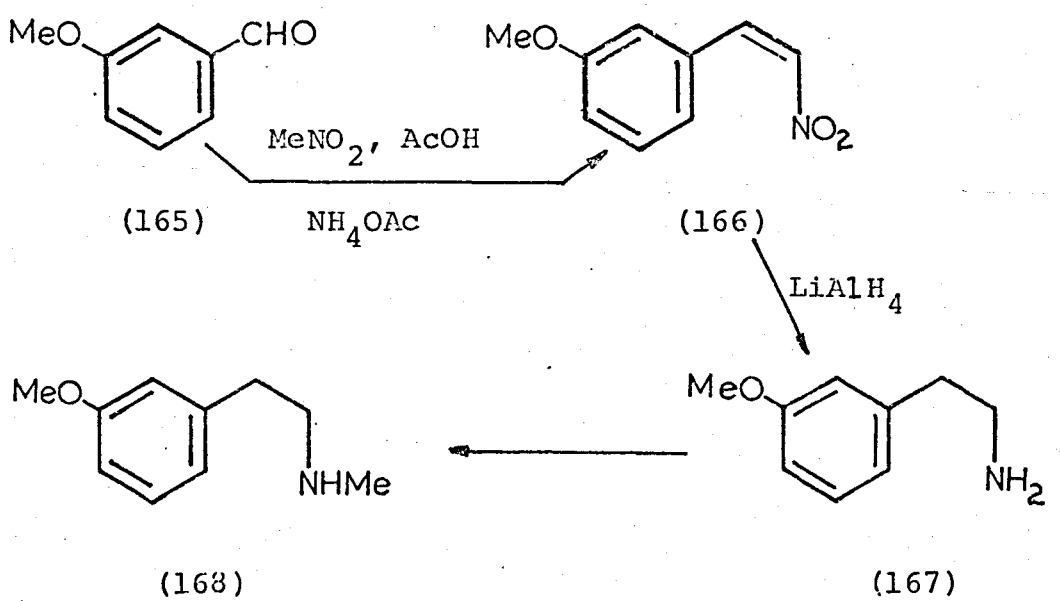

(X)
H^+/H_2O
NH_2
O
(163)
MeO
CH_2COCl
NH
O
C
O
OMe
(164)

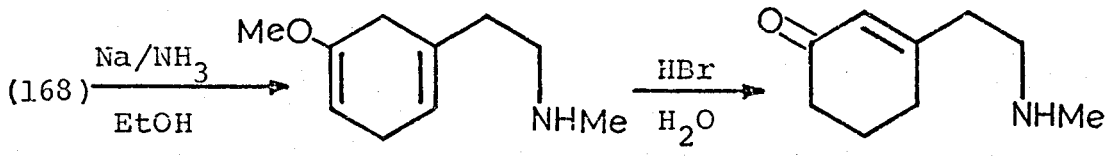
(iii) Syntheses starting from 3-methoxybenzaldehyde.

The metal in liquid ammonia (Birch) reduction of various substituted anisole derivatives has provided good synthetic routes to cyclohexenone derivatives. Birch[177] observed that reduction of anisole with sodium and ethanol in liquid ammonia gave 2,5-dihydroanisole and that mild acid hydrolysis converted the product to cyclohex-3-en-1-one separable as the bisulphite addition compound, whereas vigorous acid hydrolysis converted it to the conjugated cyclohex-2-en-1-one.[177]



Rudolf Grewe and co-workers[179a] following the method of A.J.Birch[178] reported the synthesis of 3-(β-methylamino)-ethylcyclohex-2-enone (169) by the route shown in scheme 17

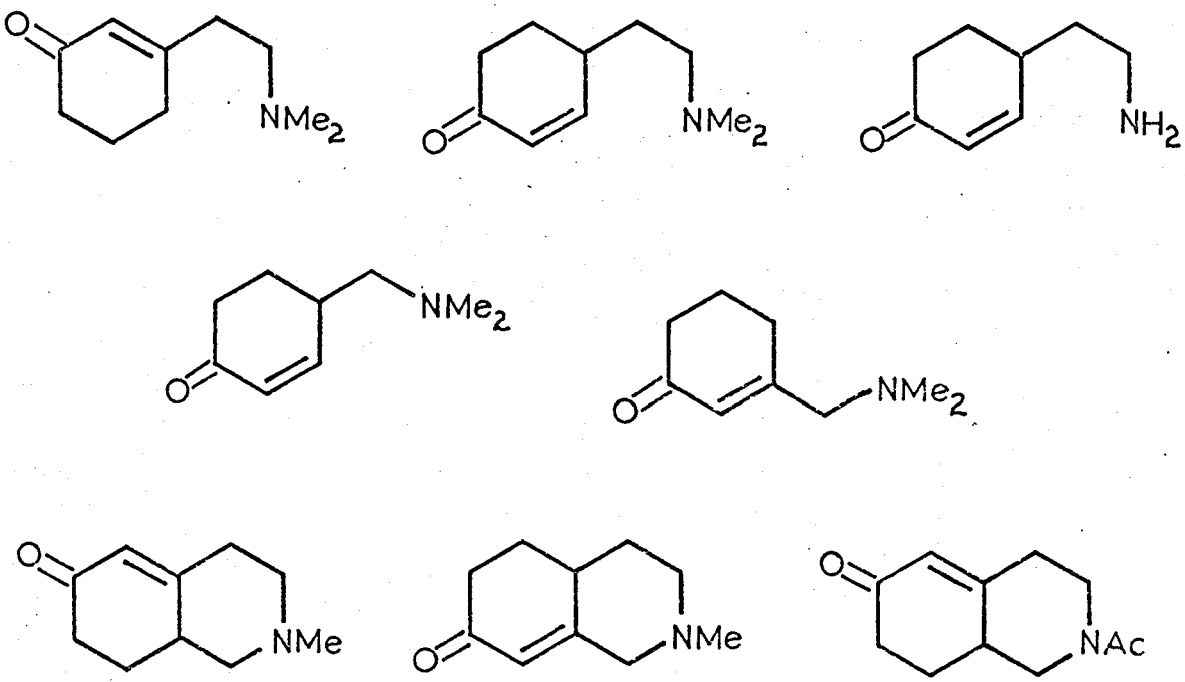




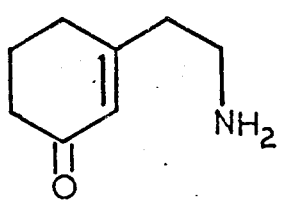
(169)

Scheme 17.

C.B.Clarke and A.R.Pinder[180] reported the synthesis of the substituted cyclohexenone amines depicted below utilising a similar technique.

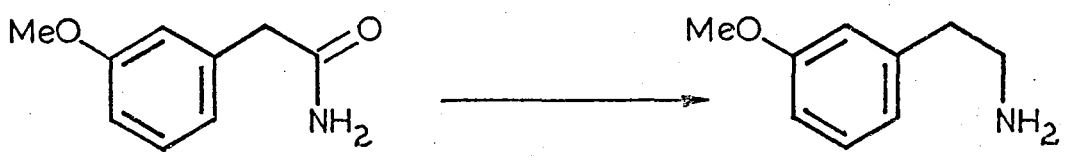


In view of the wide application of the technique we set out to synthesise the amine (163) by this method.



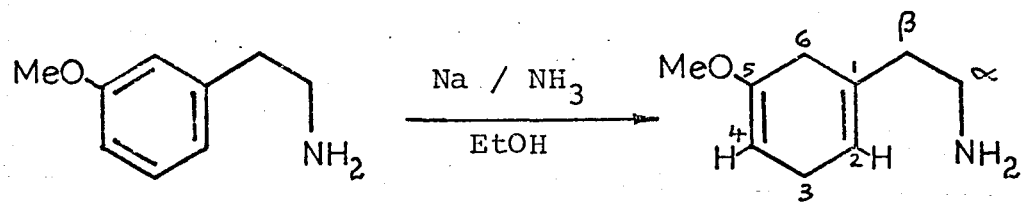
(163)

Condensation of 3-methoxybenzaldehyde (165) with nitromethane in the manner of Grewe et.al.[179a] afforded us the nitrostyrene (166). Lithium aluminium hydride reduction of the nitrostyrene (166) in a Soxhlet apparatus[179b] afforded β-(3-methoxyphenyl)ethylamine (167) in extremely good yield (90.0%). We also obtained the same product (167) by diborane reduction[181] of 3-methoxyphenylacetamide (170). The amide (170) was prepared from the commercially available 3-methoxyphenylacetic acid via the acid chloride and ammonia. The overall yield of (167) from the acid was 93.0%, as compared with 84% from the aldehyde (165).



(170) (167)

Birch reduction of β-(3-methoxyphenyl)ethylamine had not been reported in the literature, unlike the N-methyl derivative (168). We found that the 1,4-cyclohexadienylamine (171) was obtained in good yield (91%) utilising sodium in liquid ammonia and ethanol.



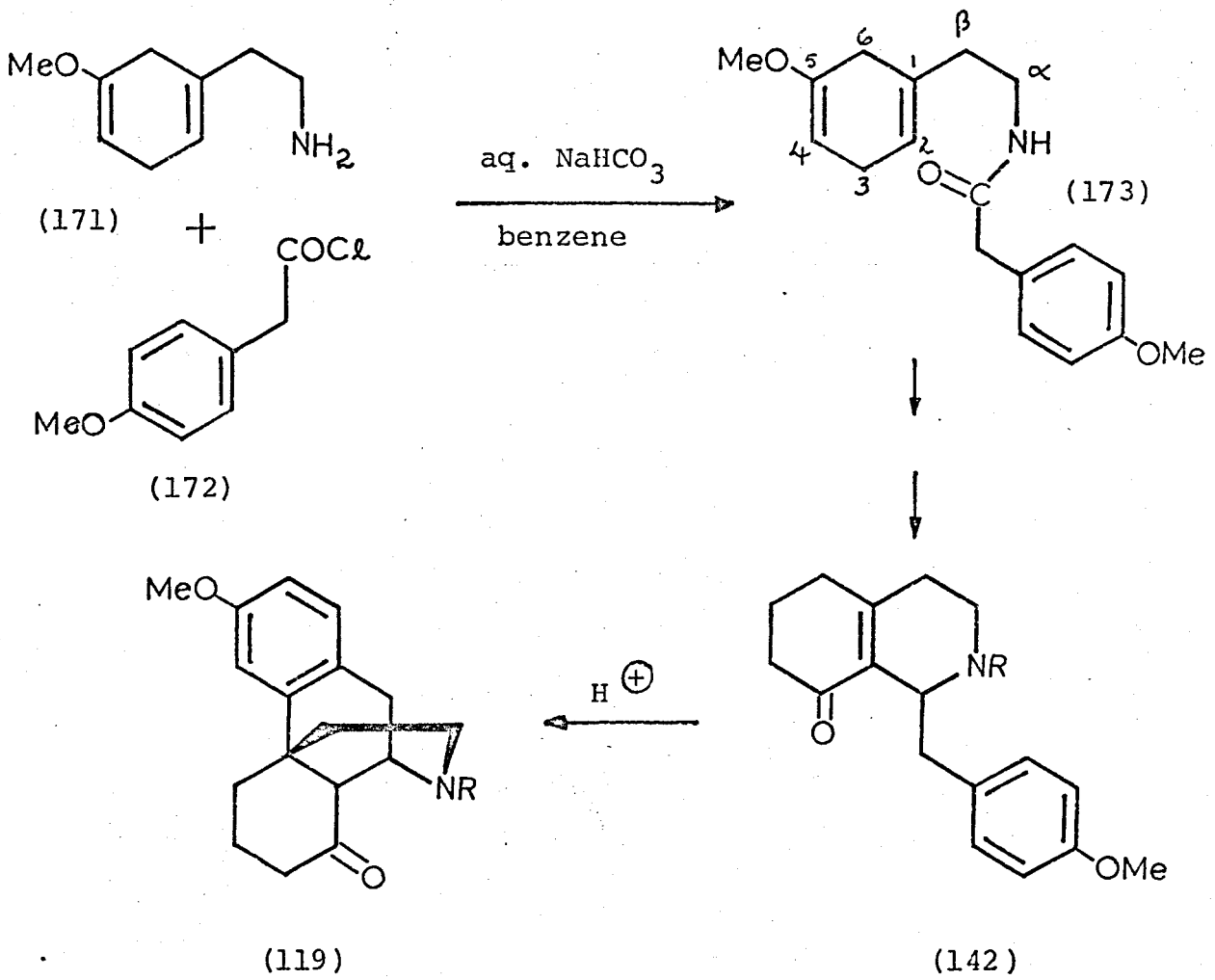
(167 (171)

Birch[177,182] observed that in general αδ-addition of hydrogen takes place preferentially at positions carrying carboxyl groups and avoids positions substituted by methoxy, dimethylamino and alkyl groups in the order given.

The infrared spectrum (liq. film) of the prepared amine (171) showed two characteristic bands at 3370 and 3280cm^{-1} attributed to the NH_2 group together with two peaks at 1696 and 1666cm^{-1} due to the two double bonds of the dihydroanisole system.[185,187,188a] In the nmr spectrum the olefinic protons at C-4 and C-2 appear as two broad singlets at δ4.5($W_{\frac{1}{2}}$=6Hz) and δ5.43($W_{\frac{1}{2}}$=8Hz) respectively. The olefinic protons show no clearly defined splitting pattern and this is found to be the case in related compounds synthesised later. The width of the olefinic signals may be attributed to vicinal coupling with the two C-3 protons (J~3Hz) and allylic coupling with the C-6 and the C-β protons (J~1.5Hz), assuming J values which are typical for cyclohexene systems.[183] Olefinic protons have also been reported to occur as singlets in the nmr spectra of 3-alkylcyclohexa-1,4-dienes[184], 2,5-dihydro-3-methylanisole[185] and 1,2,3,4,5,8-hexahydroisoquinolines.[186] The protons of the carbons at C-3 and C-6 of the dihydroanisole system appear as a broad singlet at δ2.65, the methylene group α to the amino function appears as a multiplet (J,7Hz) at δ2.75, coupled with the β-methylene of the side chain which appears as a triplet (J,7Hz) at δ2.13. The methoxy group appeared as a sharp singlet at δ3.50 and the NH_2 as a broad singlet at δ1.20. Subsequent to out findings the amine (171) has been synthesised by H.C.Beyerman et.al.[188b] by a direct Birch reduction of the nitrostyrene(166) with lithium in liquid ammonia, t-butanol and tetrahydrofuran. Their spectroscopic data is in good agreement with our findings.

Due to the unstable nature of the prepared amine (171) we condensed it directly with p-methoxyphenylacetyl chloride (172) in benzene in the presence of aqueous sodium bicarbonate solution and obtained the amide (173) in good yield (73%). The choice of (172) as acid chloride was made because if was envisaged the amide (173) could ultimately be progressed to the 8-ketoisoquinoline (142) which could then permit examination of cyclisation to the morphinan (119).

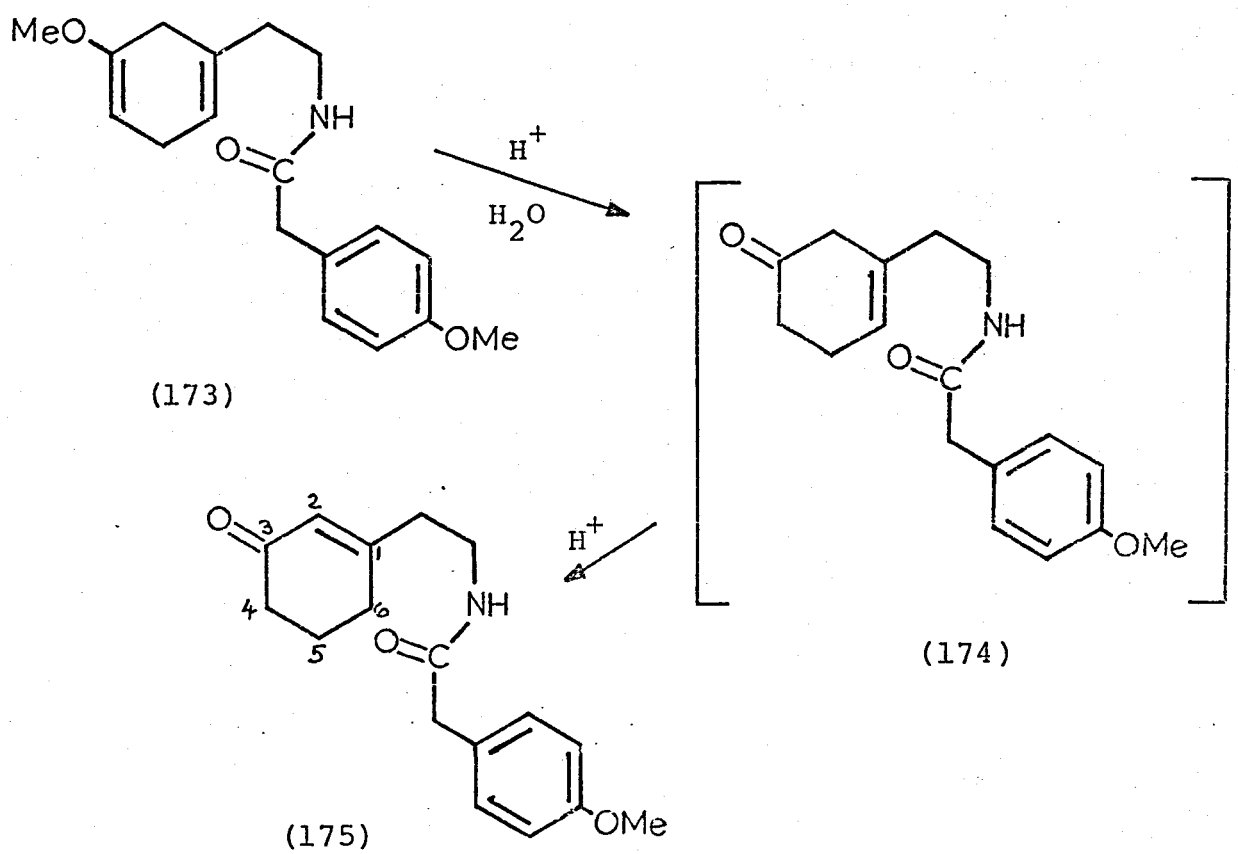
The infrared spectrum of the prepared amide (m.pt. 60-61^{o}C) showed characteristic amide NH and C=O absorptions at 3280 and 1640cm^{-1} respectively[189b] together with the two



peaks associated with the dihydroanisole system at 1698 and 1666cm^{-1}.[188a] The n.m.r. spectrum of (173) showed two sharp singlets for the methoxy group of the dihydroanisole system at δ3.52 and the methoxy group of the aromatic ring at δ3.80. The benzylic methylene appeared as a singlet at δ3.46; the aromatic protons appeared as an A_2B_2 quartet centred at δ6.83 and δ7.13 (J_o=9Hz). A broad singlet at δ4.56 ($W_{\frac{1}{2}}$=6Hz) was assigned to the olefinic proton at C-4 and the broad singlet at δ5.27 ($W_{\frac{1}{2}}$=8Hz) to the olefinic proton at C-2 which unlike the proton at C-4 is allylically coupled to four protons. A triplet at δ2.1 (J, 7Hz) was assigned to the methylene β to the amide nitrogen, the protons on the carbon atom α to the amide NH appeared as a multiplet centred at δ3.30 due to coupling with the β-methylene protons and the amide NH. Since the secondary amide NH exchange rate is slow coupling is observed with the protons on the adjacent carbon atom.[189a]

The remaining protons of the dihydroanisole system ie. at C-3 and C-6 occurred as a broad signal at δ2.60. The amide NH appeared as a broad peak centred at δ5.72 (exchangeable with D_2O/DCl).

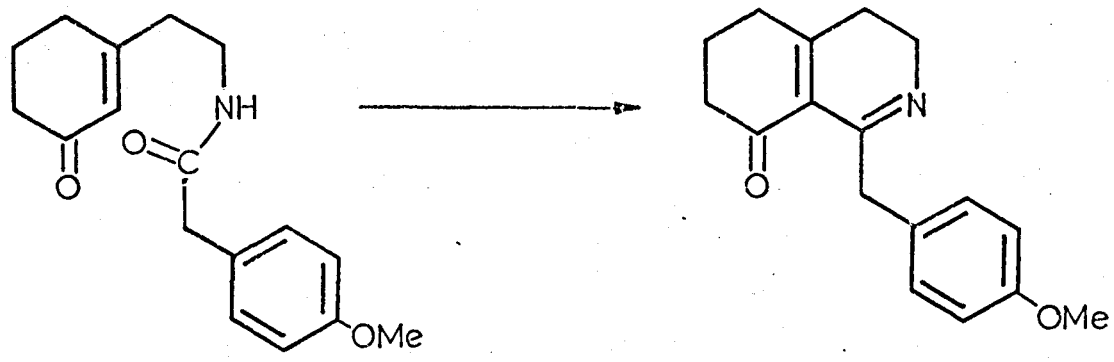
Upon allowing the amide (173) to stand in tetrahydrofuran and 10% aqueous hydrochloric acid for 24hrs at room temperature quantitative conversion to the required amide (175) was achieved. The amide (175) was obtained as translucent leaflets m.pt. 62-63°C after recrystallisation from diethyl ether. The conversion of the methoxy-diene



(173) into the conjugated enone (175) is presumed to proceed via the intermediate β,γ-unsaturated compound (174) which under the acidic conditions is converted into the more stable β,γ-unsaturated compound (175). In the n.m.r. spectrum the olefinic proton appeared as a singlet at δ5.76 ($W_{\frac{1}{2}}$=4Hz) consistent with allylic coupling (ca 1-2Hz) with four protons and no vicinal coupling. Only one methoxyl absorption is

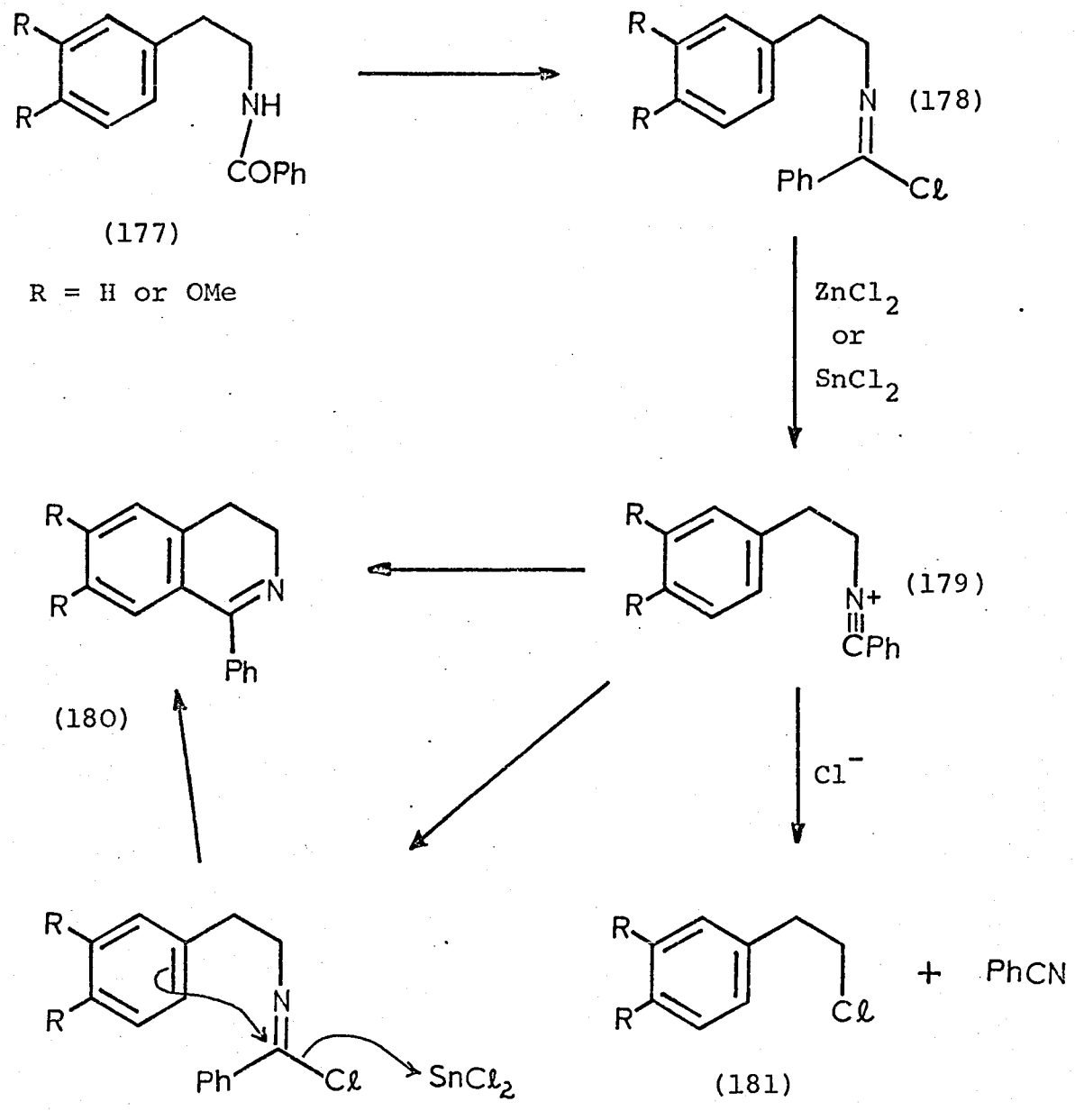
present at δ3.8. The amide NH appears as a broadened peak just discernable as a triplet at δ6.16. The infrared spectrum shows characteristic peaks at 3250 and 1640cm^{-1} due to amide NH and C=O absorptions;[189a] the conjugated enone carbonyl appeared as a shoulder at 1660cm^{-1}. The ultraviolet spectrum showed absorptions at 230(ε, 17930); 277(ε, 1950) and 284nm(ε,1600). The value of λ_{max} for the enone chromophore in (175) calculated by the Woodward-Fieser rules[190] is 239nm. e.g. mesityl oxide $Me_2C{=}CHCO.Me$ shows λ_{max} 237(ε, 12600).[191] In contrast non-conjugated cyclohex-3-enone shows λ_{max} 187(ε, 7000), 217(2500), 277 (107) being due to C=C π → π*, non-classical E.T. (electron transition) band, and and C=O n → π* respectively.[192] The second band sometimes appears only as a shoulder in such compounds. The weak n → π* of the C=O group in conjugated enones is seldom recorded but occurs 300-350nm(ε=100).[193] However,the 230nm band in (175) is likely to contain in its envelope both the enone absorption and that of the aromatic ring. Anisole C_6H_5OMe shows λ_{max} 217(ε, 6400), 269(ε, 1480):[194] a para $-CH_2-$ group would raise these values.

Bischler-Napieralski cyclodehydration[195] of the amide (175) was investigated utilising all the commonly employed reagents for the cyclodehydration ie. phosphoryl chloride[196] in refluxing benzene, toluene and xylene, polyphosphoric acid[197] at 100°C, phosphorus pentoxide[196] in xylene at reflux and polyphosphate ester[198] in chloroform. In all these cases the only discernable product was shown by t.l.c. and infrared analysis of the crude products obtained to be the amide (175). No basic material could be obtained; in the case of phosphorus pentoxide in xylene some polymeric tar was obtained suggesting decomposition was occurring. None of the required 3,4-dihydroisoquinoline (176) could be isolated by this means.



(175) (176)

Since its discovery in 1893[195], the cyclodehydration of β-arylethylamides under acidic conditions to form 3,4-dihydroisoquinolines has been very extensively studied and reviewed.[196,197,198] A large variety of experimental conditions and condensing agents have been used over the years. The mechanism of the Bischler-Napieralski reaction involves an electrophilic attack by the side chain on to the aromatic ring (or olefinic double bond) to which ring closure is to occur.[199] A recent development in an understanding of the mechanism of the Bischler-Napieralski reaction has been made by Fodor et. al.[200] and Gal et.al.[201] Fodor and co-workers[200] showed that the intermediate preceding the cyclisation is a nitrilium ion, species (179) in scheme 18 arising from the amide (177) with phosphorus pentachloride to give (178) which loses hydrogen chloride, especially in the presence of a Lewis acid. Furthermore, they proposed that the von Braun degradation of amides[202] also proceeds via a nitrilium ion (eq 1). Several groups have observed the formation of a nitrile (a von Braun product) in Bischler-Napeiralski reactions.[203] Gal and co-workers[201] reported the first instance of the characterisation of an alkyl halide among the products of a Bischler-Napieralski reaction. The intermediate nitrilium ion can cyclise, possibly in a synchronous process, to form the dihydroisoquinoline (180) or undergo the von Braun reaction (eq 1) to yield the halide (181) and the nitrile. The reason von Braun products are

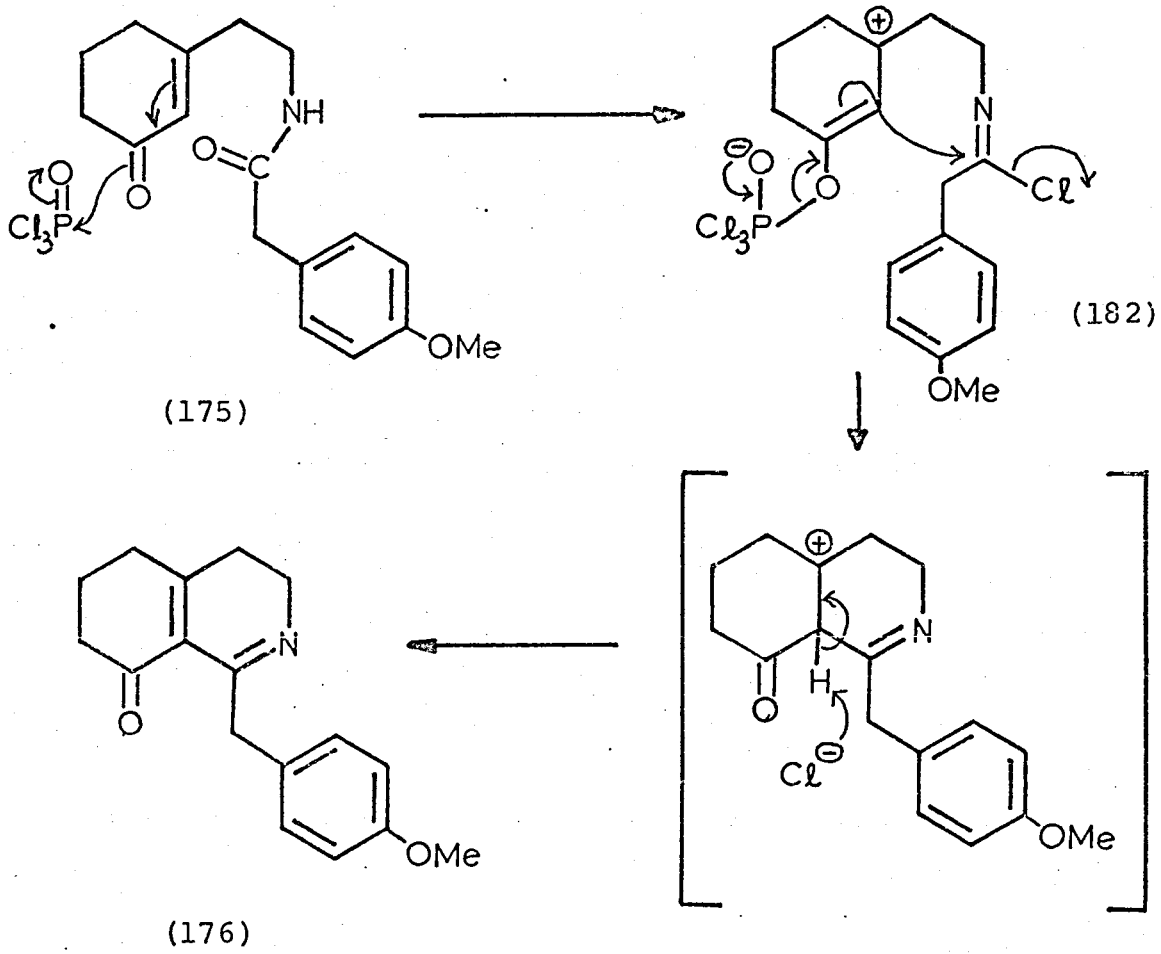


$$R - \overset{O}{\overset{\|}{C}} - NHR' \xrightarrow{PX_5} RC \equiv \overset{+}{N}R' \xrightarrow{X^-} RCN + R'X \quad (1)$$

Scheme 18

formed may be because the temperature of the reaction is too high and because of the relatively weak nucleophilicity of the aromatic ortho position. A realisation of this mechanism has enabled higher yields to be achieved where previously poor yields had been reported,[198] by careful modification of the reaction conditions employed and addition of Lewis acids as catalysts to generate the required intermediate (179) 'in situ'.

In our case the amide (175) gave no detectable von Braun degradation products and the failure of the Bischler-Napieralski cyclodehydration was attributed to the electron-

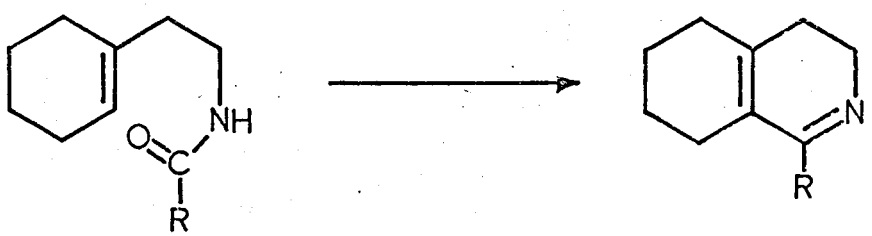


withdrawing influence of the carbonyl group of the cyclohex-2-enone system. It had been anticipated that this would not

prevent the reaction from occurring since under the conditions of the ring-closure, an intermediate such as (182) could be involved.

Perhaps the use of phosphorus pentachloride in the presence of a Lewis acid catalyst such as aluminium chloride[198,204,205] would lead to a successful cyclisation; a reagent combination which we did not investigate. It is apparent that the conditions of the reaction (ie. temperature and duration of heating) can have a decisive influence on the result.

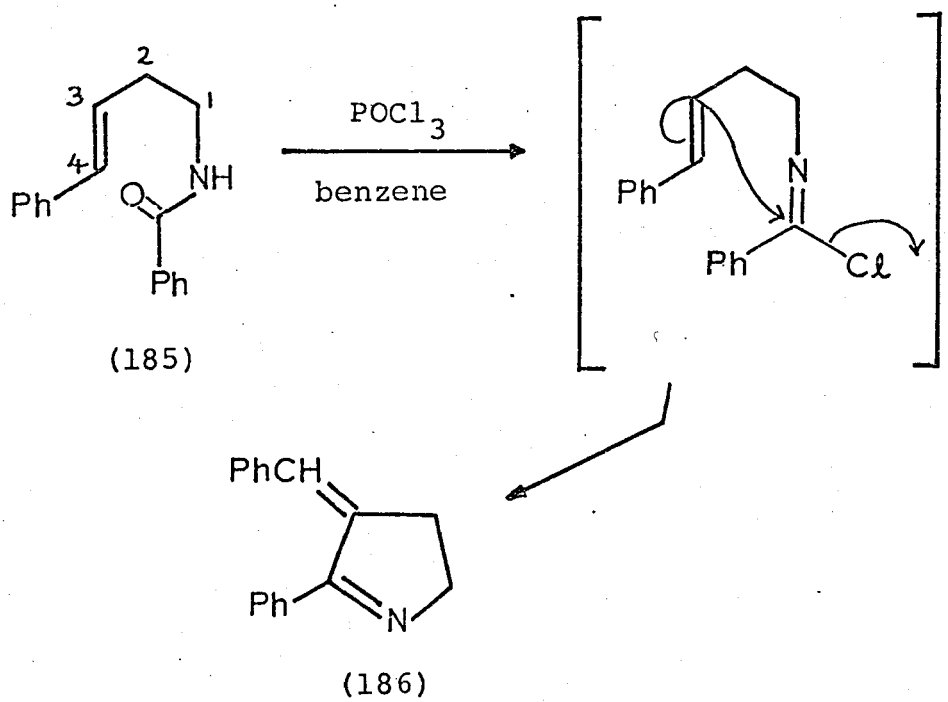
Hexahydroisoquinolines of structure (184) have been



(183) (184)

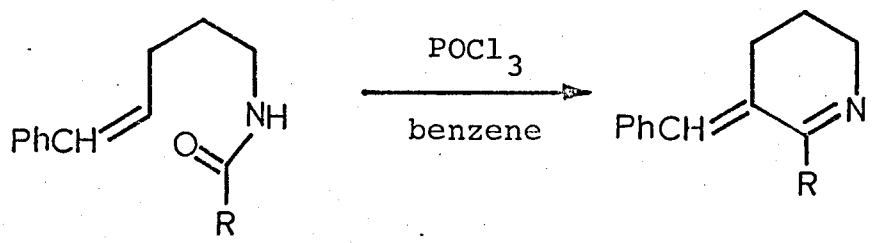
successfully synthesised from cyclohexenylethylamides (183) by the Bischler-Napieralski cyclodehydration conditions.

Schnider and Hellerbach first reported this



(185) (186)

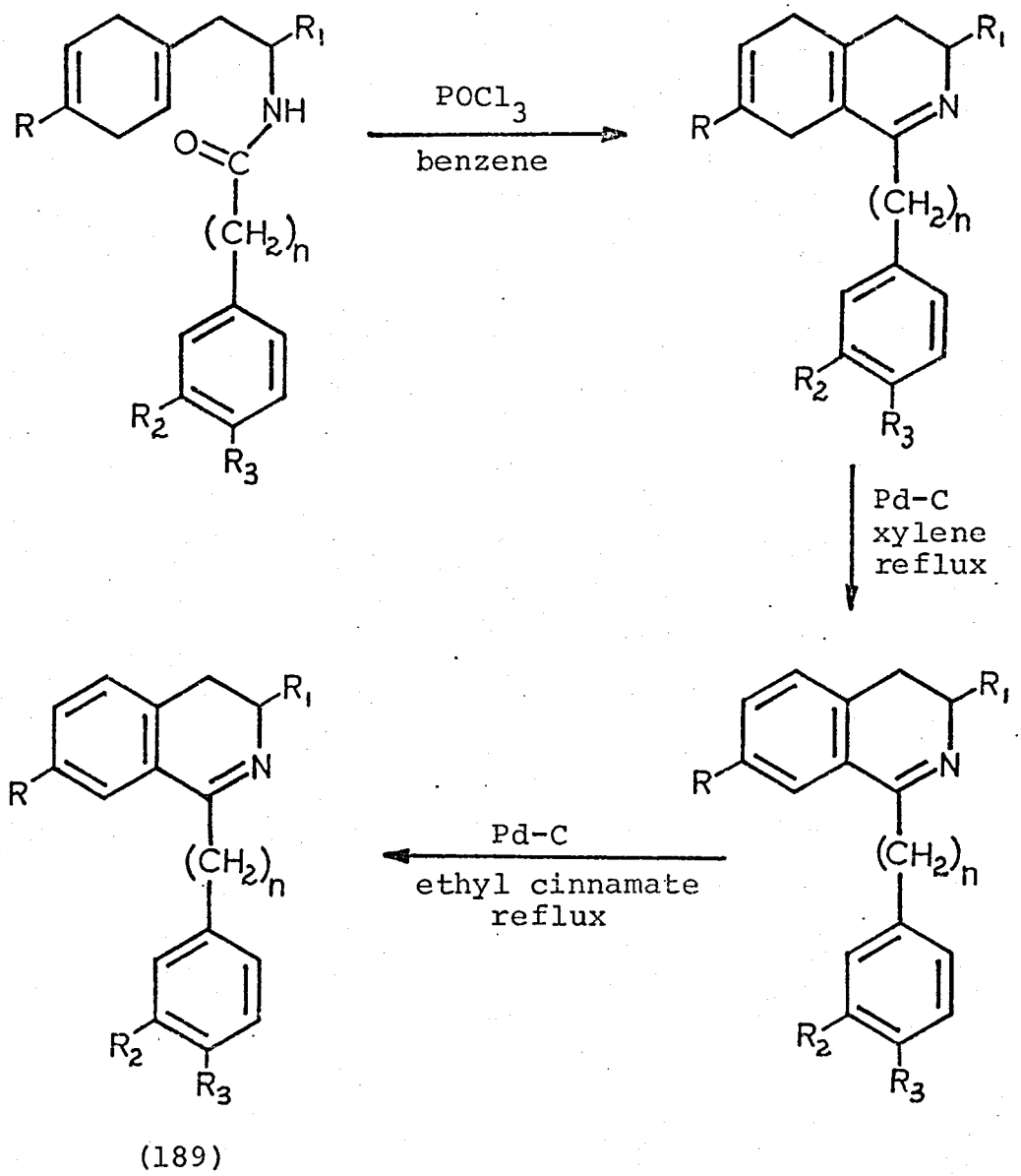
modification in 1950.[117] Sugasawa and Ushioda[206] utilised the Bischler-Napieralski cyclodehydration to synthesise pyrroline derivatives such as (186) from amides of type (185). Presumably involvement of a (favourable) benzylic carbonium ion intermediate results in the formation of the five-membered ring rather than the six-membered in this case. Cyclisation occurs at the 3-position of (185). Fujisawa and Sugasawa[207] cyclised acyl derivatives of 5-phenylpent-4-enylamine (187) to give 2-substituted 3-benzal-3,4,5,6-tetrahydropyridines (188) in good yield.



(187) (188)

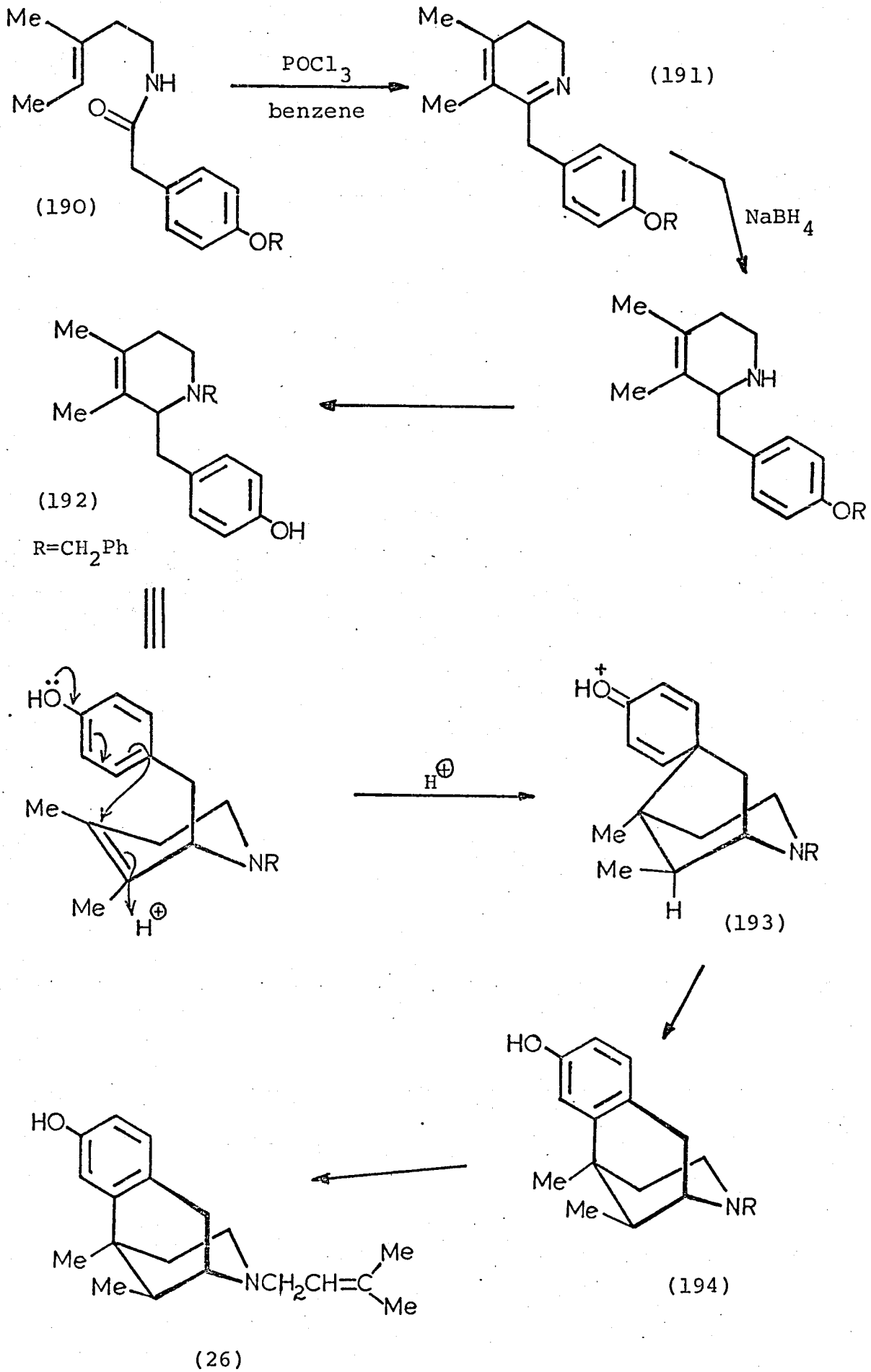
Tachikawa[208] utilised the Bischler-Napieralski cyclisation conditions to synthesise 7-substituted isoquinolines (189) as outlined below.

In their synthesis of pentazocine (26), Kametani and co-workers[209a] utilised the cyclodehydration of amides of type (190) to give 5,6-dihydropyridines (191) with phosphoryl chloride in refluxing benzene as outlined in scheme 19 . The cyclisation of the 1-benzyltetrahydropyridine (192) to the benzomorphan (194) is analogous to the morphinan cyclisation and also demonstrates that an oxygenated function ortho to the position of ring-closure is not necessary. Presumably either the benzylic $-CH_2-$ provides sufficient activation or possibly the para phenolic hydroxy directs the cyclisation via rearrangement of a spirodienone intermediate (193). The stereochemistry of the



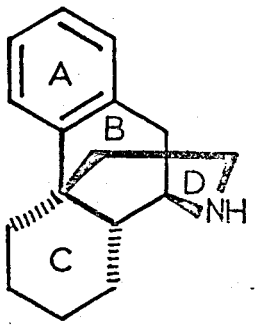
(189)

benzomorphans e.g. (194) is analogous to the cis B and C ring fusion of the morphinan(65). This result is due to trans addition to the double bond of the tetrahydropyridine (192). This mode of reaction is quite general. When a variety of related tetrahydropyridines, (192a), were cyclised under acidic conditions[209b] the major product was always that in which the substituents at the new ring junction are cis with respect to the B ring. May and Eddy[45] have called this isomer α. Small quantities of trans (with respect to ring B) or β isomer can also be isolated in certain

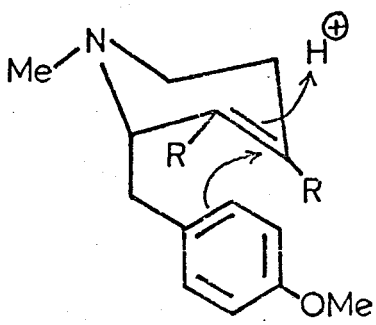

Me
Me
NH
O
OR
(190)
POCl3
benzene
Me
Me
N
OR
(191)
NaBH4
Me
Me
NH
OR
Me
Me
NR
OH
(192)
R=CH2Ph
HO
Me
NR
Me
H⊕
H⊕
HO
Me
Me
NR
H
(193)
HO
Me
Me
NR
(194)
HO
Me
Me
NCH2CH=C
Me
Me
(26)

Scheme 19

instances. Grewe[113] has previously shown the B and C rings of morphinans like (65) to be cis fused, and the C-6 and C-11 methyls in analogously prepared benzomorphans were also considered to be cis. If cyclisation can be viewed as a trans addition to a double bond, then this is not unexpected since protonation should occur from the less hindered β side as depicted in Fig 4.[47]

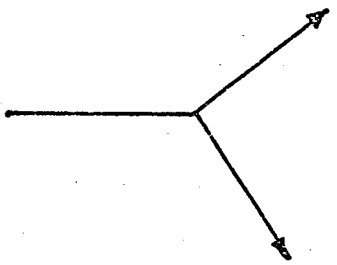


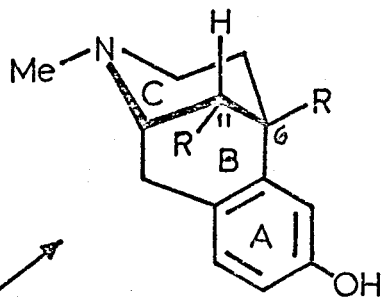
(65)



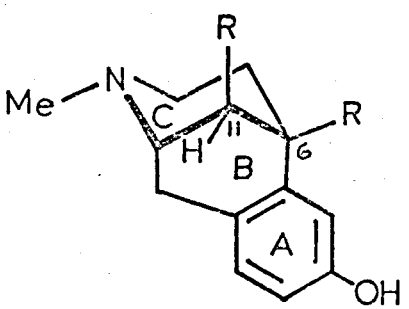
(192a)

(±) only one enantiomorph shown.





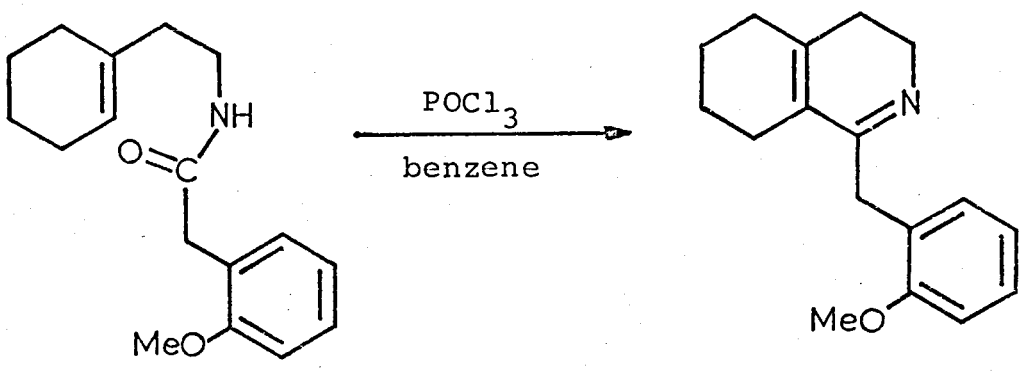
(±) cis,α major product, only one enantiomorph shown.



(+) trans, minor product, only one enantiomorph shown.

Fig.4.

R.Wittekind and co-workers[210] synthesised the hexahydroisoquinoline (196) by heating the amide (195) with phosphoryl chloride in refluxing benzene.

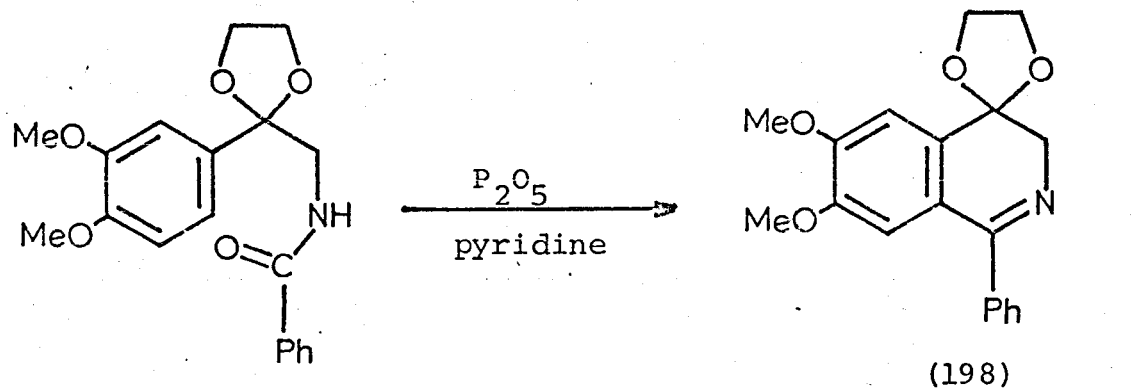


(195) (196)

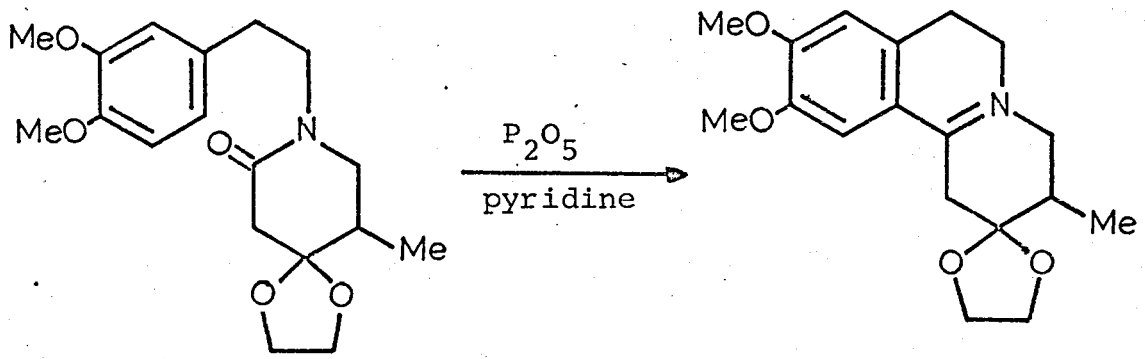
Although a large number of cyclisations onto an unactivated double bond have been reported, the cyclisation of arylethylamides are generally found to be more facile. We decided to investigate protection of our enone carbonyl function in (175) in order to examine cyclodehydration on to the isolated C=C bond.

(1) Protection of the potential 8-substituent by ketalisation.

The ketalisation of α,β unsaturated ketone systems has been employed extensively as a method of protection particularly in the steroid field. It has been reported that Bischler-Napieralski cyclodehydrations can be carried out on phenylethylamides containing acid sensitive groups. Sugasawa and Itoh[211] successfully synthesised the isoquinolines (198) and (200) from the phenylethylamides (197) and (199) respectively utilising phosphorus pentoxide-pyridine (as a new combination for cyclodehydration) the ketal functions being preserved intact. Earlier[212] they had found that upon subjecting the ethylene-ketal (201) to cyclodehydration with phosphoryl chloride in boiling benzene an isoxazoline derivative (202) was obtained rather than the expected 3,4-dihydro compound (203). The former was probably produced via the hydrolysis product (204) of (203) by the agency of



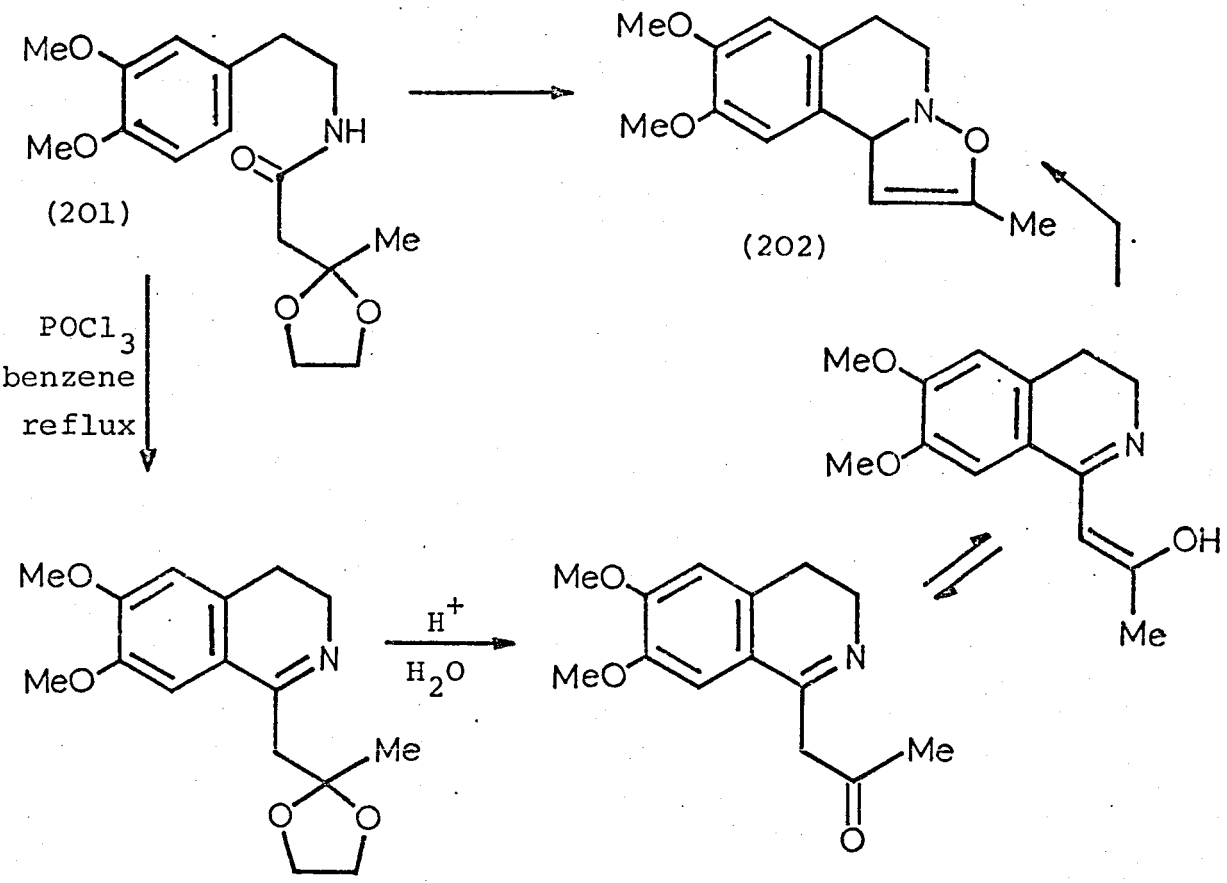
(197) (198)



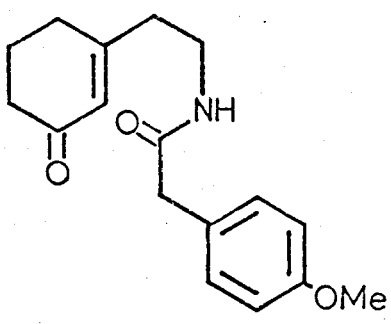
(199) (200)

the water formed during the acidic cyclisation reaction. It was anticipated that utilisation of phosphorus pentoxide-pyridine would effect cyclisation of the ethylene ketal derivative (205) of the amide (175) to give the hexahydro compound (206) which could be progressed to the 8-keto morphinan as discussed earlier. The amide (175) was refluxed for 24h with ethylene glycol in benzene in the presence of p-toluenesulphonic acid catalyst with simultaneous separation of the water formed. The ketal (205) was also prepared by exchange dioxolanation with 2-methyl-2-ethyl-1,3-dioxolane.[213] Each method afforded a

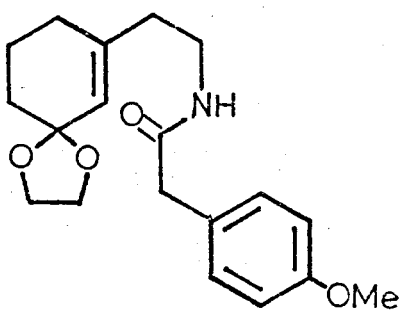
clear viscous syrup (b.pt.216-218°C/0.1mm) which did not crystallise upon refrigeration or when treated with various



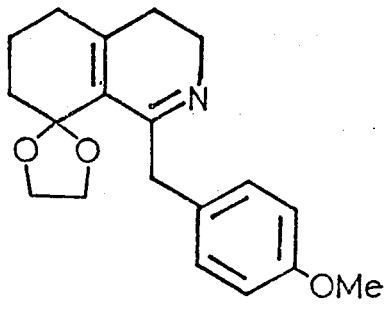
solvents. It is known in the steroid field that ketalisation of α,β unsaturated enones can be accompanied by a shift of the



(175)

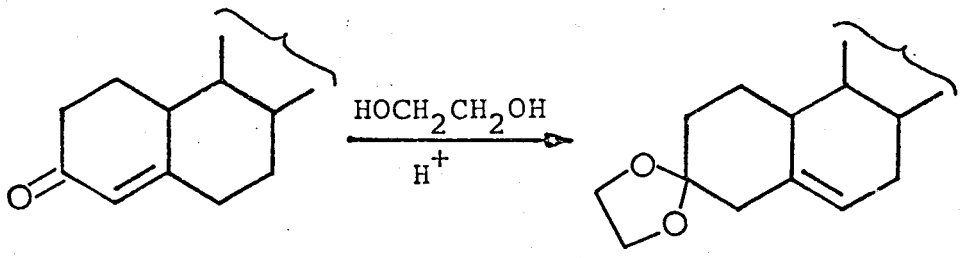


(205)

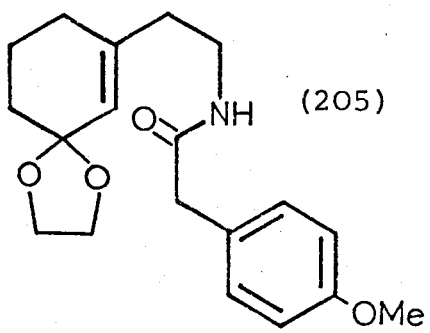


(206)

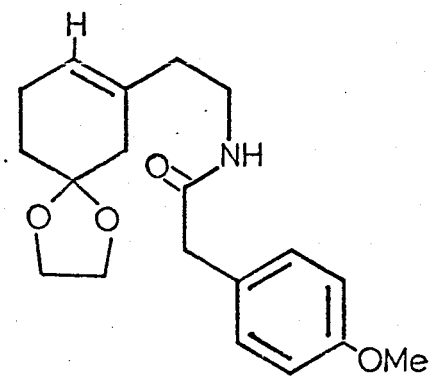
double bond from the α,β to the β,α position,[214] viz :



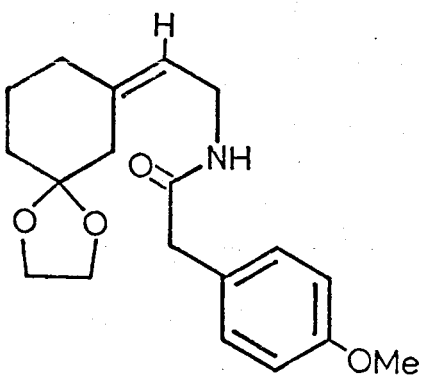
Thus, we considered two other possible isomeric products (207) and (208). A double bond exocyclic to a six-membered ring is slightly less stable than endocyclic,[215] making (208) less likely.



(205)



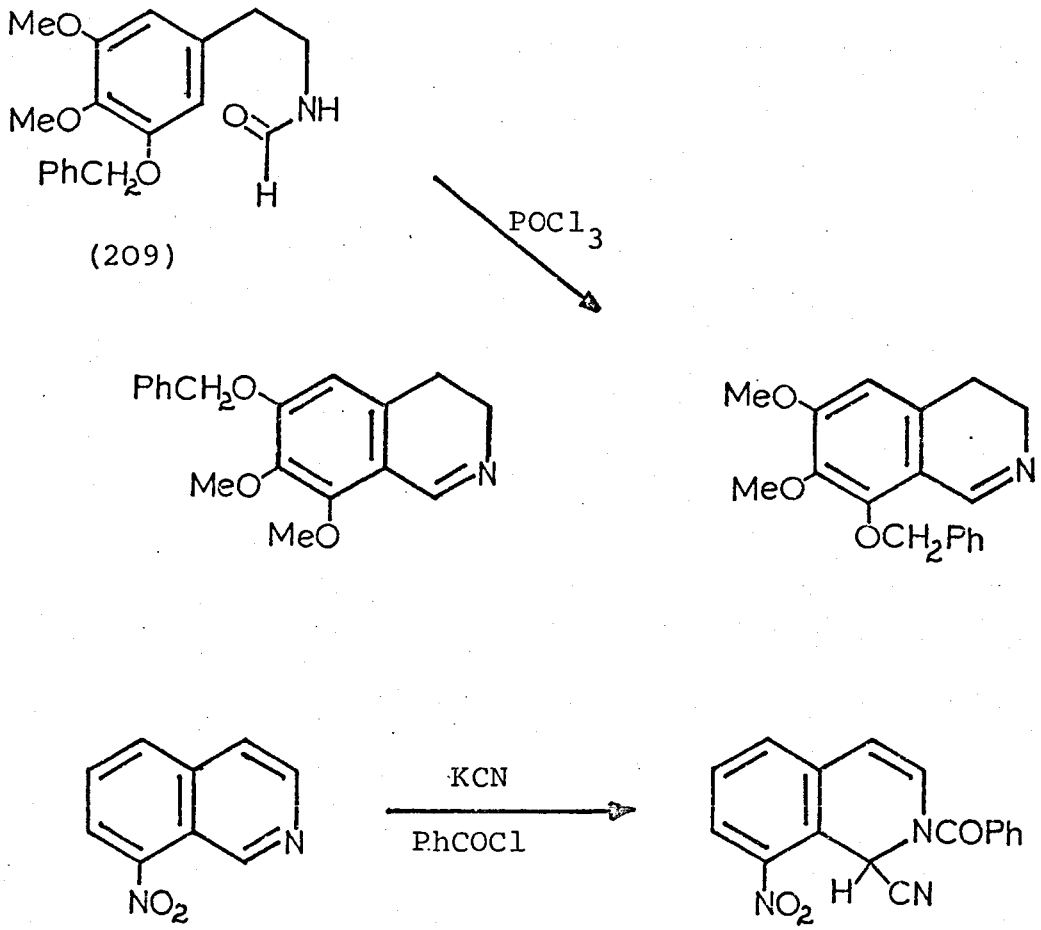
(207)



(208)

The infrared spectrum of the prepared ketal exhibited

peaks at 3300 (amide NH) and 1640 (amide C=O) and 1615cm^{-1} (C=C). The n.m.r. spectrum of the ketal supported isomer (205). In particular the $-CH_2-N$ protons at δ3.28 appeared as a triplet (J, 7Hz) so excluding isomer (208), and the olefinic proton signal at δ5.3, was a broad singlet with $W_{\frac{1}{2}}$=5Hz. This would be consistent with allylic coupling to four protons, as in (205), assuming a typical splitting[183,216] of 1.5Hz for allylic coupling (4 x 1.5 = 6Hz). In isomer (207) the olefinic proton would experience vicinal coupling with two protons at C-5 (typical value[216] J_{vic}=7Hz) in addition to that with four allylic protons hence giving $W_{\frac{1}{2}}$=2 x 7 + 4 x 1.5=20Hz. This value may be reduced by unfavourable dihedral angles. The signal width at half height ($W_{\frac{1}{2}}$) has been used particularly to determine the conformation of protons in cyclohexanes.[217] The method assumes that the hump observed as a result of multiple coupling has a width at half-height approximately equal to the sum of the coupling constants involved. The protected amide (205) was treated with phosphorus pentoxide in refluxing pyridine[211] in order to effect cyclodehydration to the hexahydroisoquinoline (206). After work-up only an intractable tar was obtained. Utilising phosphoryl chloride in refluxing benzene in the presence of pyridine, and phosphoryl chloride in refluxing toluene for periods of 1-8h also produced only intractable basic tarry material. This lack of success of the Bischler-Napieralski cyclodehydration was disappointing in view of the removal of the deactivating influence of the carbonyl group in (175). It would appear that steric factors must play a part in affecting the cyclisation of (205). Examination of models of (205) indicated that the dioxolan function could exert some steric hindrance of approach of the amide carbonyl group to the double bond of the cyclohexene ring for carbon-carbon bond formation to occur. It was not anticipated this would be a major effect, since, for example, 8-substituted 3,4-dihydroisoquinolines can be formed by Bischler-Napieralski cyclisation [e.g. of (209)[218]]. Nevertheless a steric effect has been noted in the formation of 8-substituted 1,2-dihydroisoquinolines of the Reissert type in some instances (e.g. with 210).[219]



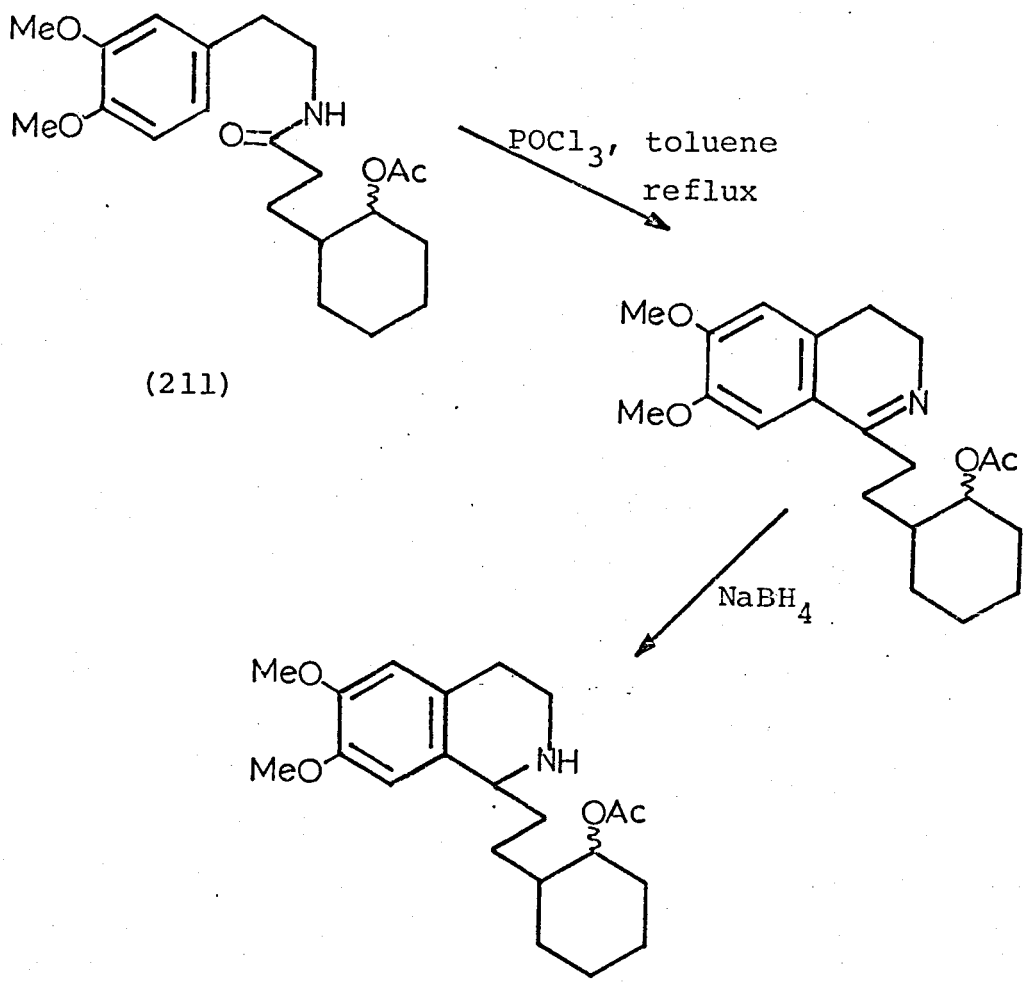
(209)

(210)

(9%)

(2) Other methods of Protection of the potential 8-substituent.

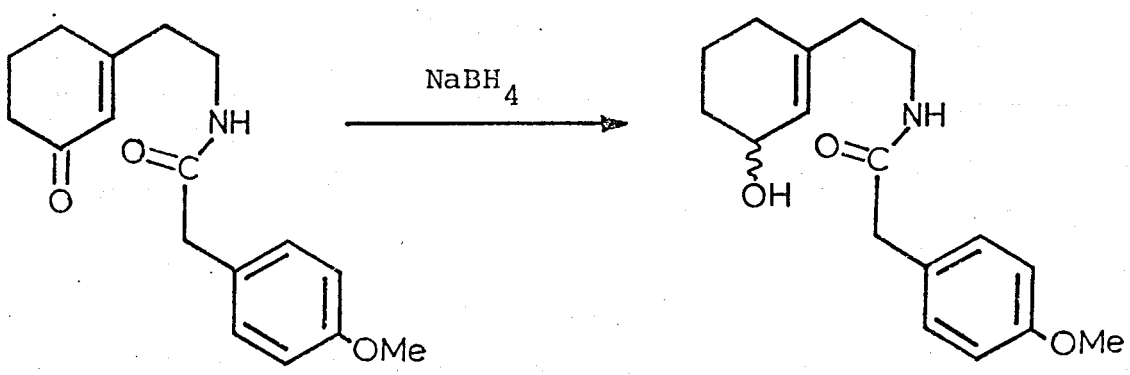
To reduce the steric bulk at the potential 8-position we decided to reduce the carbonyl to hydroxyl and convert it to the acetate. Schneider and Bernauer[220] showed the acetate ester (211) would survive Bischler-Napieralski conditions, giving (212).



(211)

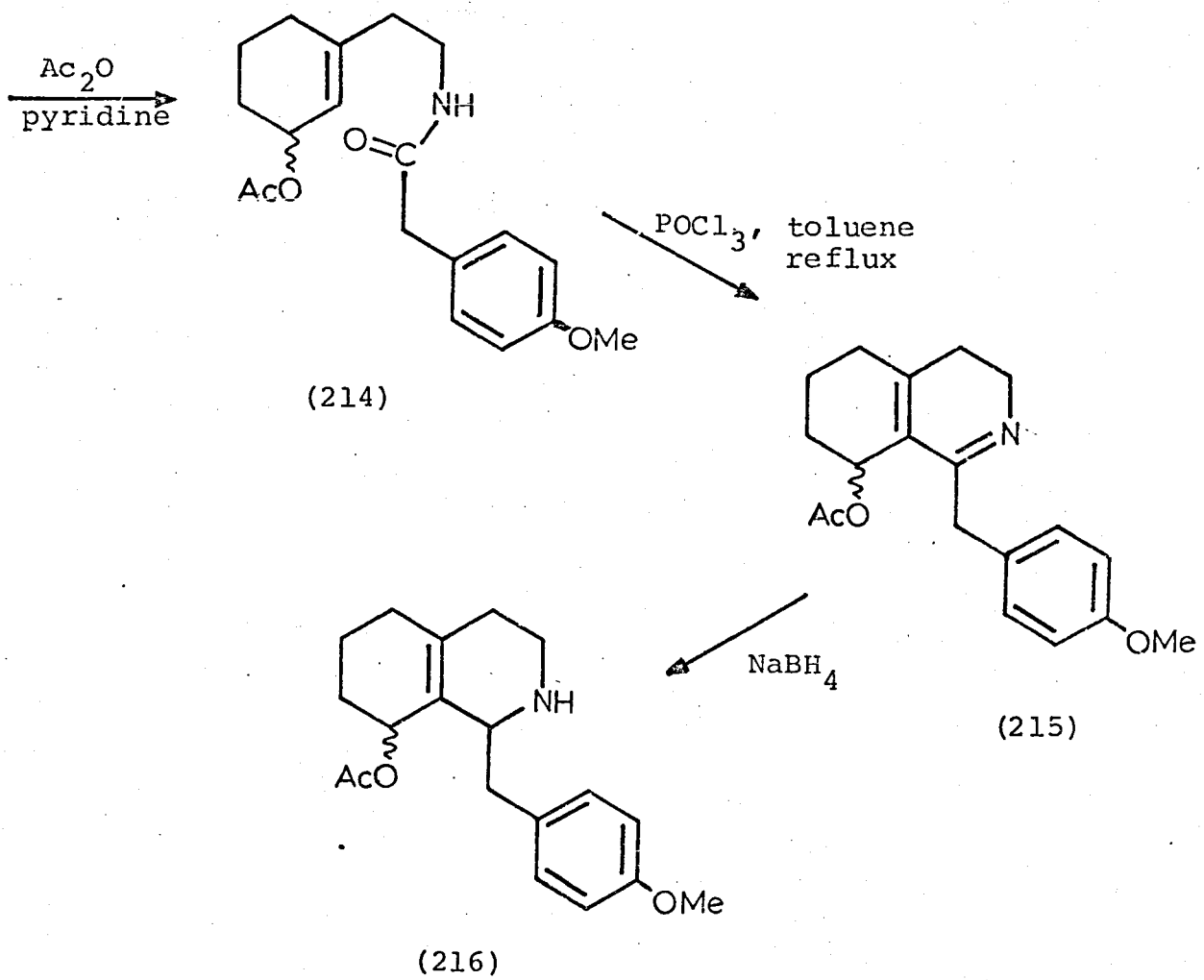
(212)

Hence we sought to effect the following sequence:-



(175)

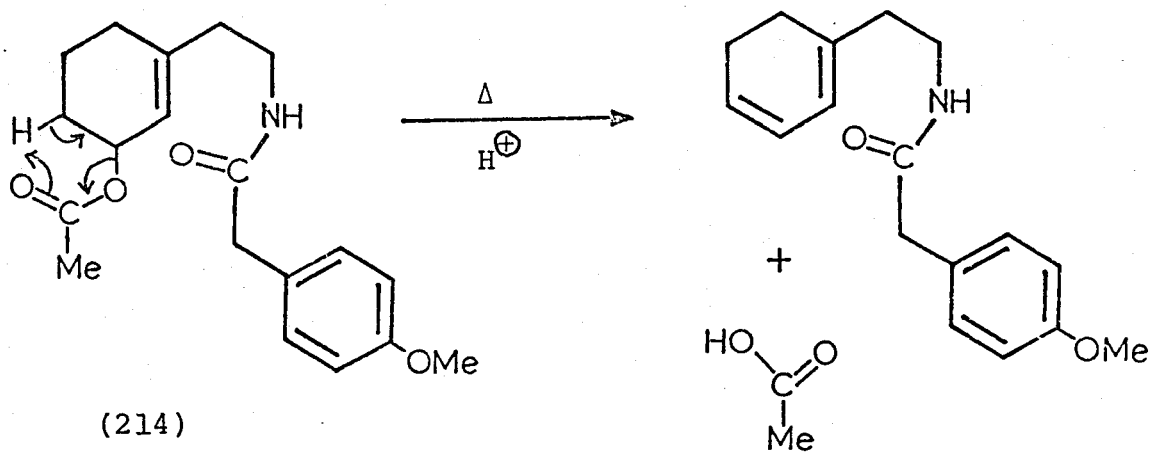
(213)



The amide (214) could then be investigated as a potential precursor for an 8-functionalised morphinan via the octahydro-1-benzyl compound (216). Sodium borohydride reduction of the amide (175) proceeded smoothly to afford the allylic alcohol (213) as colourless crystals m.pt. 65-67°C. The infrared spectrum of the alcohol (213) showed characteristic absorptions at 3250 (amide NH) and 1640cm^{-1} (amide C=O) together with a broad band centred at 3350cm^{-1} due to the alcoholic hydroxyl group. The n.m.r. included an absorption ascribed to the olefinic proton, which appeared as broad singlet at δ5.4 ($W_{\frac{1}{2}}$=6Hz). The alcoholic hydroxyl appeared as a broad singlet (exchangeable with D_2O) at δ2.23, and the adjacent methine proton at δ4.1. Treatment of the allylic alcohol with an excess of acetic anhydride in pyridine for 24h at room temperature afforded

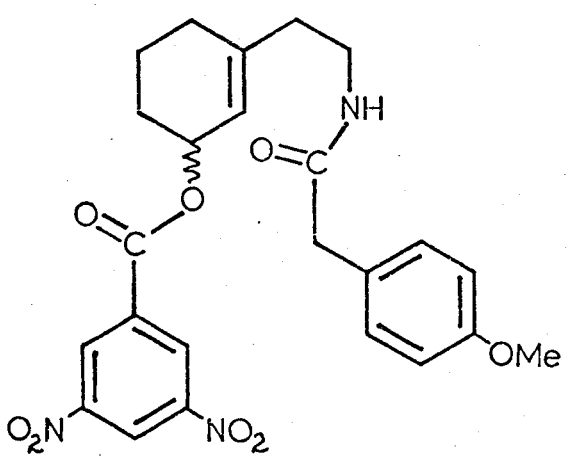
the O-acetylated amide (214) as a viscous syrup. The infrared spectrum of the acetate (214) showed strong bands at 3250 (amide NH), 1725 (ester C=O), 1640 (amide C=O), and 1610cm^{-1} (C=C). The n.m.r. showed the acetoxy methyl singlet at δ2.02 and a shift of the adjacent methine proton, which resonated at δ4.1 in (213), to lower field[221] at δ5.17 in (214).

Extensive attempts were carried out to effect Bischler-Napieralski cyclodehydration of the amide (214) to give the hexahydro-1-benzylisoquinoline (215). Phosphoryl chloride in refluxing benzene, toluene and acetonitrile were employed as the dehydrating reagent. A.Brossi and co-workers found that acetonitrile was particularly effective as a solvent for the cyclodehydration of aromatic phenylacetamides to afford isoquinolines in excellent yields.[222] We did not at first investigate the isolation of the intermediate hexahydro-compound (215). The crude product from the cyclodehydration reaction was reduced directly with sodium borohydride in methanol so that the unstable 3,4-dihydroisoquinoline (215) could be converted into the octahydro compound (216). Spectroscopic analysis of the gum obtained by this method indicated absence of amide NH and C=O in the infrared spectrum, it was also observed that the acetate carbonyl had disappeared. N.m.r. spectroscopy showed that the product was impure; the only discernable peaks being aromatic methoxyl and phenyl resonances. Thin layer chromatography indicated that the product was extremely polar suggesting that polymerisation of some kind had occurred. Isolation of the product from the cyclodehydration reaction prior to reduction also proved disappointing, again the acetate group was seen to be absent. The loss of the acetate group may be due to cyclic cis-elimination of acetic acid from the amide (214) by the mechanism shown. Such eliminations occur usually under pyrolysis[223] : diene production could lead to polymerisation.



(214)

The allylic alcohol (213) was also converted into the 3,5-dinitrobenzoate ester (217) by treatment with 3,5-dinitrobenzoyl chloride in pyridine. The amide (217) was obtained as pale-yellow plates m.pt.135-136°C after recrystallisation from ethanol.



(217)

The infrared spectrum of the prepared amide showed amide (3320 and 1640) and ester (1730cm^{-1}) absorptions. Bischler-Napieralski cyclodehydration of this amide utilising phosphoryl chloride in acetonitrile at varying temperatures and reaction times gave no cyclised 3,4-dihydroisoquinolines.

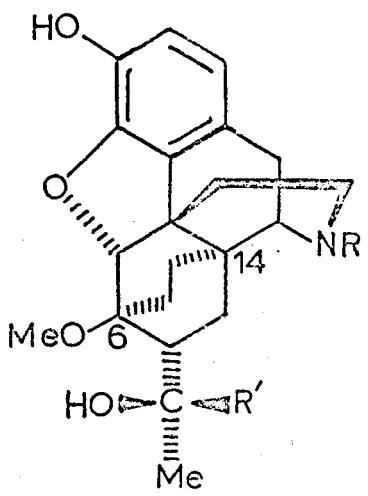
From the repeated lack of success with the cyclodehydration of the series of phenylacetamides examined it would seem evident that a synthesis of the required 3,4-dihydroisoquinoline (176) needs to be approached along different lines to the route we chose and we did not pursue the investigation further.

PART 2

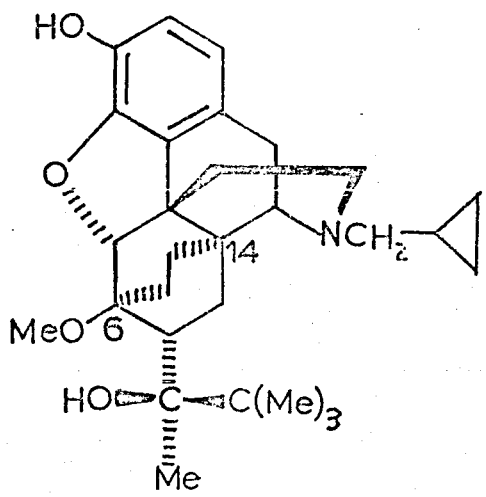
The Synthesis of Ring-A Bridged Isoquinoline

Preamble

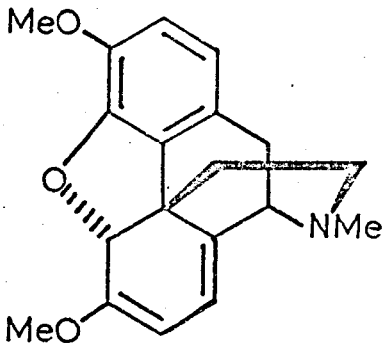
In view of the remarkable analgesic potency of the series of tertiary carbinols (218) developed in the laboratories of Reckitt and Colman from Diels-Alder adducts of thebaine (3)[86,108,109] it was of interest to develop a synthetic route to related compounds. Buprenorphine (219) was introduced into clinical practive in April 1978 under the name 'Temgesic', as a partial agonist which has low dependence liability. The 4,5-deoxy analogues (220) are morphinan derivatives and so could possibly be produced by synthesis, i.e. without the dependence upon the natural alkaloid thebaine (3). We also considered that the synthesis of morphinans with other bridges may be possible, such as compounds (221). All these should provide interesting pharmacological profiles and might lead to a separation of analgesic and respiratory depressant effects present in morphine.



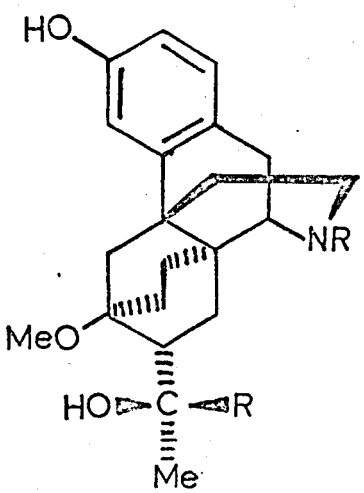
(218)



(219)



(3)



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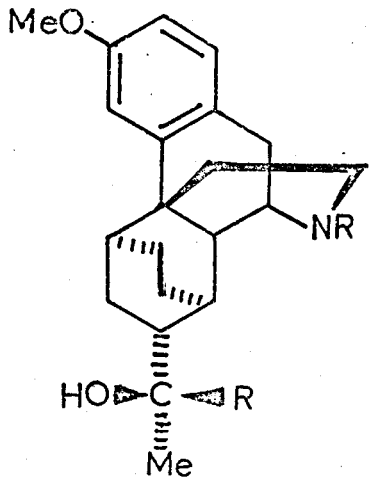
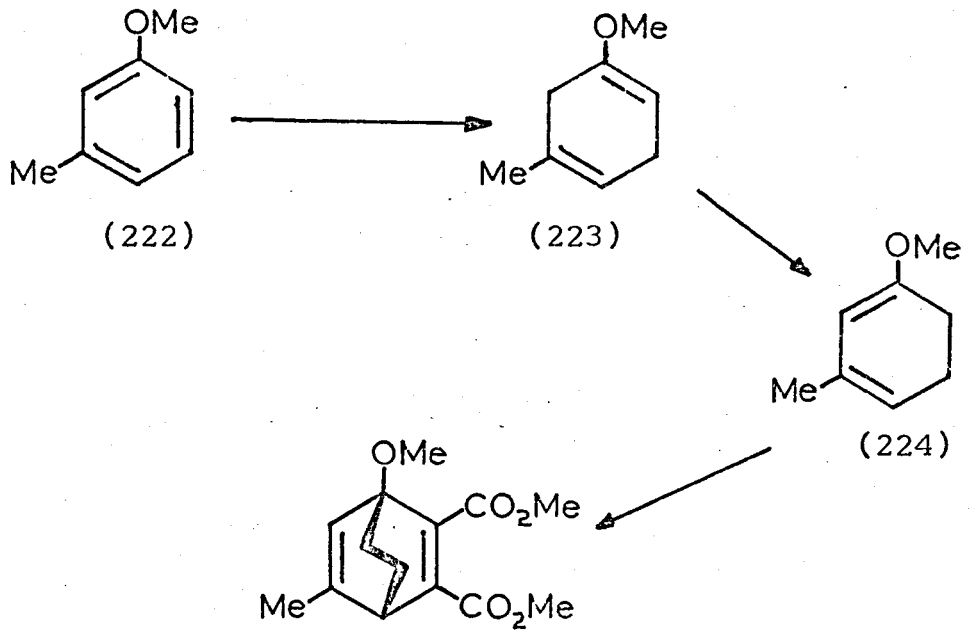


(221)

Any synthetic programme with ring-C bridged morphinans as ultimate goal would first have to investigate the synthesis of ring-A bridged isoquinolines as precursors, unless the bridge is to be introduced after morphinan formation. We therefore studied routes to ring-A bridged isoquinolines.

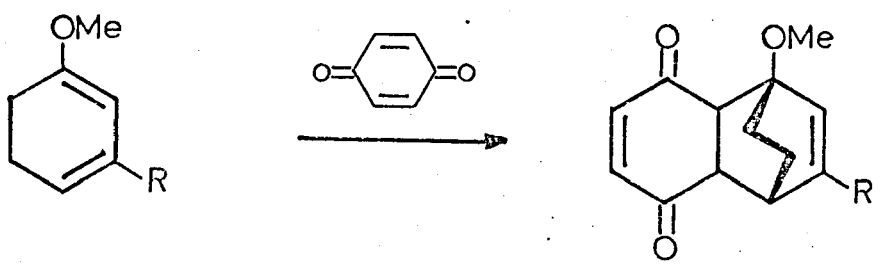
1,4-Dihydroaromatic compounds obtained by the metal in liquid ammonia reduction (Birch reduction) of a wide range of aromatic substrates have been employed as precursors of conjugated dienes suitable for Diels-Alder cycloadditions.[224,225,226] A.J.Birch and P.Hextall[224] isomerised the 1,4-dihydroanisole (223) obtained by Birch

reduction of 3-methylanisole (222) with potassium amide in liquid ammonia to obtain the 2,3-dihydro-compound (224) which underwent Diels-Alder condensation with dimethyl-acetylenedicarboxylate to afford the bridged adduct (225) as outlined below:



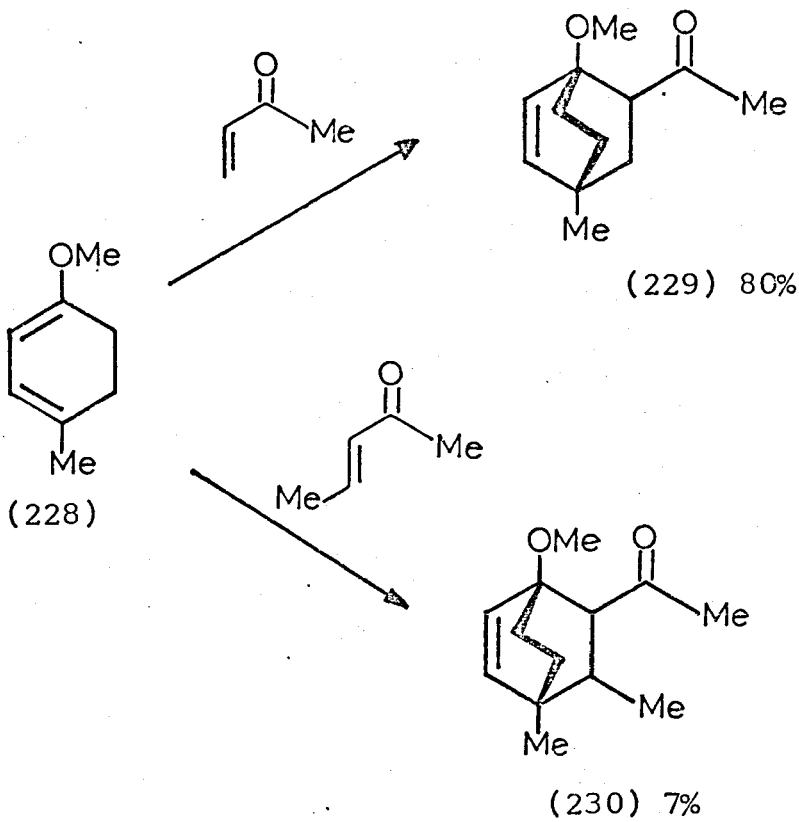
(222) (223) (224) (225)

Birch et.al.[225] also condensed the 1-methoxy-cyclohexa-1,3-dienes (226, R=H, or OMe) with p-benzo-quinone in refluxing benzene to afford the adduct (227, R=H, or OMe) in 60% yield.

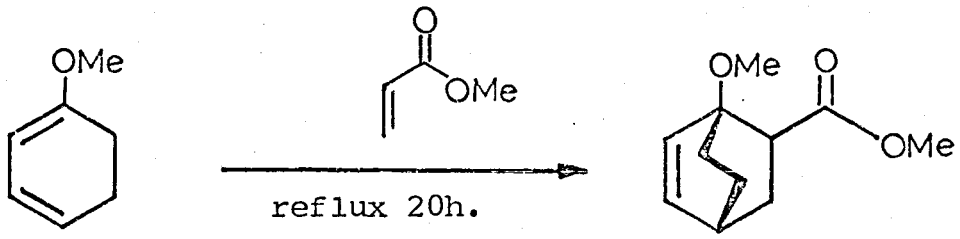


(226) (227)

Birch and Hill[227] condensed the diene (228) obtained in a similar manner, with methyl vinyl ketone and trans-pent-3-en-2-one to give the corresponding adducts (229) and (230) in 80% and 7% yield respectively.



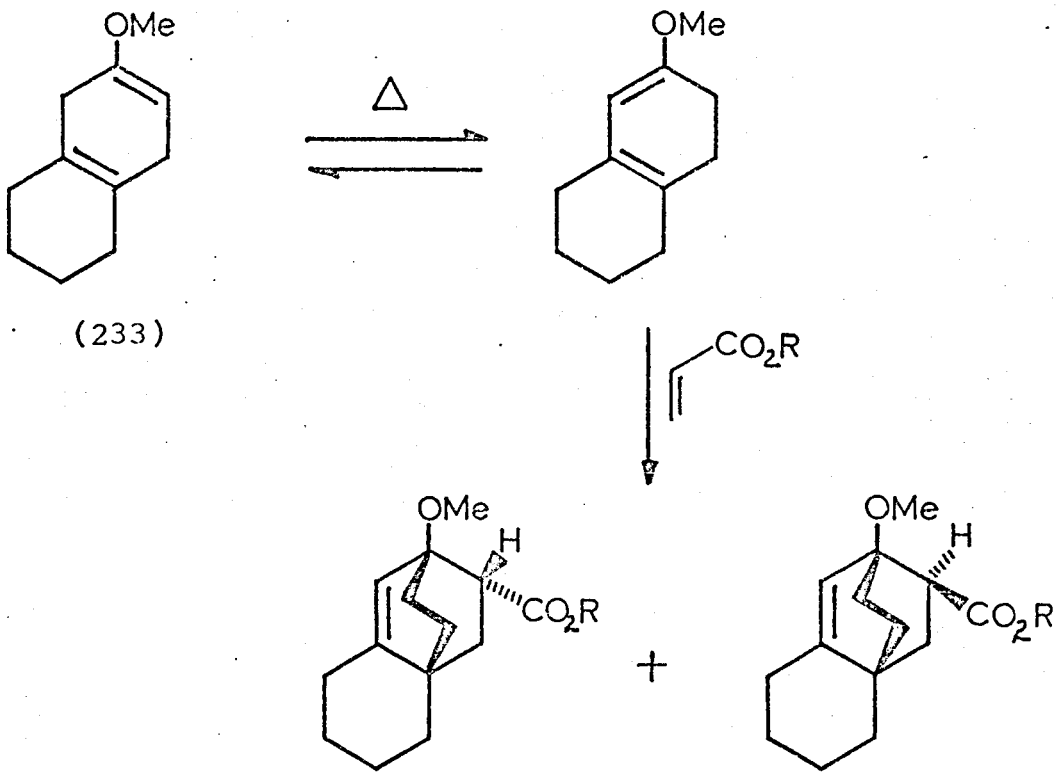
Presumably the low yield of (230) can be attributed to the steric hindrance to the formation of a transition state shown by the trans- substituted dienophile. The yield of (230) was increased to 20% by heating the reactants at 180°C in a sealed Carius tube. Cis-trans isomerisation of the trans-pent-3-en-2-one can occur at higher temperatures and there will be more of the less stable cis isomer available for Diels-Alder condensation. The same workers also reported that the Diels-Alder addition of methyl acrylate to 2,3-dihydroanisole (231) proceeded regiospecifically to afford the ester (232) in 75% yield.



(231) (232)

Previously the 1,3-dienes were obtained by isomerisation of the 1,4-dihydroanisoles with potassium amide in liquid ammonia[228] or by metal alkoxides in t-butyl, or t-amyl alcohol.[229,230] N.A.J.Rogers and co-workers[230,231] observed that the diene isomerisations could be accomplished thermally by heating in a glass vessel. The conjugated dienes could be produced in situ and condensed with suitable dienophiles.

When 6-methoxy-1,2,3,4,5,8-hexahydronaphthalene (233) was heated in a sealed tube with ethyl acrylate, a high yield of the mixed esters (234 and 235, R=Et) was obtained.[230]



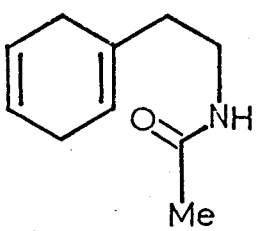
(233) (234) (235)

The esters (234 and 235, R=Et) were found to be stable to the conditions of the Diels-Alder reaction, and were not interconverted, even at much higher temperatures.

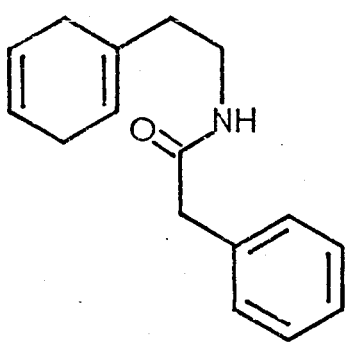
(1) Diels-Alder Reactions with Dihydrophenylacetamides.

A priori ring-A bridged isoquinolines could either have the bridge introduced before or after construction of ring-B. We looked first at the former possibility.

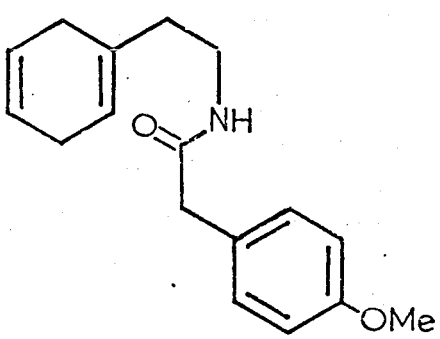
S.Sugasawa and R.Tachikawa[232,233] reported the synthesis of N-[2-(1,4-cyclohexadienyl)ethyl]acetamide (236),[232] N-[2-(1,4-cyclohexadienyl)ethyl]phenyl acetamide (237)[232] and N-[2-(1,4-cyclohexadienyl)ethyl]-4-methoxyphenyl acetamide (238)[233] which they utilised as substrates in Bischler-Napieralski syntheses of isoquinolines



(236)

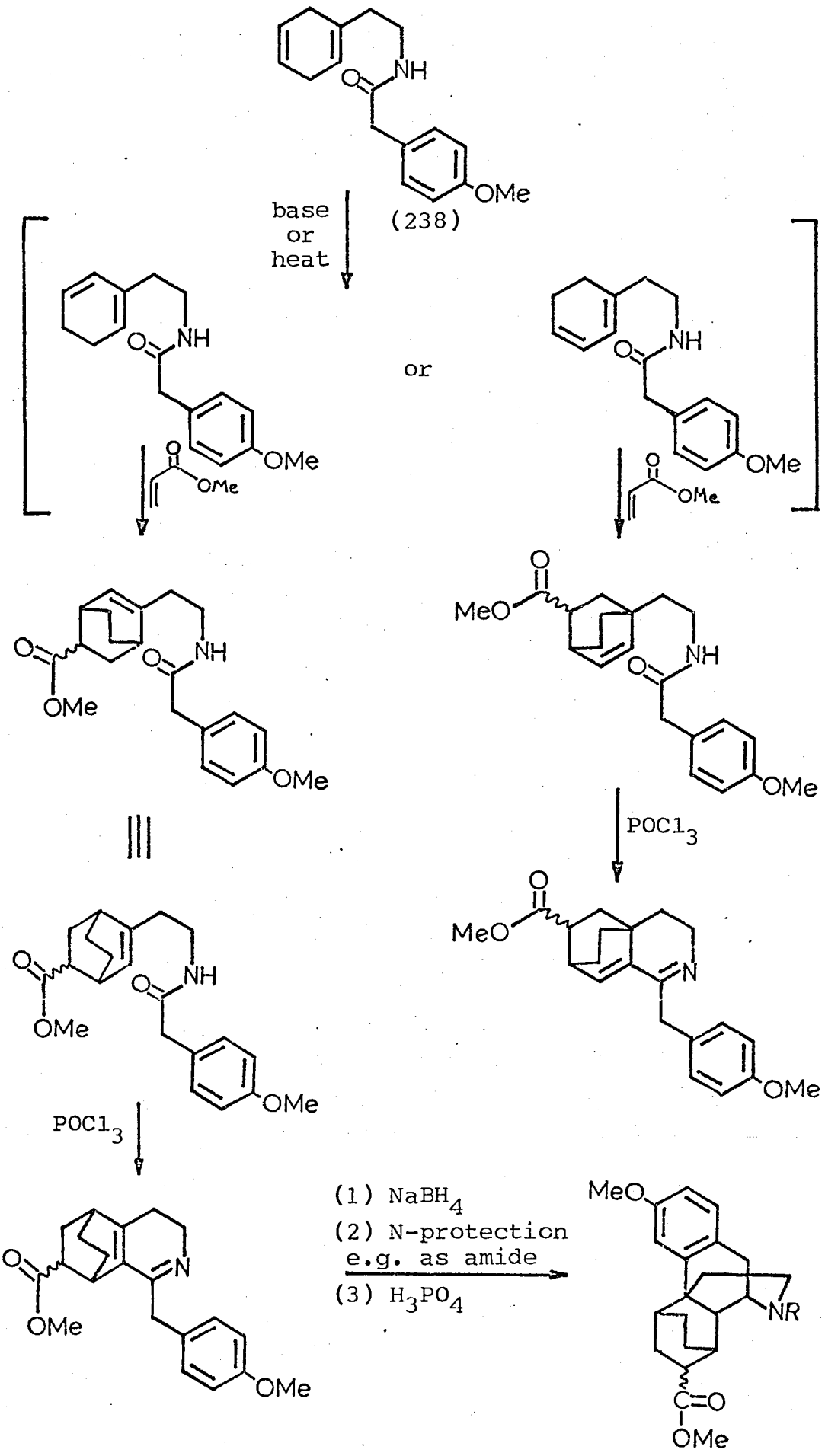


(237)



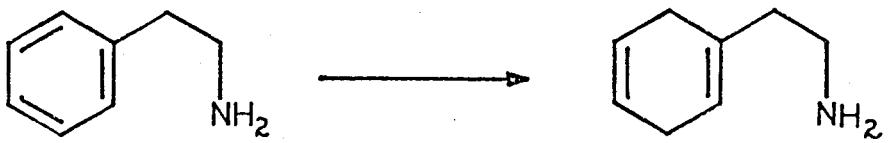
(238)

We wished to investigate the synthetic utility of these amides as precursors for ring-A bridged isoquinolines. A synthesis of ring-C bridged morphinans could be envisaged as in Scheme 20 .


NH
OMe
(238)
base
or
heat
or
NH
OMe
OMe
NH
OMe
OMe
MeO
NH
OMe
POCl3
MeO
N
OMe
NH
OMe
OMe
POCl3
N
OMe
OMe
(1) NaBH4
(2) N-protection
e.g. as amide
(3) H3PO4
MeO
NR
C=O
OMe

Scheme 20.

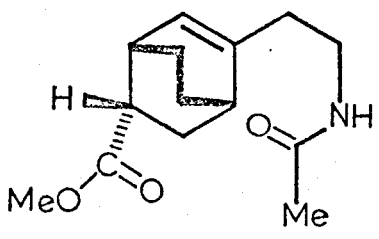
β-Phenylethylamine (239) was reduced with lithium in liquid ammonia and ethanol[232] to afford β-(1,4-cyclohexadienyl)ethylamine (240).



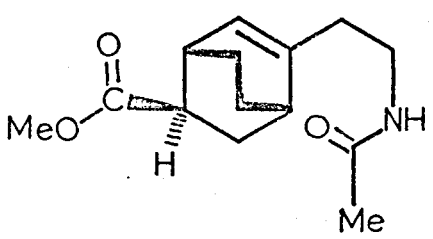
(239) (240)

The amine (240) was acetylated with acetyl chloride in the presence of sodium hydroxide solution to afford the amide (236) and also with 4-methoxyphenylacetyl chloride in the presence of sodium bicarbonate solution to afford the amide (238). The crystalline amides showed agreement with the reported literature melting points.[232,233] The n.m.r. spectrum of amide (238) showed MeO at δ3.8 and a singlet at δ3.5 due to the benzylic methylene. The olefinic proton at C-3 resonated as a broad singlet at δ5.27 and the two protons at C-5 and C-6 as a broad singlet at δ5.65. The infrared showed amide bands at 3250 (NH) and 1640cm^{-1} (C=O).

The amides were each heated in sealed glass Carius tubes with excess methyl acrylate in the presence of hydroquinone at 150°C for 72h. After removal of excess dienophile and chromatography, the oily product obtained from the Diels-Alder reaction of the acetyl amide (236) showed an ester carbonyl at ν_{max} 1730cm^{-1}, together with characteristic amide NH and C=O at 3290 and 1650cm^{-1}. The n.m.r. spectrum was consistent with the formation of the epimeric Diels-Alder adducts (241) and (242). Unfortunately the epimers could not be separated nor obtained analytically pure.



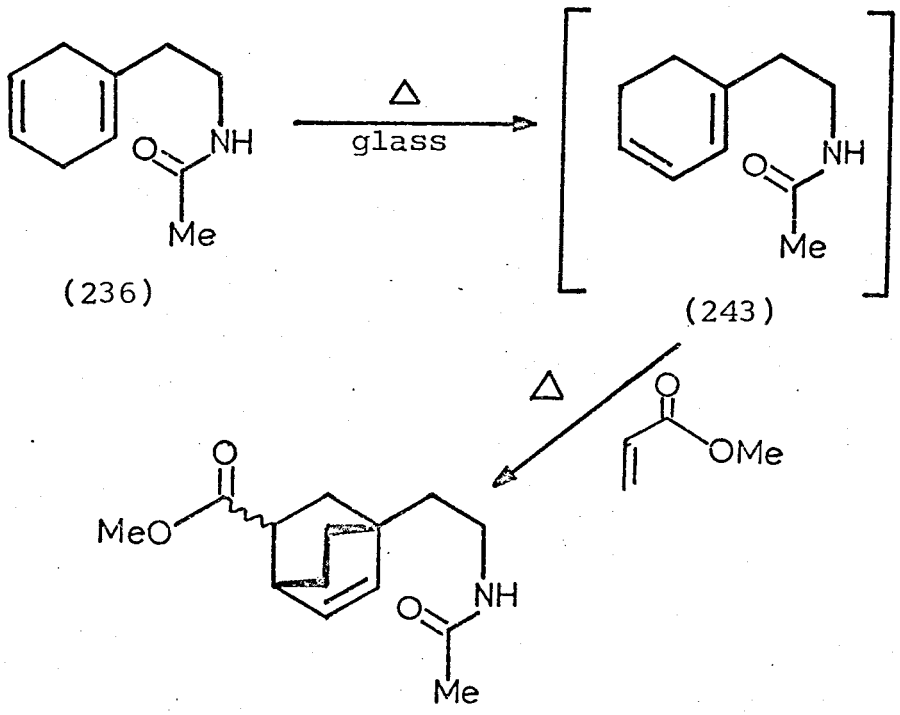
(241)



(242)

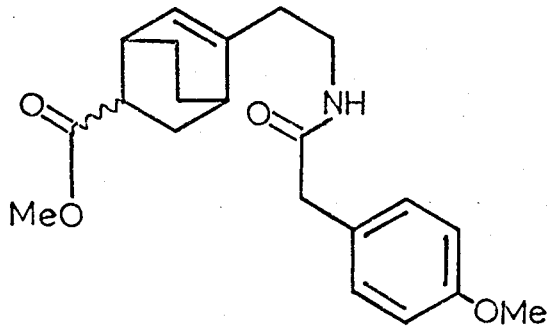
Mass spectral examination showed a molecular ion corresponding to the assigned structures.

The alternative isomers that could be formed from the in situ conjugation would arise from the diene (243) and possess the structure (244). However, the n.m.r. spectrum of the epimeric esters exhibited only one olefinic proton and not two as would be expected if (244) had been obtained.



(236) (243) (244)

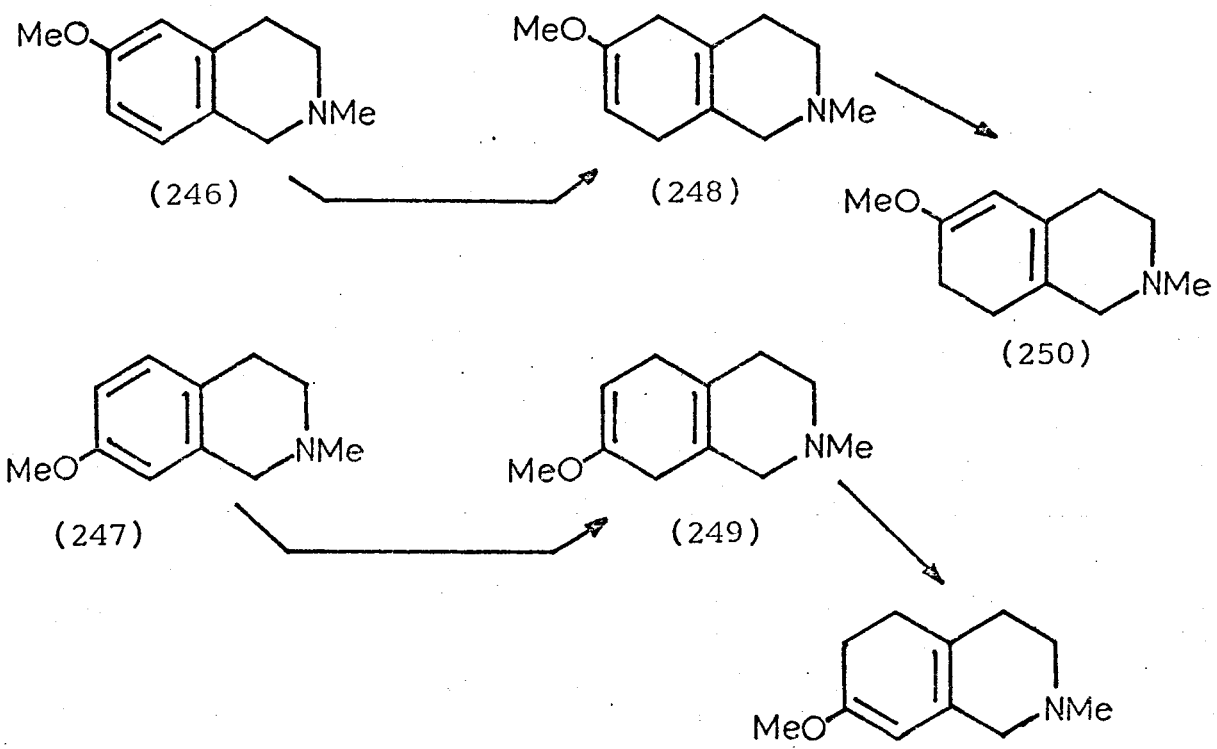
When the benzyl amide (238) was utilised in the sealed tube reaction with methyl acrylate at 150°C for 72h. extensive polymerisation and aromatisation of the diene (238) was found to occur and no evidence for the formation of the expected epimeric esters (245) was found. In view of the difficulties encountered this approach was discontinued.



(245)

(2) Diels-Alder Syntheses with Hexahydroisoquinolines.

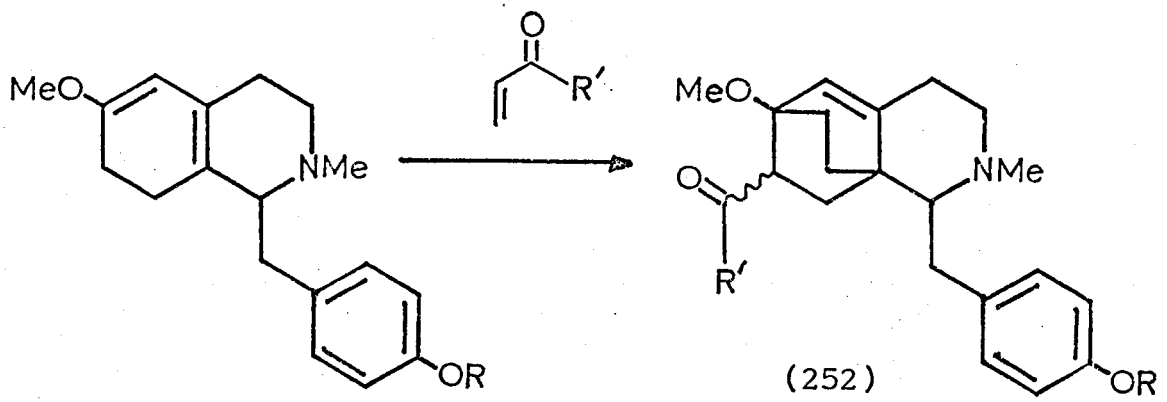
During the course of the above studies T.A.Crabb and J.R.Wilkinson[234] reported the synthesis of the hexahydroisoquinolines (250) and (251) containing a 1,3 diene system, via the base-catalysed isomerisation of the 5,8 dihydro unconjugated compounds (248) and (249);



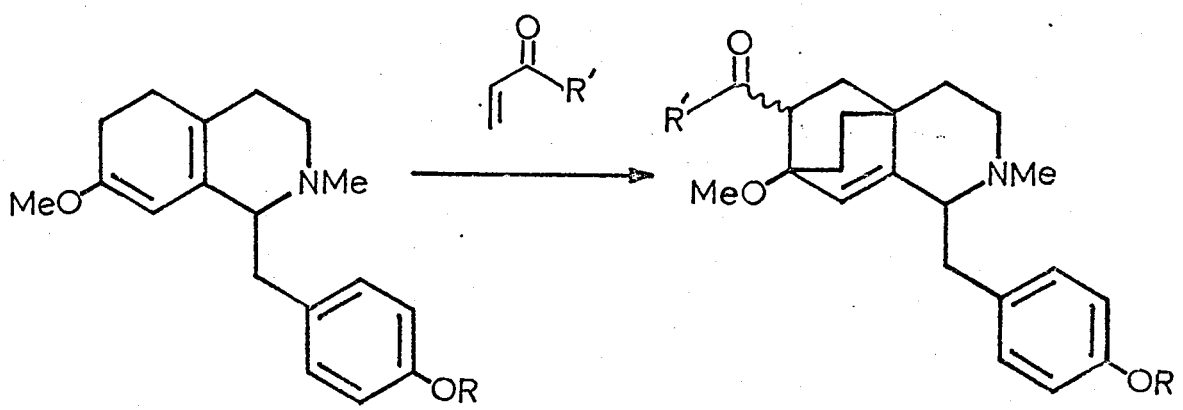
Scheme 21.

obtained by metal in liquid ammonia reduction of the 1,2,3,4-tetrahydroisoquinolines (246) and (247) as outlined in Scheme 21. These dienes (250 and 251) were exactly the

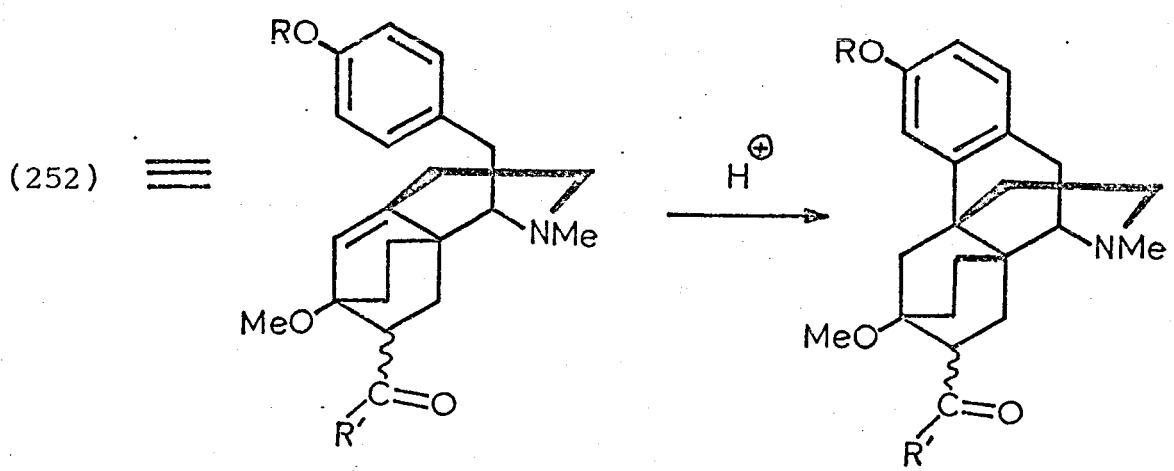
type we required if ring-A bridged isoquinolines were to be obtained by Diels-Alder addition to dienes in which ring-B of the isoquinoline was already formed. Furthermore



(252)



(253)



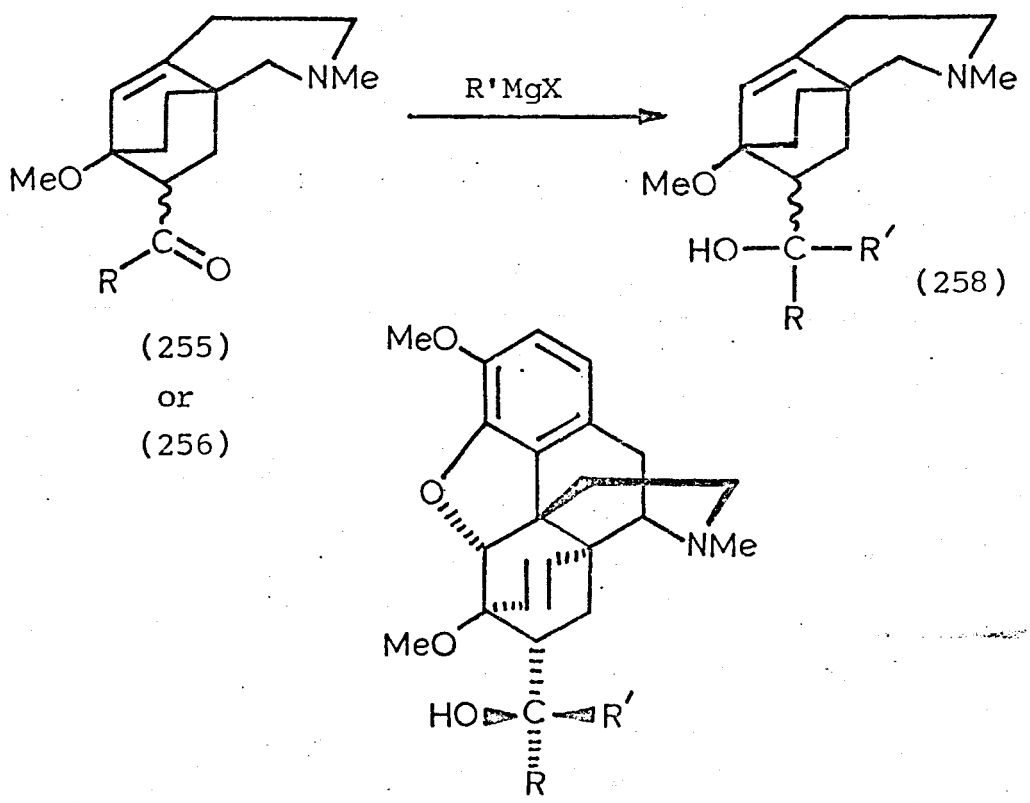
(254)

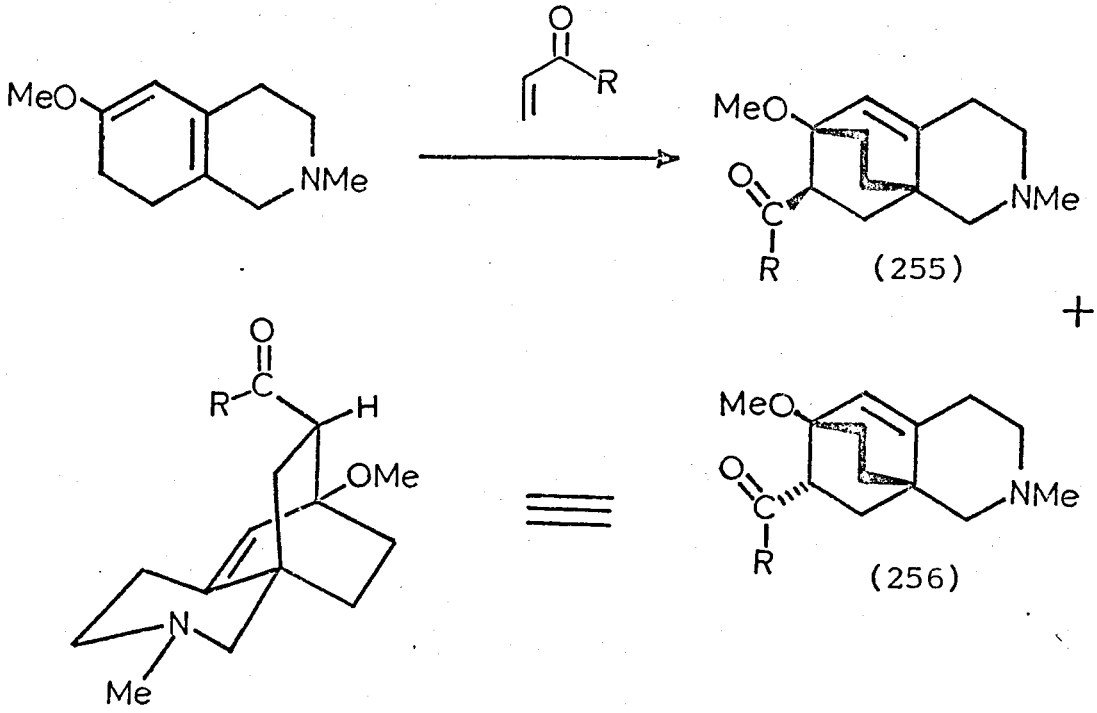
Scheme 22.

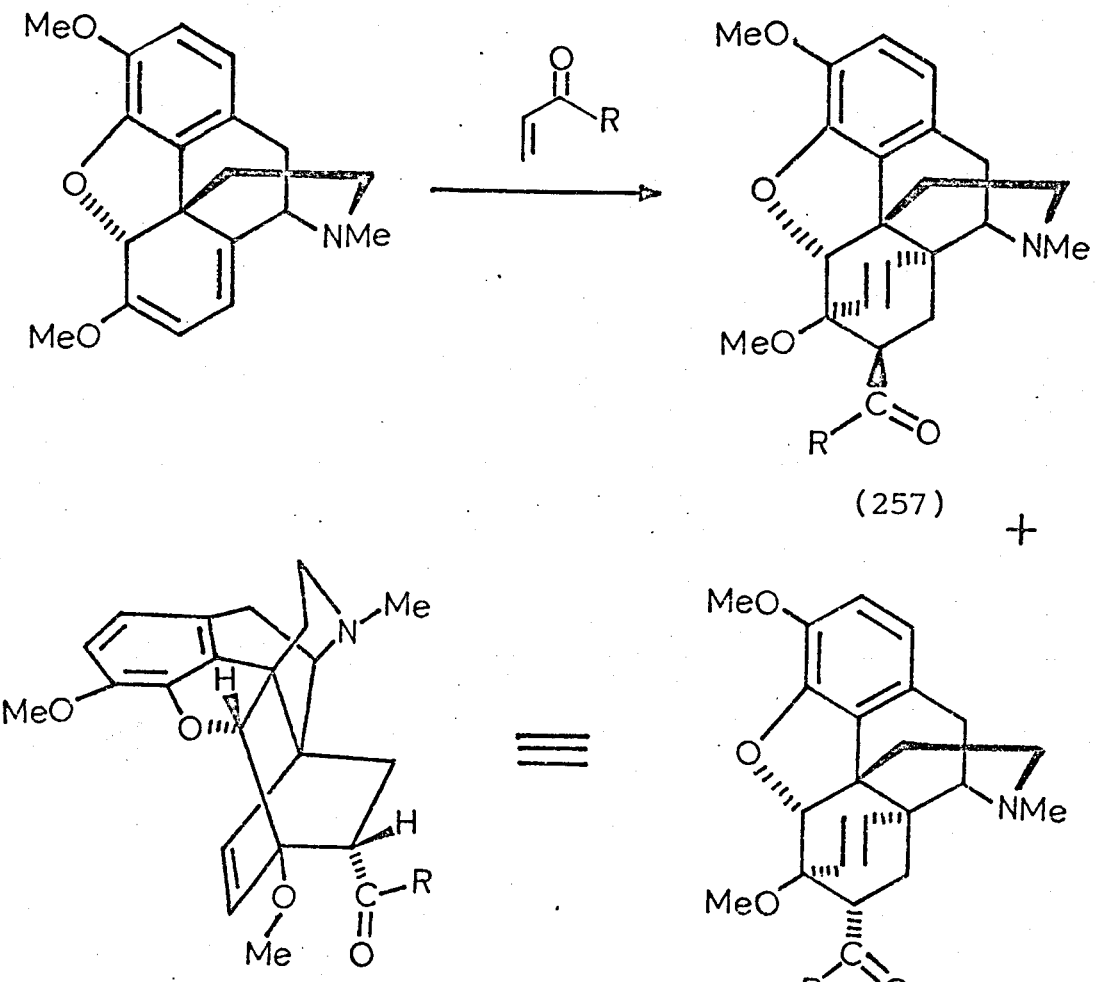
incorporation of a 1-benzyl group into the hexahydroisoquinoline moeity (250) or (251) would permit Diels-Alder condensation to afford bridged ring-A 1-benzylisoquinolines of type (252) or (253), of which (252) could possibly be progressed to the morphinan (254) scheme 22 .

We therefore set out to examine Diels-Alder cycloadditions to the conjugated 6-methoxydiene (250). Later we studied the synthesis of the 1-benzyl analogues and their Diels-Alder behaviour.

A likely course of the cycloaddition of (250) with a vinyl ketone is shown in scheme 23 and compared with the known reaction of thebaine.[86] The stereochemistry shown in (256) would probably be the favoured outcome since its formation would permit optimum orbital overlap in the transition state - the so-called "secondary effect" in Diels-Alder reaction[235] - not possible in that leading to (255). This assumes regioselectivity as observed for the thebaine case, i.e. the acyl function results at position 7 and not position 8 in (56/257). Diels-Alder adducts obtained in this fashion (255) and/or (256) could afford carbinols (258) structurally analogous to the 6,14-endo-etheno-carbinols (57) mentioned earlier.



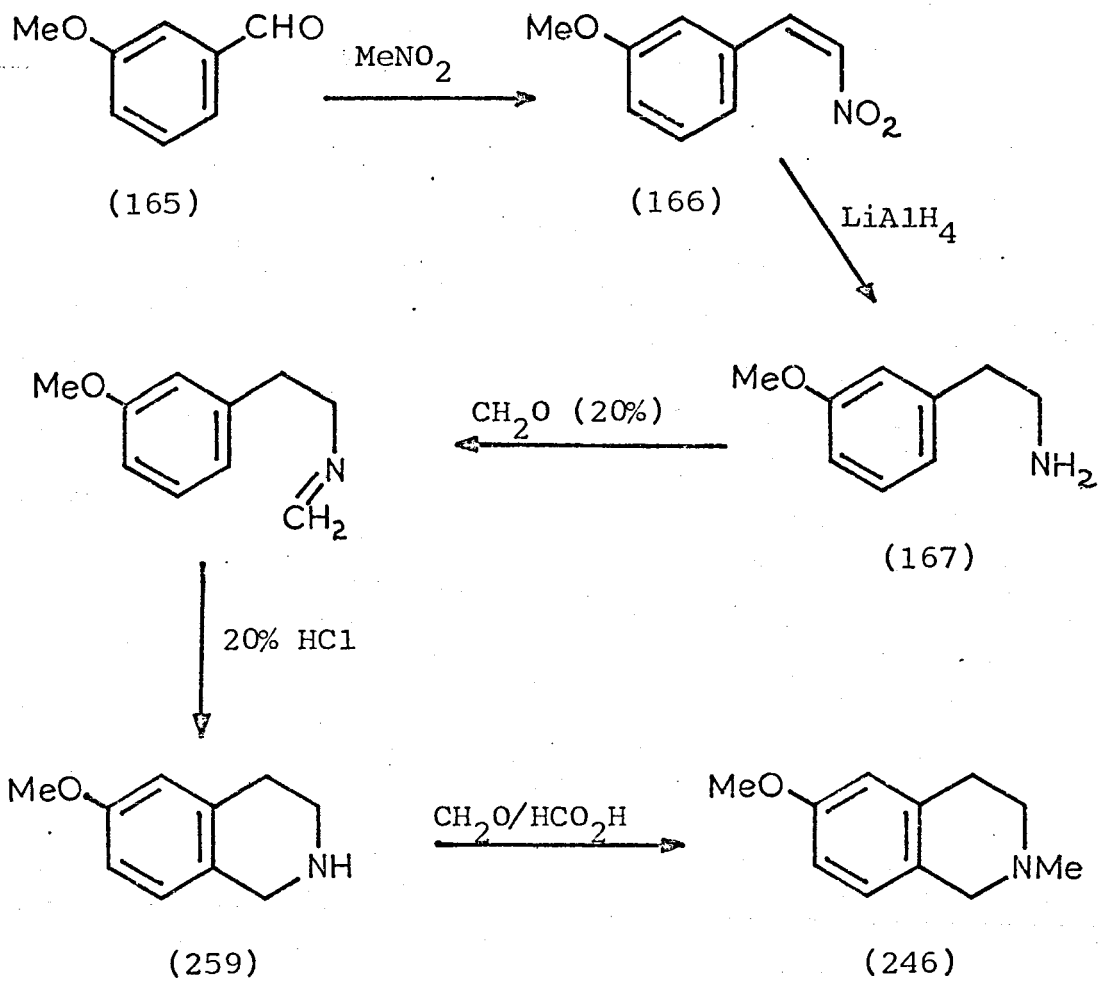




Scheme 23.

(A) Synthesis of Hexahydroisoquinolines.

Marchant and Pinder[236] had previously carried out the Birch reduction of 1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (246) with sodium and methanol in liquid ammonia; they hydrolysed the crude product without isolating the pure hexahydroisoquinoline. We obtained 1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline as indicated in scheme 24 , based on Marchant and Pinder's[236] approach.

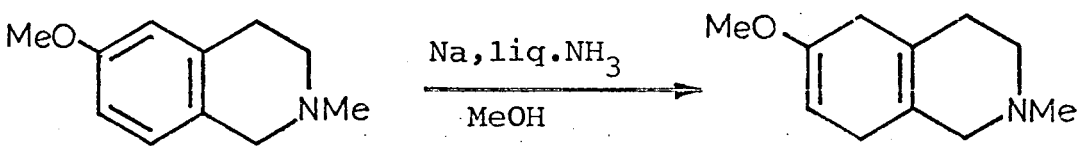


Scheme 24.

However, we found that the nitrostyrene (166)

could be more conveniently synthesised by the method of Grewe et.al.[179a] (cf. earlier p. 82). Marchant and Pinder condensed 3-methoxybenzaldehyde with nitromethane in the manner reported by Gulland and Virden[237] in the presence of methylamine hydrochloride, anhydrous sodium carbonate and absolute ethanol for 48h at room temperature. Grewe et.al.[179a] obtained the same nitrostyrene (166) in 71% yield by condensation of 3-methoxybenzaldehyde with nitromethane in the presence of ammonium acetate and glacial acetic acid for 3h at 130°C. Lithium aluminium hydride reduction of (166) is best carried out with the nitrostyrene placed in a soxhlet thimble.[179b]

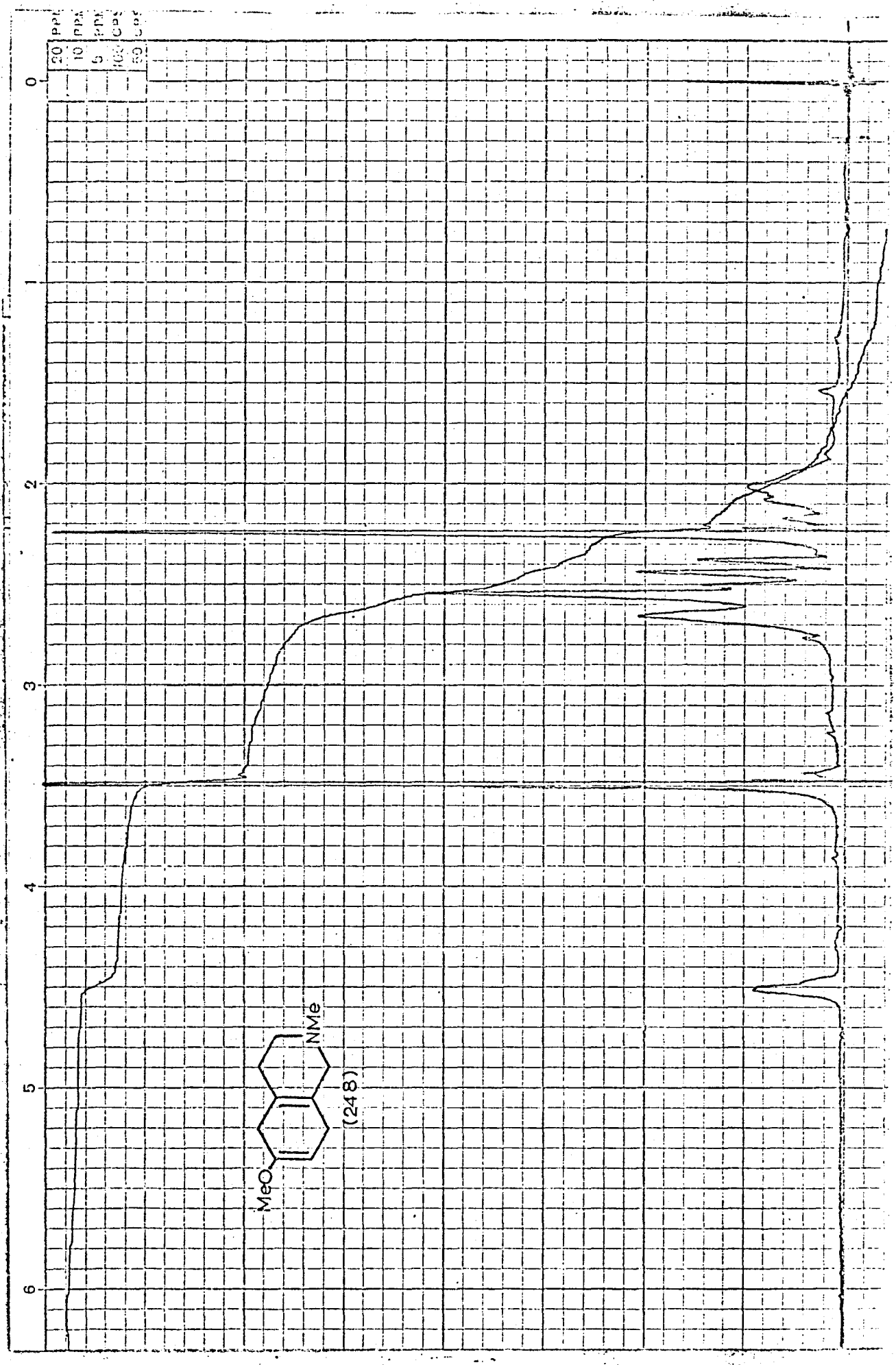
Birch reduction of the 6-methoxy compound (246) with Na/MeOH/liq. NH_3 proceeded smoothly, according to the method of Crabb and Wilkinson,[234] and Marchant and Pinder[236] and the unconjugated diene (248) was obtained as a colourless oil. It shows no U.V. absorption above 220nm and bands in the infrared spectrum at 1670cm^{-1} and 1705cm^{-1} due to the dihydroanisole system.[188a,241] The n.m.r. spectrum (Fig. 5) exhibits O-methyl and N-methyl singlets at δ3.50 and 2.24 respectively, and a broad singlet at δ4.52 corresponds to one olefinic proton.



(246) (248)

As mentioned earlier the absence of clearly split signals for the olefinic protons appears to be a not uncommon characteristic of such dihydroaromatic systems, only broad signals often being observed. This phenomenon has also been reported by Crabb et.al.[234] The formation of the diene (248) is analogous to the Birch reduction of the carbocyclic analogue 6-methoxytetralin which yields

Fig.5. 90 MHz n.m.r. spectrum of the hexahydroisoquinoline (248).



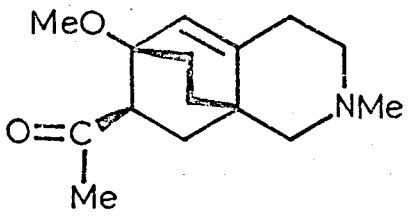
1,2,3,4,5,8-hexahydro-6-methoxynaphthalene.[177,187,238]

Isomerisation of the diene (248) was carried out with potassium t-amyl oxide in t-amyl alcohol[229,230] by the method of Crabb and Wilkinson.[234] The diene (248) being heated at 100°C over a 4h period. We found that when the isomerisation was carried out under a nitrogen atmosphere no aromatic material was observed in the isomerisation mixture as shown by the n.m.r. spectrum; the conjugated diene olefinic proton appeared at δ4.62 and that of the unconjugated compound at δ4.52. The infrared spectrum of the isomerisation mixture showed strong bands at 1675cm^{-1} and 1620cm^{-1} indicating the presence of the conjugated 1,3 diene (250).[188a] The estimated composition of the isomerisation mixture from the n.m.r. integrals was ca 75% conjugated diene (250) and 25% unconjugated diene (248). The progress of the isomerisation was monitored by u.v. spectroscopy; the conjugated diene (250) showed an absorption maxima at λ_{max} 272nm. [λ_{max} calculated for (250) by Woodward-Feiser rules[190] is 279nm.].

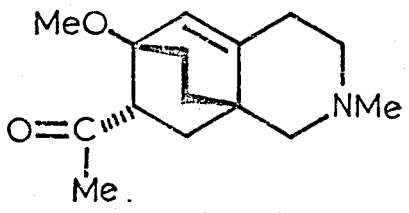
(B) Diels-Alder Condensation of 1,2,3,4,7,8-Hexahydro-6-methoxy-2-methylisoquinoline (250).

1) With methyl vinyl ketone.

The isomerisation mixture containing approximately 75% of the methoxy diene (250) was heated under reflux with methyl vinyl ketone for a period of 4-6h at 100°C. After removal of excess dienophile in vacuo distillation of the residue afforded a forerun of unchanged hexahydroisoquinoline (248) together with aromatic material (246). Then the major fraction consisted of a mixture of epimeric adducts (260) and (261), it was estimated from the n.m.r. spectrum of the mixture that the two isomers (A and B) were present in the approximate ratio of 2:3.



(260)

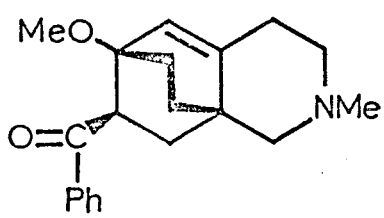


(261)

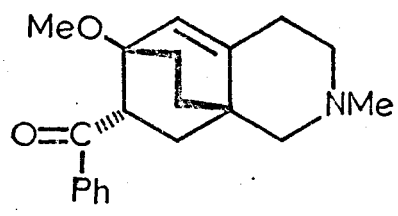
A separation of the epimeric adducts (260) and (261) was achieved by column chromatography over neutral alumina using light petroleum and ether as eluents. The first component to be eluted, (A), was obtained as a liquid and the second component (B), as a crystalline solid (m.p. 35°C). The infrared spectrum of both isomers showed a strong band at 1710cm^{-1} (C=O). The n.m.r. spectra include singlets representing one olefinic proton, the N-methyl group, the O-methyl group and the acetyl methyl group. Components A and B were assigned the exo and endo stereochemistry (260) and (261) respectively (see discussion p. 131).

2) With phenyl vinyl ketone.

A mixture of adducts was similarly obtained by heating the methoxy diene (250) with freshly distilled phenyl vinyl ketone in refluxing benzene for 6-8h. Distillation of the viscous oily product afforded a mixture of epimers (262) and (263) in the ratio of ca. 2:3.



(262)

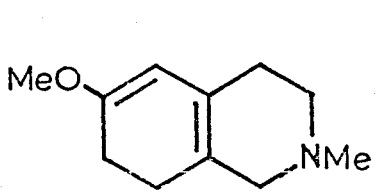


(263)

Separation of the mixture of adducts was achieved by preparative thick layer chromatography on alumina plates with petroleum ether, diethyl ether (50:50) as eluent solvent. The exo adduct (262) was the least polar component and the endo adduct (263) was eluted as the more polar component of the mixture. The infrared spectra of the prepared adducts (262) and (263) show a strong band at 1680cm^{-1} (C=O stretching in an aromatic ketone). The u.v. spectra show absorptions at λ_{max} 210(,14000); 245(15,000) and 280nm (1,800) [λ_{max} for acetophenone = 243nm[239]]. The n.m.r. spectra include singlets representing one olefinic proton, the O-methyl group and the N-methyl group. The exo adduct (262) was characterised as its methiodide (m.p. 250-251°C) and the endo adduct (263) as its picrate [m.p. 212°C (dec)].

3) With N-phenyl maleimide.

On heating the isomerisation mixture containing the conjugated methoxy diene (250) with N-phenyl maleimide in refluxing toluene a mixture of isomeric adducts (264) and (265) was obtained after column chromatography over neutral alumina.



(250)

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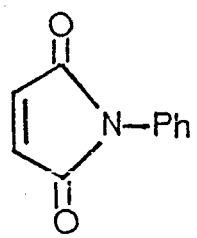
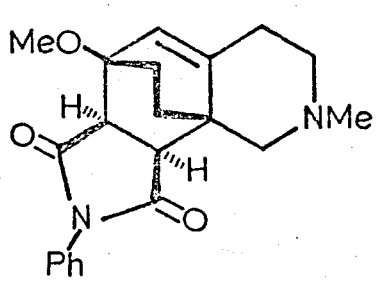
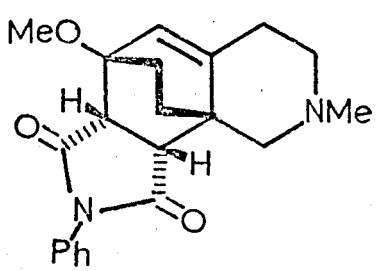




(264)



(265)

The mixture of adducts could not be separated into the analytically pure epimers by column chromatography nor by fractional recrystallisation of a mixed picrate salt. The infrared spectrum of the mixture of adducts showed a strong carbonyl absorption at 1710cm^{-1} together with a weaker absorption at 1775cm^{-1} indicative of the succinimide structure.[240,241] The nmr spectrum showed N-methyl resonances together with singlets for the olefinic protons of both isomers.

4) With other dienophiles.

(a) With p-benzoquinone (A).

No expected Diels-Alder adduct was isolated when the conjugated methoxy diene (250) was heated under reflux with p-benzoquinone in benzene. Extensive aromatisation of the diene (250) occurred to afford aromatic material. Quinhydrone structure was also obtained suggesting that the p-benzoquinone was dehydrogenating the diene rather than undergoing Diels-Alder addition.

(b) With coumarin (B).

Extensive periods of reflux of the conjugated diene (250) with coumarin in xylene yielded no isolatable Diels-Alder adduct; only aromatised diene and coumarin were obtained.

(c) With anisylidene acetone (C).

Extensive reflux of the conjugated diene (250) with anisylidene acetone[242] in xylene did not yield any Diels-Alder cycloadduct; aromatised diene and anisylidene acetone being the only compounds isolated.

(d) With tetracyanoethylene (T.C.N.E.) (D).

When the conjugated methoxy diene (250) was heated under reflux with T.C.N.E. in both tetrahydrofuran and benzene and the resultant dark oily product chromatographed on neutral alumina a bright pink band was seen to pass down the column and was eluted and obtained as a crimson oil.

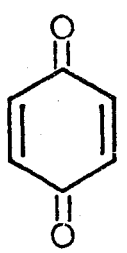
Infrared analysis indicated the presence of conjugated diene (250) and a weak nitrile absorption at 2200cm^{-1}. The n.m.r. spectrum was identical with the starting isomerisation mixture. The mass spectrum confirmed that the diene (250) was indeed present and no molecular ion for the expected adduct was seen. It is considered that some form of charge-transfer complex had been formed perhaps involving the tertiary amine lone-pair as donor and the dienophile as acceptor which could not be progressed to a Diels-Alder adduct.

(e) With 4-phenyl-triazoline-3,5-dione (P.T.A.D.) (E).

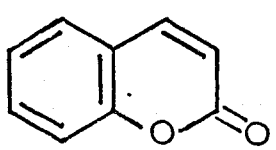
Addition of P.T.A.D. (generated by oxidation of 4-phenylurazole with t-butyl hypochlorite[243]) in methylene chloride to the conjugated methoxy diene (250) at -30°C resulted in rapid decolourisation of the deep-red triazoline dione solution. After work-up a tan-coloured amorphous solid was obtained. Spectroscopic analysis showed that no expected Diels-Alder adduct was present and polymerisation appeared to have occurred.

(f) With dimethylacetylenedicarboxylate (D.M.A.D.) (F).

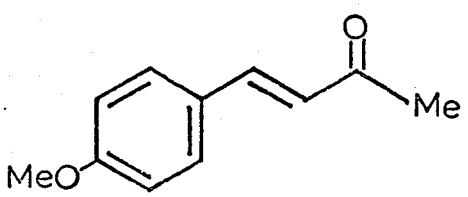
When the isomerisation mixture containing the conjugated diene (250) was heated with D.M.A.D. in toluene at 50°C for 24h a tan coloured oil was obtained which was shown by t.l.c. and spectroscopic analysis to be starting materials, no Diels-Alder adduct was obtained.



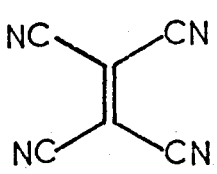
(A)



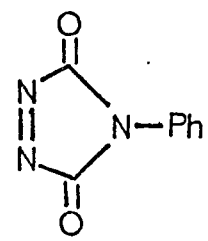
(B)



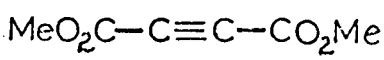
(C)



(D)

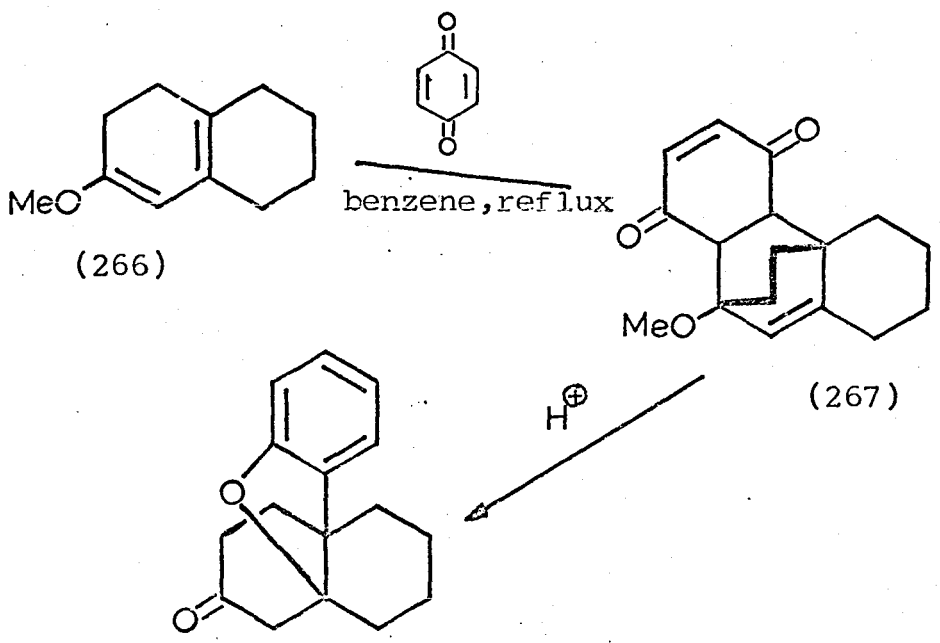


(E)



(F)

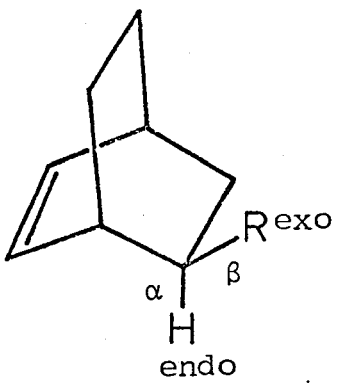
It would seem from the lack of reactivity of the diene (250) with dienophiles (A), (D), (E) and (F) that both the steric bulk of the dienophile and the presence of the tertiary amine function play a part in preventing the formation of a cycloaddition product. In general, the Diels-Alder reaction is reversible, and in the case of steric hindrance to addition, as here equilibrium clearly lies on the side of dissociation. A.J.Birch and co-workers[225] have reported that the Diels-Alder addition of benzoquinone (A) to the hexahydronaphthalene (266) gave the adduct (267) in rather poor yield (ca. 6%), the adduct was not obtained analytically pure but was rearranged under acid conditions to the benzofuran (268).



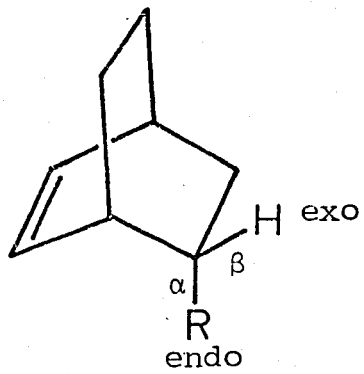
(266) (267) (268)

5) Stereochemical and Spectroscopic aspects.

The terms exo and endo are used here and throughout this discussion to designate epimeric Diels-Alder adducts and have the same stereochemical connotation as for the exo and endo-bicyclo[2.2.2]-oct-2-enes (269) and (270) respectively.



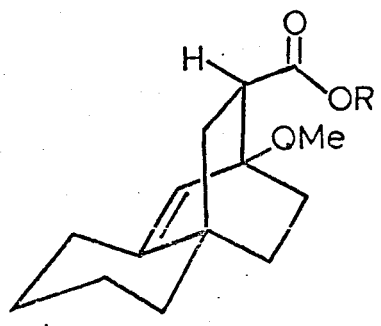
(269)



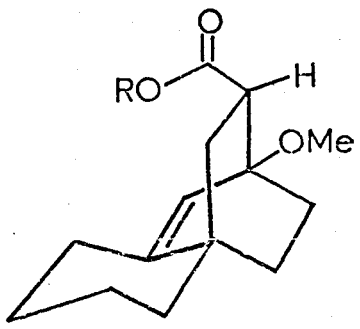
(270)

In the exo- and endo-adducts, the substituent (R) is respectively cis- and trans- to the ethano bridge. The alternative symbols α and β are also employed to indicate endo- and exo- dispositions relative to the C=C double bond by analogy with the terminology used for the thebaine adducts (cf. Introduction p.28).

The n.m.r. spectra of the ketones (260) and (261) show features analogous to those reported for the carbocyclic exo- and endo-adducts, (234) and (235).[230]



(234)



(235)

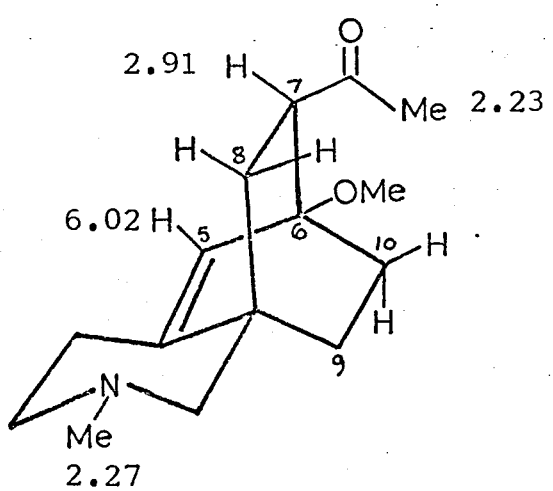
The ethyl esters, (234; R=Et) and (235; R=Et), showed olefinic proton resonances at δ5.78 and 5.67. The corresponding methyl esters showed methyl signals at δ3.64 and 3.53. The high field signals (δ5.67 and 3.53) were assigned to the endo- isomers since shielding of the methyl

protons by the double bond, and of the vinyl proton by the carbonyl group were anticipated.[230]

The stereochemistry of the cycloadducts with methyl vinyl ketone was assigned on the basis of p.m.r. and a study of molecular models. In the endo- isomer (261) the acetyl methyl group is able to come closer to the C=C than when the acetyl is exo (260). During free rotation of the endo-acetyl the methyl group spends more of its time in the shielding zone of the C=C than in the deshielding zone. Hence we allocate δ2.10 to the endo-acetyl methyl and δ2.23 to the exo-acetyl methyl.

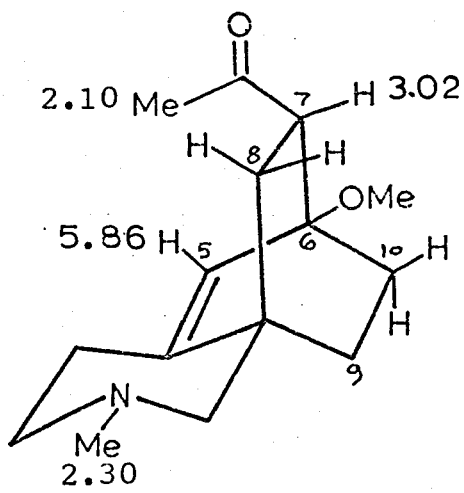
Similarly the C-5 olefinic proton is closer on average to the endo carbonyl than the exo carbonyl. During the free rotation of the endo-acetyl carbonyl group, the olefinic proton will spend more of its time in the C=O shielding zone than in its deshielding zone. Hence we assign δ5.86 to the olefinic proton of the endo-isomer (261) and δ6.02 to that of the exo-isomer (260). These independent assignments tally with the spectra.

Furthermore the chemical shift and splitting pattern of the C-7 protons was in agreement. In structure (260) the C-7 acetyl group is exo and the C-7 proton is endo. In this position the C-7 proton is more shielded by the C=C than when it is exo. We therefore allocate the C-7



(260)

exo isomer



(261)

endo isomer

exo proton to the δ3.02 signal and the C-7 endo proton the δ2.91 signal. This effect has also been shown to be present in the spectra of bicyclo[2,2,2]octenes[102,244,245] and bicyclo[2.2.1]heptenes.[246]

The n.m.r. signal for the C-7H in each isomer appears as a quartet with further fine splitting (J≐1.5Hz) evident in the case of C-7Hα in (260). This fine splitting is likely to be due to long-range coupling, through bonds making a planar-W,[247] to the C-10 Hα in (260). No similar W is present in (261).

The C-7 Hα quartet in (260) results from apparent coupling of $J_{7\alpha,8\alpha}$ 11.5Hz and $J_{7\alpha,8\beta}$ 4.5Hz, the larger values in accord with a dihedral angle about 0^{o} (Karplus equation).[248] In (261) the C-7Hβ quartet shows apparent coupling of $J_{7\beta,8\beta}$ 9Hz, $J_{7\beta,8\alpha}$ 6Hz. These may not be the true values of the coupling constants since the H_7 8α Hβ system may be of the ABX type rather than AMX. Unfortunately the AB (or AM) region cannot be examined because the $H_{8\alpha}$ and $H_{8\beta}$ proton signals are obscured by an envelope of other proton signals.

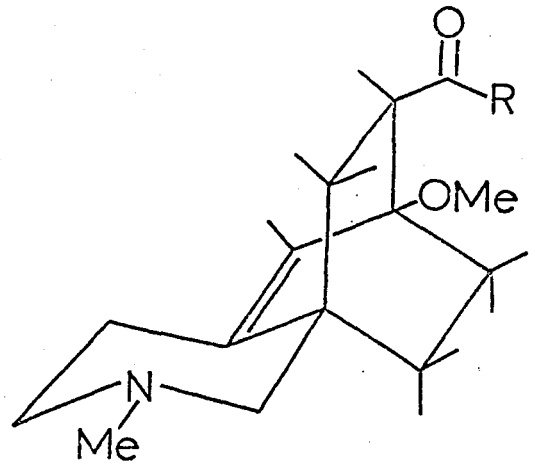
The above figures are summarised in Table 1.

In the phenyl vinyl ketone adducts (262) and (263) similar features are shown. Long range coupling of the 7αH was again observable for one isomer only, i.e. the exo-isomer (262). Also the proton was more shielded than the 7βH in (263), and so was the C-5 olefinic proton in the endo-isomer (263) compared with that in (262) (see Table 1).

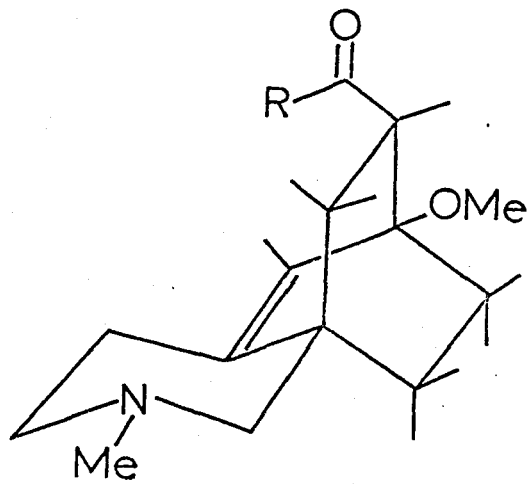
The n.m.r. spectrum of the maleimide adducts (264) and (265) showed singlets attributable to an N-methyl group at δ2.36 two O-methyl singlets at δ3.54 and 3.51 and two broad olefinic singlets at δ6.12 and 5.95. The signal at δ6.12 was assigned to the exo-adduct (264) and that at 5.95 to the endo-adduct (265) shielding of the C-5 olefinic proton in the endo-adduct (265) by the carbonyl group at C-7 being analogous to the ketone adducts previously discussed. In addition the C-7 Hα and C-8 Hα protons in the exo-adduct (264) appear as a pair of doublets (J 9Hz) at δ2.85 and δ3.15 and the C-7 Hβ and C-8 Hβ protons

TABLE 1

N.m.r. data for isomeric ketone adducts.



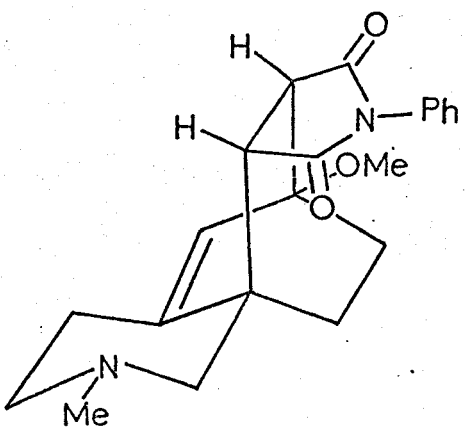
7β-epimer (exo)



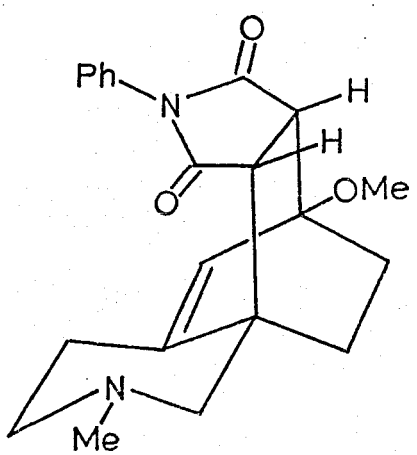
7α-epimer (endo)

ISOMER	No.	R	%	H-7α	H-7β	H-5	COR		$J_{7\alpha,8\alpha}$	$J_{7\beta,8\beta}$	$J_{7\alpha,8\beta}$	$J_{7\beta,8\alpha}$	$J_{7\alpha,10\alpha}$
7β (exo)	260	Me	38	δ2.91	-	δ6.02	δ2.23		11.5Hz	-	4.5Hz	-	1.5Hz
7α (endo)	261	Me	62	-	δ3.02	δ5.86	δ2.10		-	9Hz	-	6Hz	-
7β (exo)	262	Ph	32	δ3.56	-	δ6.03	m, p	o	12.0Hz	-	4Hz	-	1.5Hz
							7.2	8.08					
7α (endo)	263	Ph	67	-	δ3.76	δ5.83	7.33	7.85	-	9.5Hz	-	6Hz	-

in the endo-adduct (265) also as a pair of doublets (J 9Hz) at δ3.35 and δ3.20. The higher field pair of doublets assigned to the exo-adduct due to shielding of the endo protons by the C=C double bond. In this case it was observed that the exo:endo product ration was 50:50. This is in contrast to the higher proportion of the endo-adducts obtained from the ketones already discussed (i.e. 62% endo from M.V.K. and 67% endo from phenyl vinyl ketone). This was attributed to the unfavourable 1,3 type interaction the maleimide carbonyl would experience, particularly with the heterocyclic NMe or N lone-pair, when approaching to give the (normally preferred) endo stereochemistry.



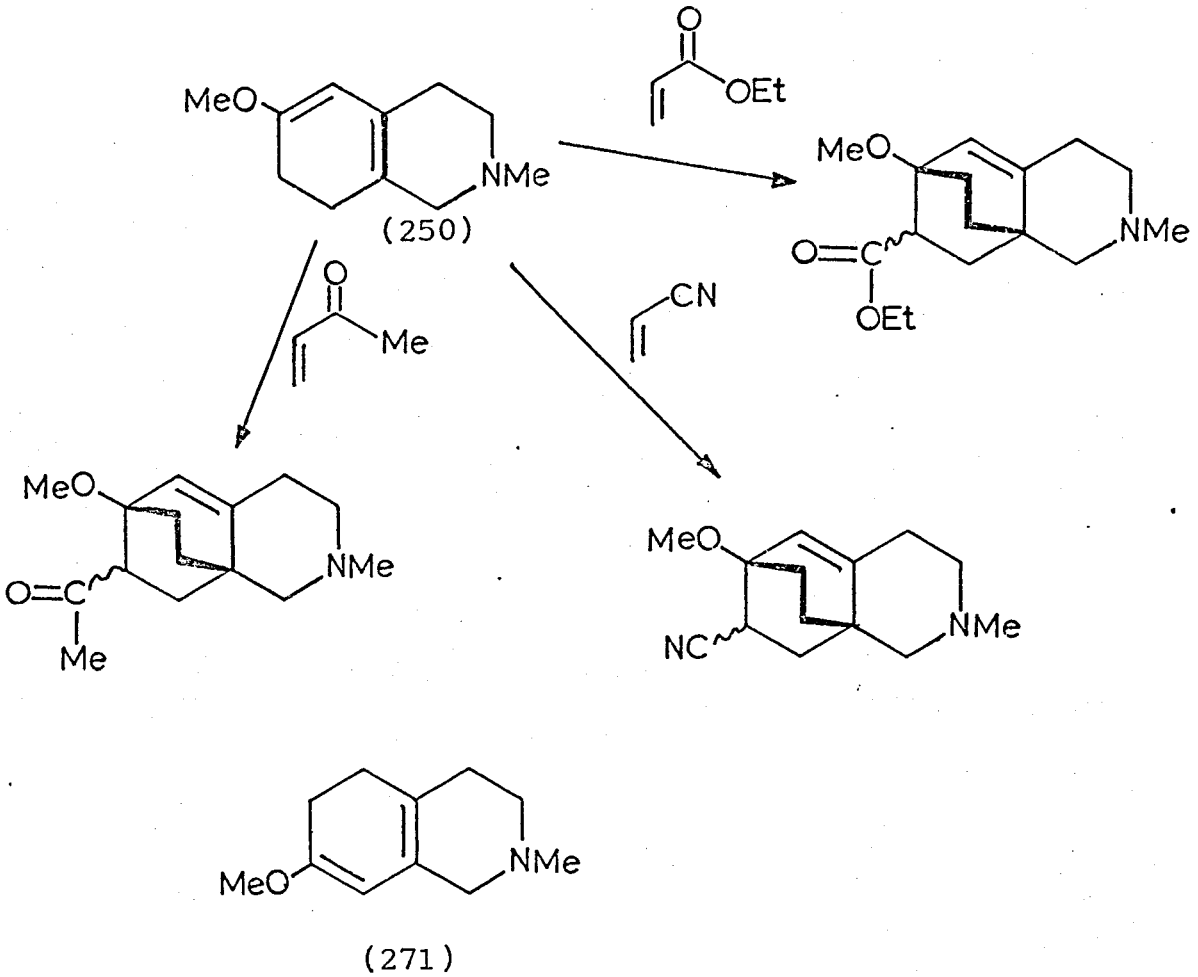
(264)



(265)

Following our successful syntheses of the Diels-Alder adducts a paper appeared in the literature by T.A.Crabb and J.R.Wilkinson[249] in which they reported carrying out one reaction identical with ours namely the Diels-Alder reaction of the 6-methoxy-diene (250) with methyl vinyl ketone. They obtained the exo and endo ketones (260) and (261). Spectroscopic data showed very close agreement with our data and their conclusions regarding stereochemical assignments also agreed with ours. They had not studied the cycloaddition of phenyl vinyl ketone

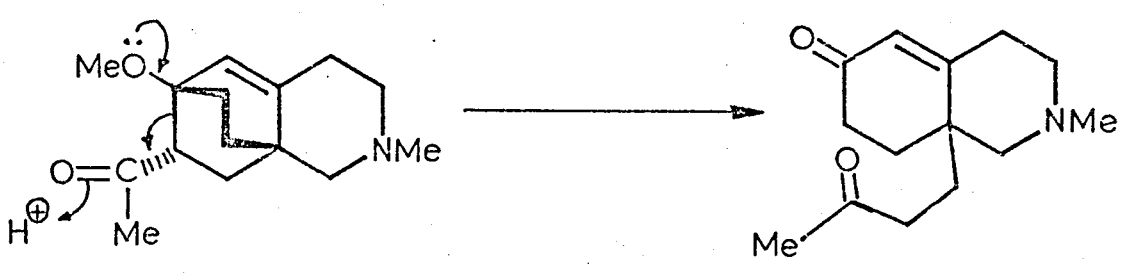
nor the other dienophiles we have described above. However, in addition to using methyl vinyl ketone they also succeeded in cycloadding ethyl acrylate and acrylonitrile. They had also effected similar Diels-Alder reactions with the 7-methoxy diene (271) as depicted in scheme 25 .



(271)

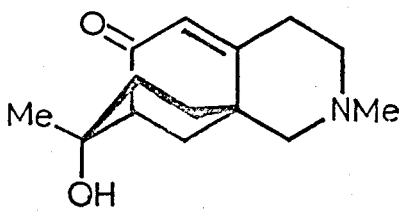
Scheme 25.

An acid-catalysed ring opening of (261) to (272) reported by Crabb and Wilkinson[249] confirmed the acetyl group was a C-7 and not at C-8.

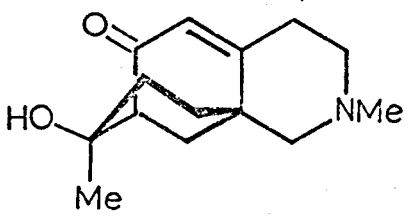


(261) (272)

Acid-catalysed rearrangements of a similar type have previously been observed with some thebaine adducts[314] and with adducts of 1,3-dihydroanisoles and methyl vinyl ketone.[227] Further acid treatment of (272) gave the two diastereoisomeric hydroxy compounds (273) and (274) arising via intramolecular aldol condensation.

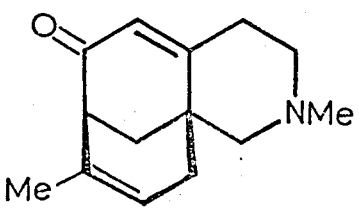


(273)



(274)

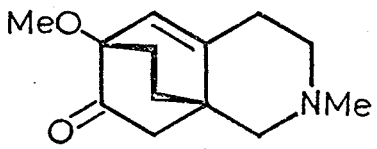
The axial alcohol (273) readily dehydrated to afford the dehydration product (275); the equatorial alcohol (274) proved resistant to similar dehydration conditions.



(275)

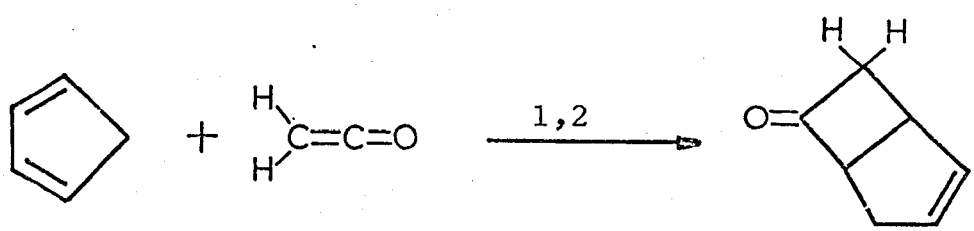
(C) Addition of the elements of Ketene to the hexahydroisoquinoline system.

Addition of the elements of ketene, $CH_2=C=O$, to 1,2,3,4,7,8-hexahydro-6-methoxy-2-methylisoquinoline would, assuming the usual regiospecificity, provide a 6,8a-ethano-bridged isoquinoline (276) with a ketone function at position 7.

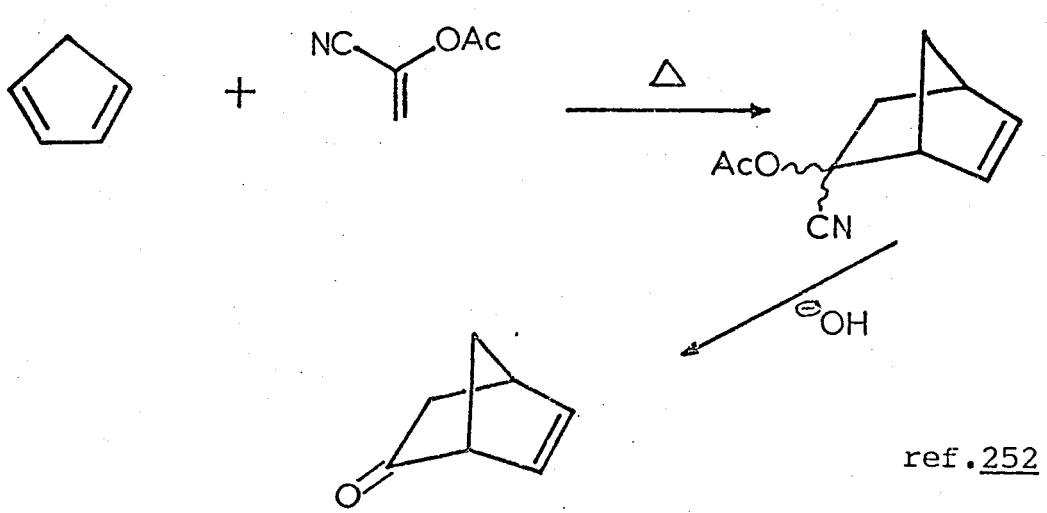


(276)

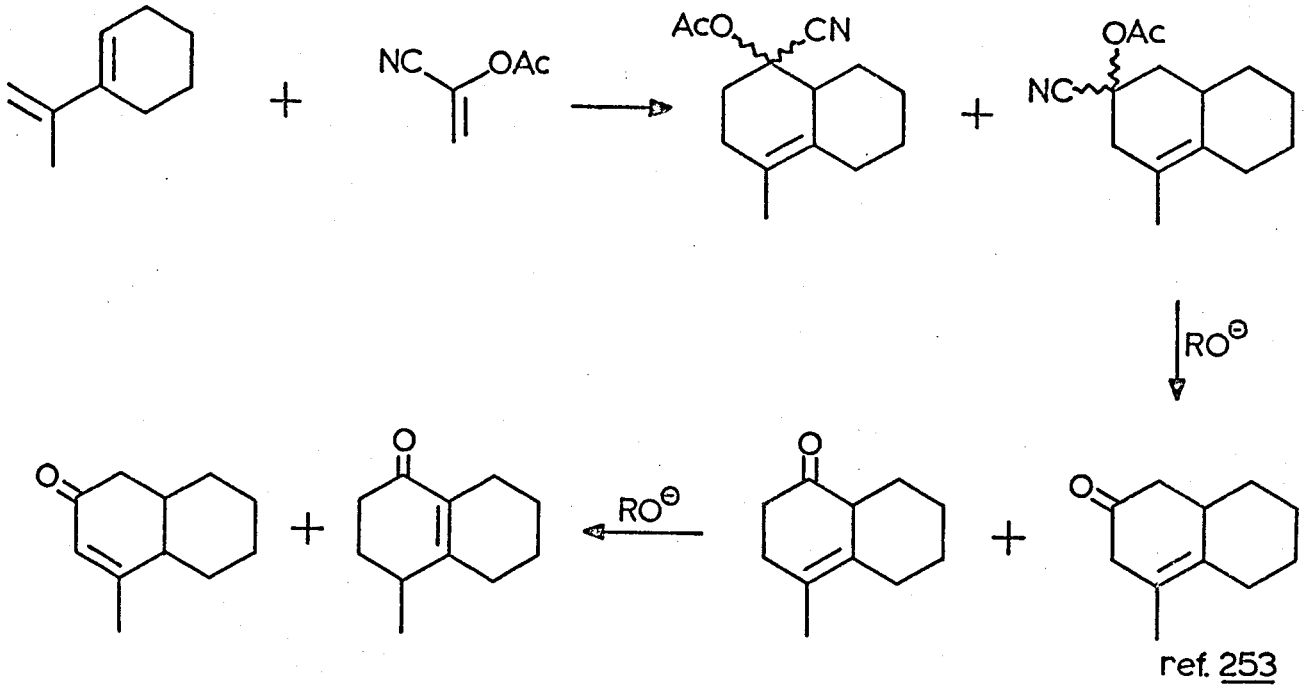
However, addition of ketene itself to conjugated dienes proceeds by 1,2-cycloaddition and not the 1,4-mode.[250]



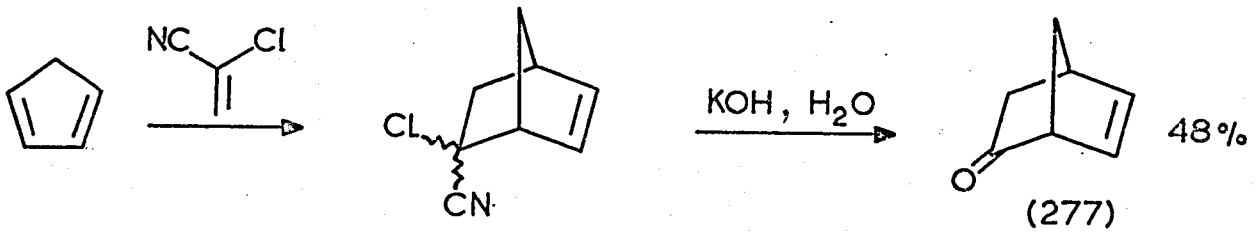
This problem has been overcome by using 2-chloro-acrylonitrile or 2-acetoxyacrylonitrile,[251] followed by hydrolysis of the resultant adducts. Examples are shown below:



ref.252



ref. 253



(277)

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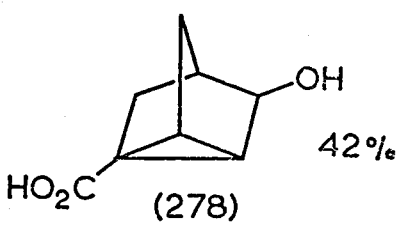
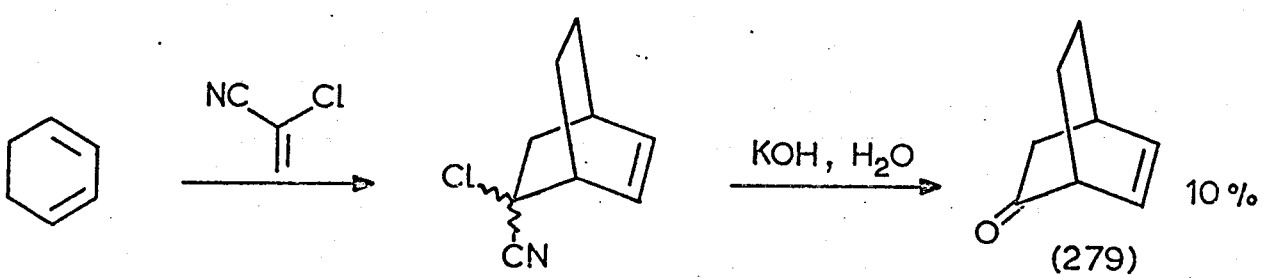


(278)

ref. 254



(279)

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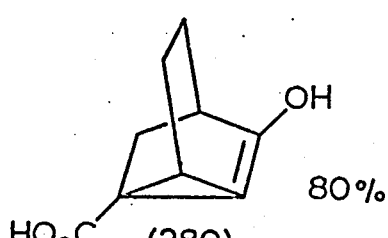
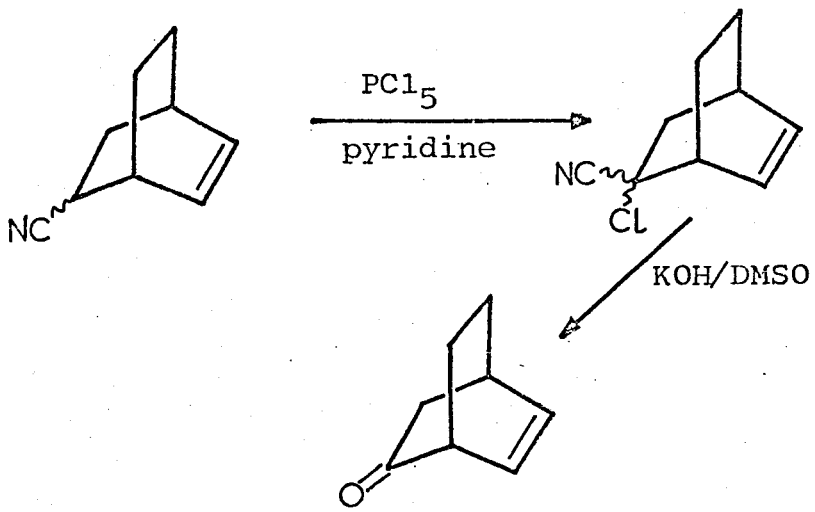


(280)

ref. 254

D.J.Brown and co-workers[255] synthesised a series of bicyclic ketones by hydrolysis of the corresponding chloronitrile adducts with DMSO-KOH. They also reported an alternative synthesis of the chloronitriles by chlorination of the corresponding acrylonitrile adducts with phosphorus pentachloride in pyridine e.g.

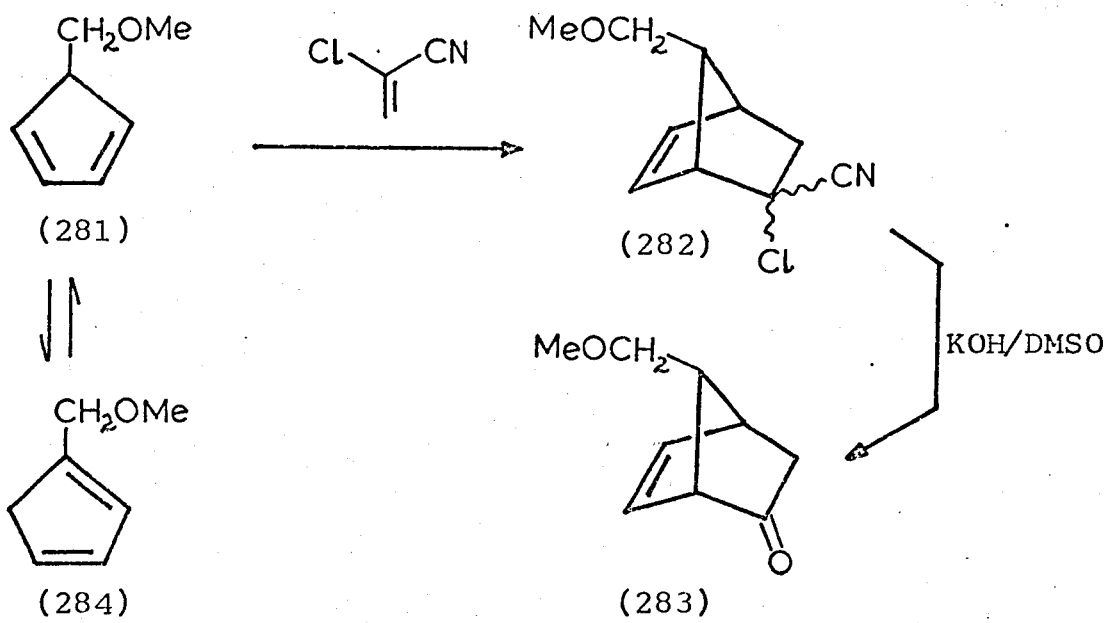


(279)

It is interesting to compare the results of Paarsivirta and Krieger (ref. 254), equation above, with those of Brown et.al.[255] for the bicyclic ketones (277) and (279). The conditions employed by the former workers (aqueous potassium hydroxide) for the conversion of the α-chloronitrile to the ketone would be expected to favour a larger S_N1/S_N2 ratio than under those employed by Brown et.al. (DMSO-KOH), which should favour a bimolecular displacement of chloride by hydroxide. This argument is based on the known ability of DMSO to enhance the nucleophilicity of anions, relative to reactions in protic solvents,[256] and is born out by the isolation of the hydroxy acids (278) and (280) by Paarsivirta and Krieger and by the high yields obtained for ketones (277) and (279) obtained by Brown et.al.

In their synthesis of prostaglandins E.J.Corey and co-workers[257] synthesised the key intermediate bicyclic ketone (283) via Diels-Alder condensation of the substituted cyclopentadiene (281) with 2-chloroacrylonitrile followed by

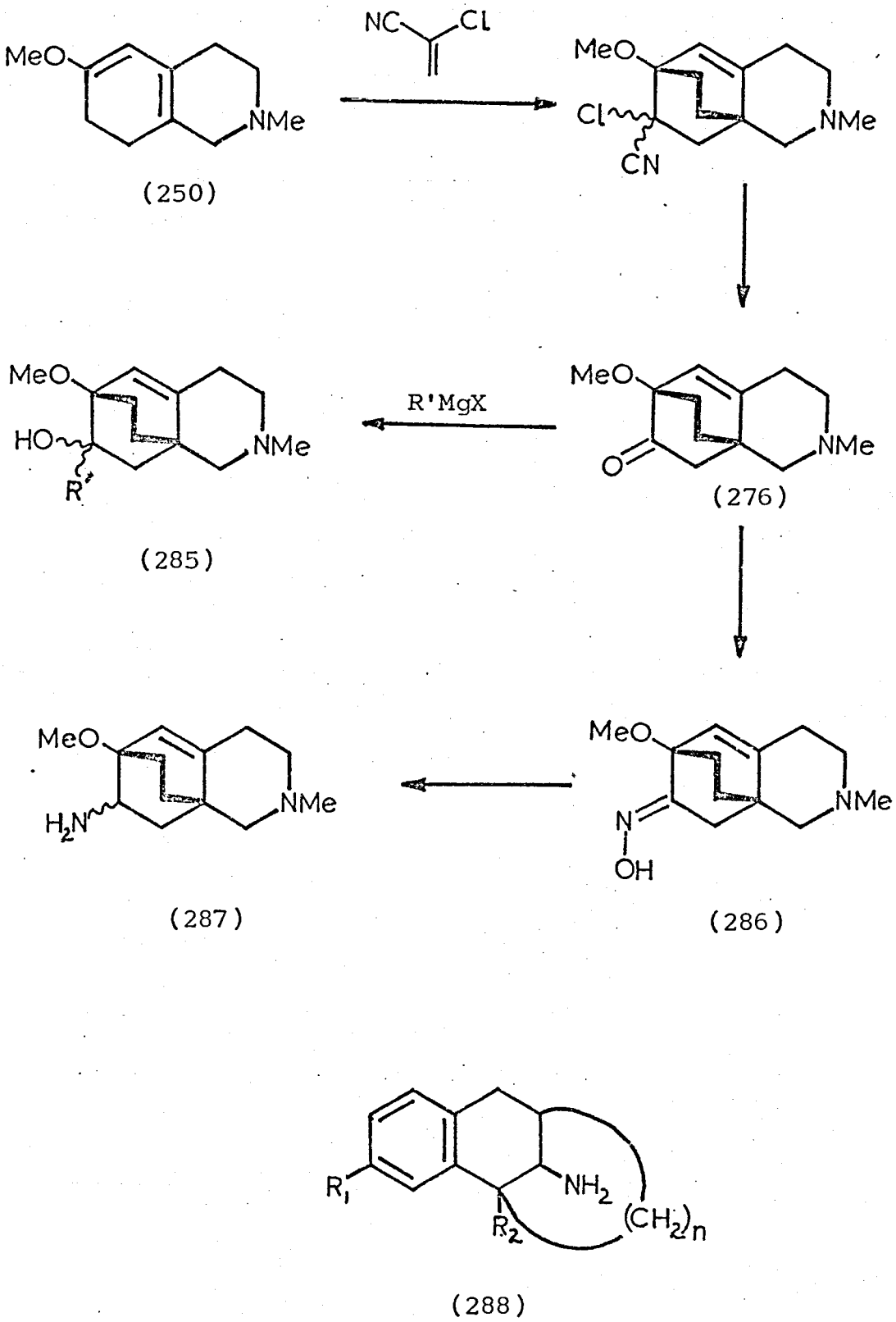
subsequent hydrolysis of the chloronitrile adduct (282) with DMSO-KOH.



(281) (282) (284) (283)

Corey et.al. found that the Diels-Alder condensation was catalysed by dry cupric fluoroborate which allowed the reaction to proceed at $0^{o}C$ in >90% yield without appreciable concurrent isomerisation of the cyclopentadiene (281) to the more stable isomer (284).

It was of interest to us to explore the 1,4 addition of a ketene equivalent to the conjugated methoxy diene (250) since the resultant bicyclo [2.2.2] octenone derivative (276) not only would be of interest itself pharmacologically but could give entry into novel 7-substituted-6,8a-ethanobridged isoquinolines. Grignard reaction of the ketone (276) could afford carbinols (285) which could be evaluated for pharmacological activity. Also of interest would be the preparation of the 7-amino compound (287) via the oxime (286) which bears some resemblance to the bridged aminotetralin agonist-antagonist series of analgesics developed recently by Wyeth laboratories[258] and typified by the general structure (288).

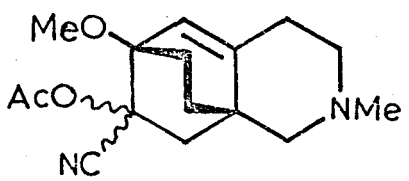

MeO
NMe
NC
Cl
Cl
CN
R'MgX
HO
R
O
H2N
N
OH
(250)
(276)
(285)
(286)
(287)

R1
NH2
R2
(CH2)n

(288)

(1) Diels-Alder reaction of 1,2,3,4,7,8-hexahydro-6-methoxy-2-methylisoquinoline with Ketene equivalents.

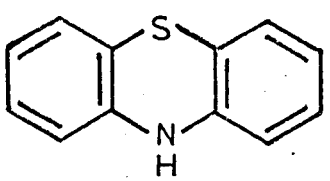
Initially we investigated the Diels-Alder condensation of 2-acetoxyacrylonitrile to the conjugated diene (250). Since 2-acetoxyacrylonitrile was not commercially available we synthesised it from chloroacetaldehyde by the method of Nowak.[251] The freshly distilled 2-acetoxyacrylonitrile was employed directly in the Diels-Alder condensation with the conjugated diene (250) in the absence of solvent at 100°C and in benzene under reflux. However, in both cases only a black viscous tar was obtained from which no pure products could be isolated and none of the expected Diels-Alder adduct (290) was seen to be present; extensive polymerisation of the reactants appeared to have occurred.



(290)

The Diels-Alder condensation of the methoxy diene (250) with 2-chloroacrylonitrile was carried out by three methods.

(1) The methoxy diene was heated at 100°C with excess 2-chloroacrylonitrile together with a trace of phenothiazine for 6 hours. The inclusion of phenothiazine was recommended by D.A.Evans et.al.[259] and acts as a stabiliser.

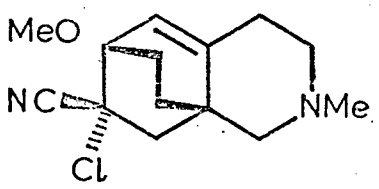


Phenothiazine

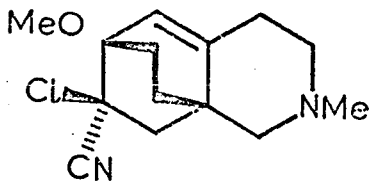
(2) The diene was heated under reflux in benzene with 2-chloroacrylonitrile for periods of 6-24h.

(3) The diene was stirred at room temperature with 2-chloroacrylonitrile in anhydrous tetrahydrofuran in the presence of dry powdered cupric fluoroborate as catalyst for 12h.

Method (1) produced excessive amounts of intractable tarry material which made product purification difficult. Methods (2) and (3) produced satisfactory amounts of the required chloronitrile adduct. The most productive method of synthesis involved dropwise addition of the diene dissolved in anhydrous benzene to 2-chloroacrylonitrile (5M equiv.) in refluxing benzene together with a trace of phenothiazine and heating the resultant mixture under reflux in a nitrogen atmosphere for 18h. Removal of the benzene and excess dienophile *in vacuo* and column chromatography of the resultant dark oily mass over neutral alumina eluting with petroleum ether and diethyl ether afforded a high yield (80%) of the chloronitrile adduct as a mixture of epimers ratio 2:1 differing in *exo*-*endo* orientation of the cyano and chloro groups. The epimers were assigned the structures (291) and (292).



(291)

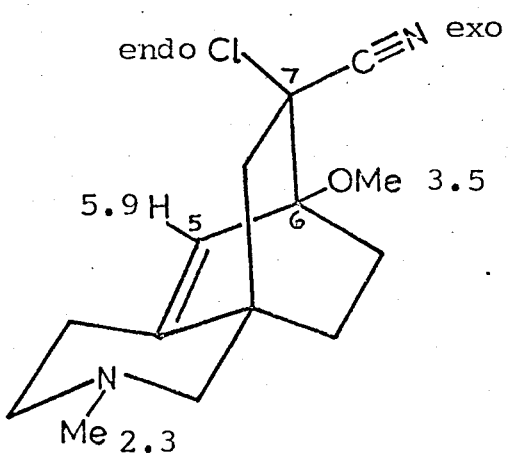


(292)

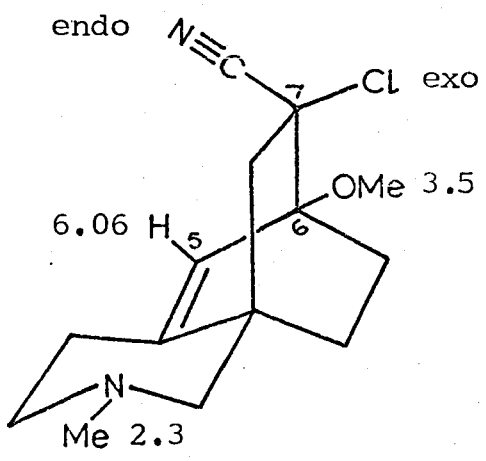
Recrystallisation of the mixture of epimers from diethyl ether/light petroleum resulted in their co-crystallisation m.p. 98-100°C. The co-existence of epimers within the same crystal structure has also been reported by S.W.Pelletier *et.al.*[260] Separation of the *exo*-nitrile (291) and the *endo*-nitrile (292) could not be

achieved by chromatography or by repeated crystallisation. However, a separation was accidentally achieved by virtue of the different rates of hydrolysis of the epimers, which is discussed below. The infrared spectrum of both the prepared adducts showed a sharp nitrile absorption at 2250cm^{-1} and C=C double bond at 1650cm^{-1}.

The 90MHz n.m.r.spectrum of the mixture of adducts (291) and (292) shows singlets at δ3.5 and 2.3 assigned to the O-methyl and N-methyl groups respectively. The olefinic region showed two signals at δ5.9 and 6.06 in the ratio of 2:1. The olefinic signal at δ5.9 was assigned to the exo-nitrile endo-chlorine adduct (291) and that at δ6.06 to the endo-nitrile exo-chlorine adduct (292). Unlike the endo-ketone adducts discussed earlier (cf. p.131), the endo-nitrile (292) gives a C-5 olefinic signal at slightly lower field than the exo-isomer (291). The C≡N group in the exo-nitrile adduct (291) exerts a shielding effect on the olefinic proton (δ5.9) but has virtually no effect on the olefinic proton in the endo-nitrile (292). The shielding cone of the C≡N triple bond has its axis common with that of the C≡N bond (ie. the converse of the situation with a double bond).

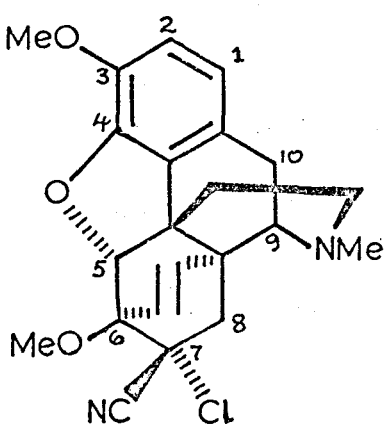


(291)

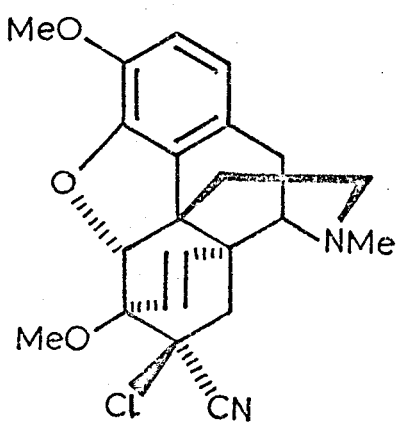


(292)

Similar shielding of olefinic protons by exo-nitrile groups in related 6,8a-ethano-bridged isoquinolines has been observed.[249] The effect of the 7α-chlorine atom in (291) and the 7β-chlorine atom in (292) is not clear since it has not been established in model compounds. J.W.Lewis et.al.[261] have shown that the alkaloid thebaine reacts readily with 2-chloroacrylonitrile to give a 4:1 mixture of epimeric adducts (293) and (294). The n.m.r. spectra of these adducts did not permit an assignment of stereochemistry at C-7 since in both there is an appreciable downfield shift of the signal due to H-5β.

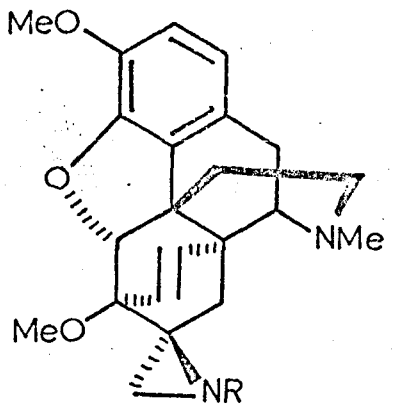


(293)



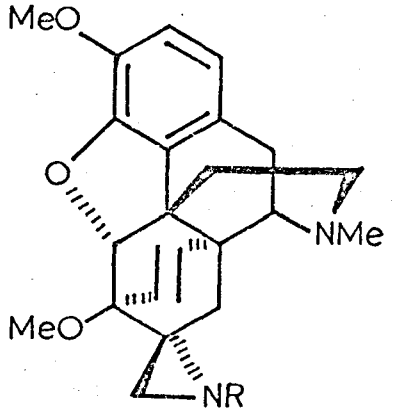
(294)

Structures of the epimeric adducts (293) and (294) were assigned from consideration of the spiroaziridines (295a) and (296a) formed by reduction of the chloronitriles with lithium aluminium hydride.[262] Cyclisation is stereospecific and results in inversion of configuration at the spiro-atom.[263] The n.m.r. spectra of the aziridines were similar but those of the p-chlorobenzoyl derivatives (295b) and (296b) showed a number of differences, from which it was established that the aziridine derived from the more abundant chloronitrile epimer had structure (295). The 7α-chloro-7β-cyano-structure (293) was thus assigned to this adduct.



(295)

a; R = H



(296)

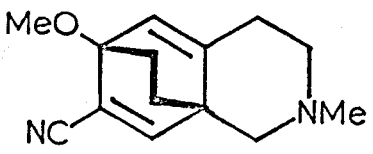
b; R = p-ClC$_6$H$_4$.CO

As was found to be the case with thebaine,[261] we found that the most abundant epimer was the 7α-chloro-7β-cyano adduct (291). It is known[264,265] that alkyl or halo groups adopt the endo position in preference to the carboxyl group. B.C.C.Cantello and J.M.Mellor[266] have also shown that halo groups adopt the endo position in preference to the carbomethoxy or cyano group. Although it may be argued that the important factor controlling the stereochemistry of addition of 2-alkylacrylic acids to dienes[265] is steric in origin it has been proposed that with halogen substituted olefins the stereochemical control is largely electronic.[266] In just the same way that multiple bonds stabilise the endo transition state relative to the exo by secondary orbital interaction,[235] halogen atoms may more effectively stabilise the endo route by mixing of the non-bonded electrons.

(2) Base-catalysed hydrolysis of the prepared chloronitrile adducts.

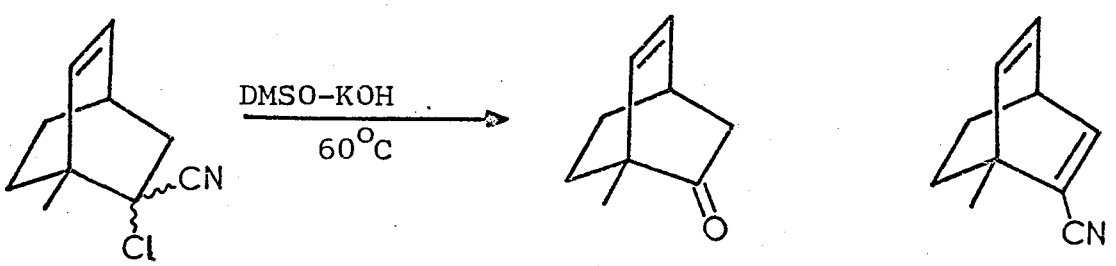
The hydrolysis of the chloronitrile adducts to the bicyclo[2.2.2]octenone derivative (276) was next investigated. When the mixture of adducts was heated in DMSO-KOH for periods of up to 48h at 100°C, t.l.c. indicated mainly starting material and two new compounds. They could not be obtained pure. Infrared analysis showed a peak at 2250cm^{-1} (C≡N) due to starting material and another weaker peak at

2210cm^{-1}. A small peak at 1730cm^{-1} was also apparent but was very weak. It was postulated on this evidence that the mixture contained unchanged starting chloronitrile together with a small trace of desired ketone and the α,β unsaturated nitrile (297) arising via elimination of HCl rather than nucleophilic substitution.



(297)

Gregson and Mirrington[267] report that hydrolysis of chloronitrile adduct (298) with DMSO-KOH under the conditions quoted by Brown et.al.[255] resulted in the recovery of the adduct (298) unchanged. However, upon heating to 60°C, the bicyclic ketone (299) was obtained in 31% yield together with the nitrile (300) in 60% yield.



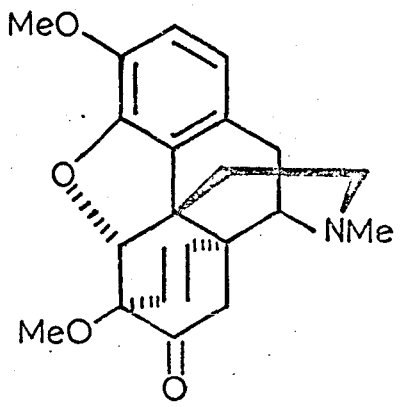
(298) (299) 31% (300) 60%

They considered that failure of the hydrolysis was due to the methyl group sterically hindering substitution at C-2. In our case a methoxy group is in the equivalent position.

Since in our case the hydrolysis of the chloronitrile adducts was not occurring in the polar aprotic solvent (DMSO), which would favour an S_N2 substitution of chloride, steric requirements of the bicyclo-octene system restricting the formation of a suitable S_N2 transition state, it was reasoned that use of a protic solvent; which would favour an S_N1 displacement of chloride could lead to a successful hydrolysis. Gregson and Mirrington[267]

hydrolysed the adduct (298) by treatment with sodium sulphide in refluxing ethanol, a reagent combination that had previously been employed by Evans et.al.[259] We refluxed the chloronitrile adducts (291) and (292) with sodium sulphide in refluxing ethanol for 24h. The product obtained after work-up was shown to be a complex mixture of five compounds by t.l.c. analysis and could not be purified adequately. The infrared spectrum of the mixture indicated a ketone absorption at 1730cm^{-1} together with C≡N absorption at 2220cm^{-1}. Preparative thick layer chromatography on alumina plates was attempted, but no ketone (276) could be isolated. The only material that could be isolated was a small quantity of crystalline material which was shown by t.l.c. and n.m.r. analysis to be the exo-nitrile (291).

The epimeric chloronitrile adducts obtained from the Diels-Alder condensation of 2-chloroacrylonitrile with thebaine (293) and (294) discussed earlier have been progressed to the 7-ketone (301) by refluxing with aqueous ethanolic sodium hydroxide.[268]



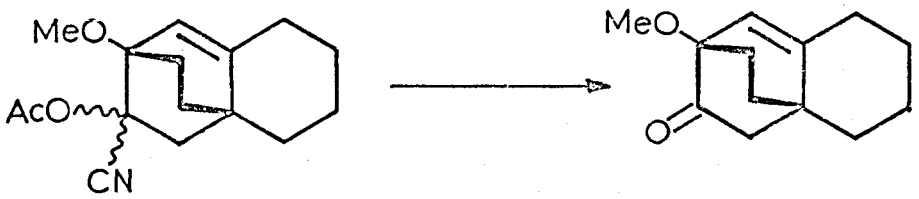
(301)

When the epimeric chloronitrile adducts (291) and (292) were heated under reflux with aqueous ethanolic sodium hydroxide only a small quantity of an oil was obtained; t.l.c. analysis indicated one compound and no starting material was apparent.

The infrared spectrum showed a strong carbonyl absorption at 1730cm^{-1}.

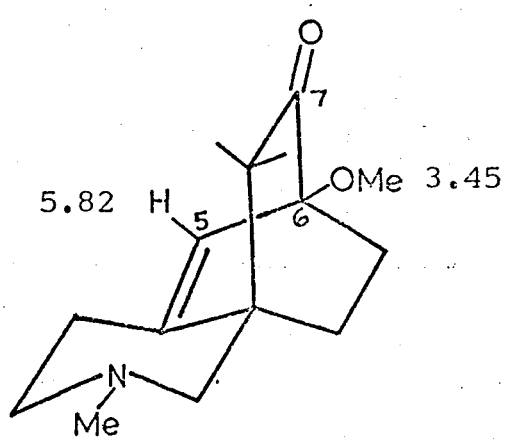
We found the most favourable hydrolysis conditions

were those employed by Rogers et.al.[269] for the conversion of the 2-acetoxyacrylonitrile adducts (302) to the ketone (303).



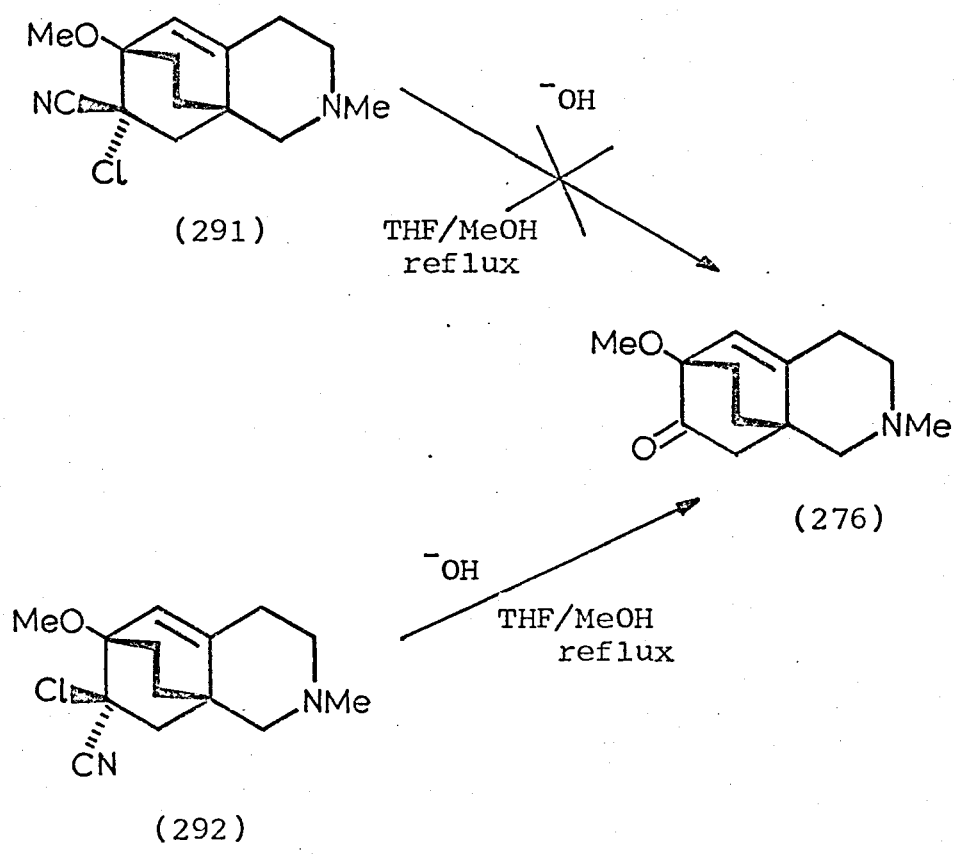
(302) (303)

When the chloronitrile adducts (291) and (292) were heated in tetrahydrofuran with methanolic KOH for 6h an oil was obtained which showed a strong ketone band in the infrared at 1730cm^{-1} together with a sharp nitrile at 2250cm^{-1}. T.l.c. analysis indicated the presence of starting material together with a new compound, which was isolated pure as a pale yellow liquid after column chromatography over neutral alumina. It gave a single peak on g.l.c., showed a strong carbonyl at 1730cm^{-1} and had λ_{max} 294nm (ε,271), characteristic of an unconjugated ketone with a double bond suitably placed for n-π^* enhancement.[269,270] The n.m.r. spectrum of the bicyclo-[2.2.2]octenone derivative (276) showed an olefinic proton at δ5.82 and a sharp methoxy at 3.45 and an N-methyl singlet at 2.30.

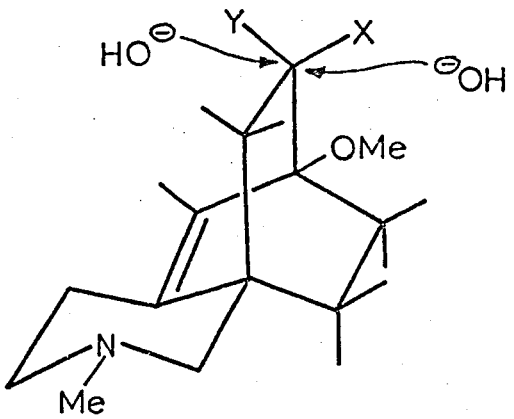


(276)

The initial eluents from the column were shown to be the exo-nitrile endo chlorine adduct (291). This suggested that the endo nitrile exo chlorine epimer (292) was undergoing hydrolysis to the ketone (276) but that under these particular reaction conditions the exo-nitrile (291) remained unchanged.



Examination of Drieding models of the respective chloronitrile adducts suggested that if some S_N2 displacement was occurring the 6,8a-ethano bridge could exert some steric hindrance for the displacement of the endo-chlorine atom in (291) by hydroxide anion. Attack from the double bond side is more favourable i.e. with the exo chlorine in (292) see Fig. 6 . Also some assistance to the loss of the exo chlorine atom may be given by the double bond through neighbouring group participation.



(291) ; X = CN, Y = Cl.

(292) ; X = Cl, Y = CN.

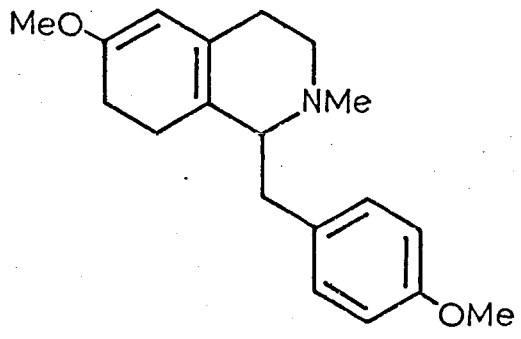
Fig.6.

When dioxan (b.p.101°) was substituted for tetrahydrofuran (b.p.65-67°) as reaction solvent it was observed that both of the chloronitrile adducts (291) and (292) underwent hydrolysis to the ketone (276); the higher reaction temperature facilitating displacement of the endo-chlorine by hydroxide.

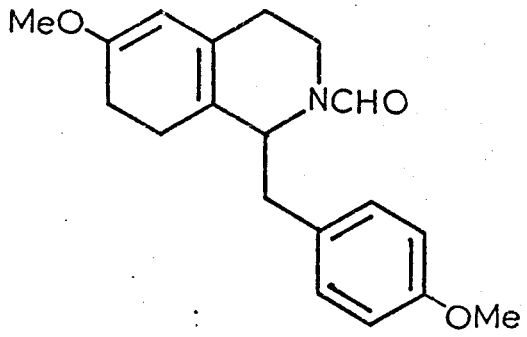
(D) Synthesis and Diels-Alder reaction of N-formyl-hexahydroisoquinolines.

Morphinan formation by acid-catalysed ring closure of 1-benzyloctahydroisoquinolines occurs in best yields with N-formylisoquinolines.[138] Yields are markedly improved over those using N-methylisoquinolines.

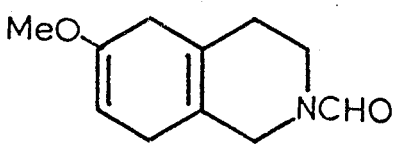
As models for the study of ring-A bridged benzylisoquinolines via (304) and (305) we examined synthesis of N-formylhexahydroisoquinolines [e.g. (306)], unsubstituted at position 1.



(304)

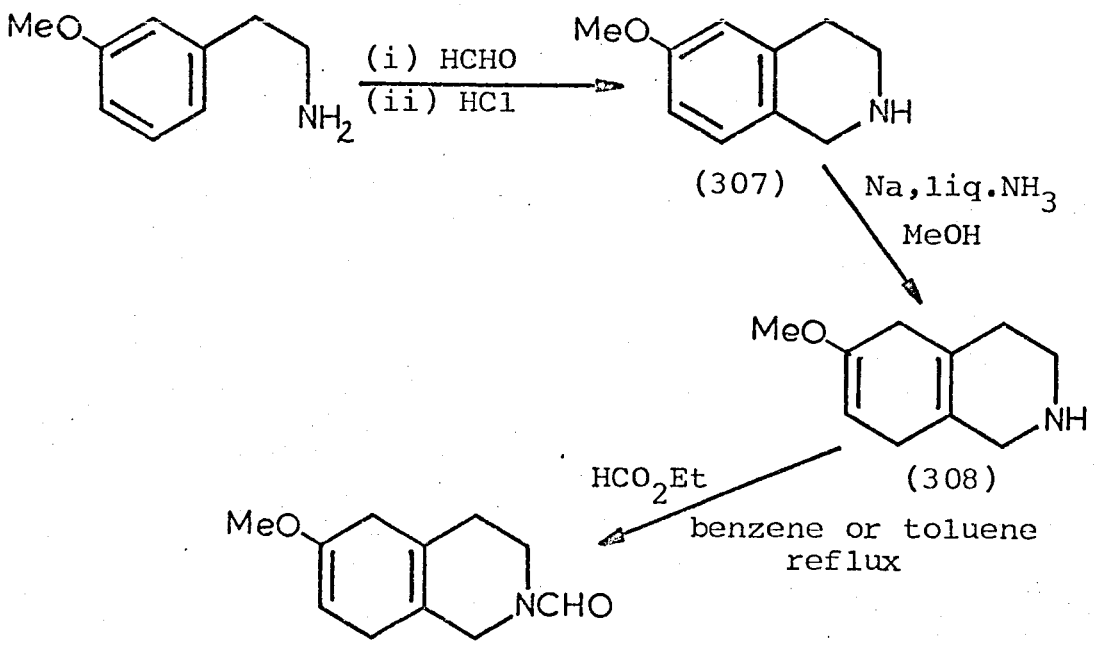


(305)



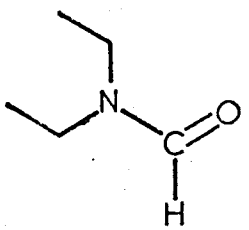
(306)

We synthesised the 6-methoxy-N-formyl-1,2,3,4,5,8-hexahydroisoquinoline (306) by the route outlined in scheme 26 . Pictet-Spengler[271] cyclisation of β-(3-methoxyphenyl)-ethylamine afforded 6-methoxy-1,2,3,4-tetrahydroisoquinoline (307). Birch reduction of (307) with sodium in liquid ammonia

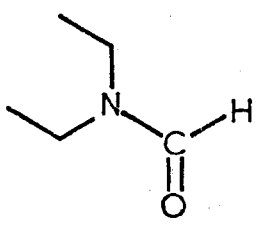


Scheme 26

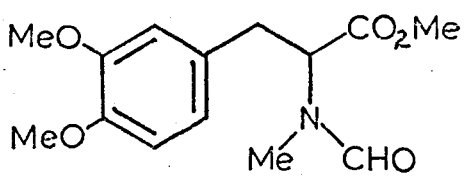
and methanol[180] afforded the hexahydro secondary base (308) in good yield (90%). Formylation of (308) was accomplished with ethyl formate[132,135] and the formyl compound (306) was isolated as a crystalline solid (m.p.57-59°). The infrared spectrum of (306) showed the amide carbonyl absorption at 1660cm^{-1} together with peaks at 1670 and 1705cm^{-1} due to the double bonds at the dihydroanisole system.[188a,241] The n.m.r spectrum showed an olefinic proton at δ4.63, a sharp methoxy singlet at 3.56, the protons at C-5 and C-8 appeared as a broad signal at δ2.65. The signal due to the proton of the formyl group appeared as two peaks in the ratio 5:4 at δ8.07 and 8.14. This may be explained by assuming two different conformations for the planar amide group (a) and (b). This phenomenon is quite common in N-substituted formamides.[272] Similar observations in the n.m.r. have also been previously reported for esters of substituted formamides[273] and the N-formylphenylethylamine derivative (309).[274]



(a)



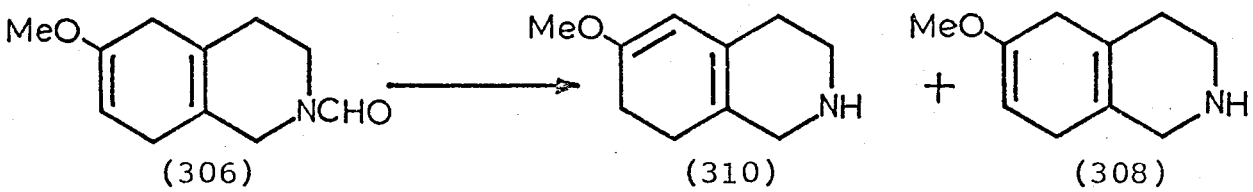
(b)



(309)

The N-formyl compound (306) was heated for 4h at 100°C in t-pentyl alcohol with potassium t-pentoxide (the isomerisation conditions employed for the N-methyl analogue[234]). The u.v. spectrum of the product showed the presence of the conjugated diene chromophore at λ_{max} 272nm. The infrared spectrum showed two strong bands at 1670 and 1615cm^{-1}

together with a peak at 3300cm^{-1}. The n.m.r. clearly showed the absence of a formyl proton resonance, and a one proton singlet at δ2.2 which was exchangeable with D_2O indicated NH. Cleavage of the formyl group had occurred during the isomerisation conditions. The presence of the conjugated and unconjugated dienes (310) and (308) was confirmed by the vinyl proton resonances at δ4.72 and 4.62 in the ratio ca. 2:1.



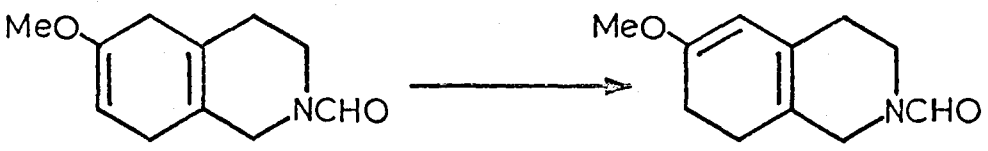
(306) (310) (308)

2 : 1

The isomerisation is similar to that of unconjugated dihydroanisoles to conjugated products by potassamide or sodamide in liquid ammonia.[275] The cleavage of the formyl group was not expected due to the bulky nature of the t-amylate anion, however it must be acting as a nucleophile in order to produce the secondary amines (308) and (310).

We sought for alternative isomerisation conditions for the isomerisation of the unconjugated N-formylhexahydroisoquinoline. It has been reported[276] that potassium t-butoxide shows strongest basicity in the polar aprotic solvent dimethylsulphoxide (DMSO). In fact this combination is so active in forming carbanions that temperatures may be lowered 100-150°C to obtain rates comparable to those obtained with the oxide in t-butyl alcohol. The reason for the high basicity in DMSO is that in protic or non-polar solvents t-butoxide exists as an aggregate whereas in DMSO it is near monomeric. Crown ethers are also effective, acting as ligands for the cation. When the unconjugated hexahydroisoquinoline (306) was isomerised with a catalytic amount of potassium t-pentoxide (freshly prepared from potassium metal and t-pentyl alcohol and dried at 80-100°C and 0.1mm) in dry DMSO the conjugated diene(311) was obtained together with the unconjugated isomer (306, ca.

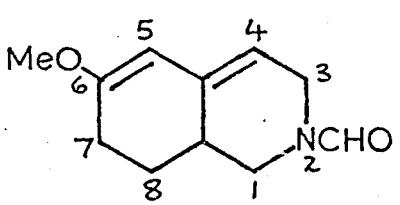
20-25%) as seen by the n.m.r. spectrum of the isomerisation mixture. The isomerisation mixture showed λ_{max} 272nm and



(306) (311)

a strong band in the infrared at 1620cm^{-1} indicated the presence of the conjugated diene (311). The product from the isomerisation was freed of any excess DMSO by successive partitioning between ether and water and thoroughly dried *in vacuo*.

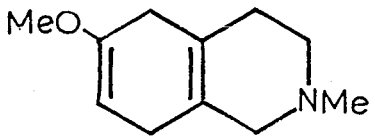
Another isomerisation medium we employed was potassium *t*-butoxide in dimethylformamide. Upon addition of the unconjugated *N*-formyl diene (306) to this medium at room temperature a deep orange-red solution formed indicating carbanion formation. After 2h at room temperature and heating for 30 minutes at 100°C the solution was quenched into water. U.v. spectral analysis showed absorption at λ_{max} 245nm (ε, 7000) indicating heteroannular conjugation as in structure (312). (Calc. λ_{max} 240nm). In the n.m.r. spectrum two singlets at δ4.65 (sharp) and 5.20 (broad), representing two olefinic protons, are respectively assigned to the C-5 and C-4 protons of structure (312).



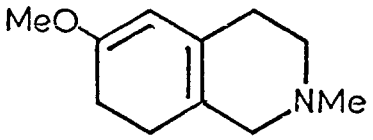
(312)

Birch *et.al.*[277] have obtained exocyclic conjugated dienes with relatively low u.v. extinction coefficients (ε < 6000), by isomerising various unconjugated 3-alkyldihydroanisoles with sodamide in liquid ammonia. Crabb and Wilkinson[234] have also observed that isomerisation of compound (248) with potassamide in liquid ammonia gave a complex mixture

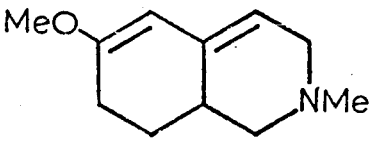
of products. The major product being the conjugated diene (250) and one of the minor compounds the heteroannular conjugated compound (313) which showed λ_{max} 245nm (ε, 7100).



(248)

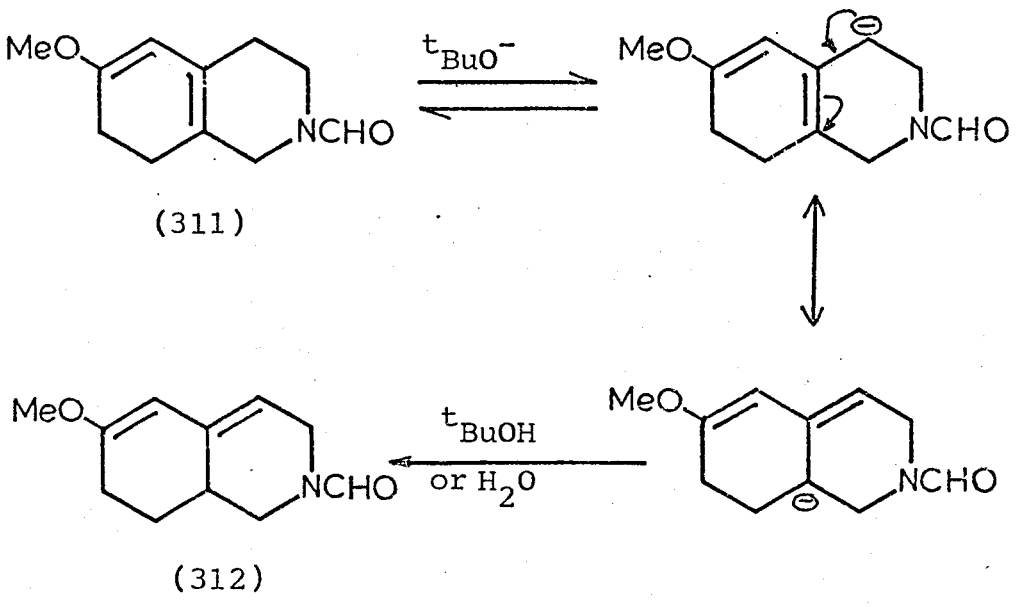


(250)



(313)

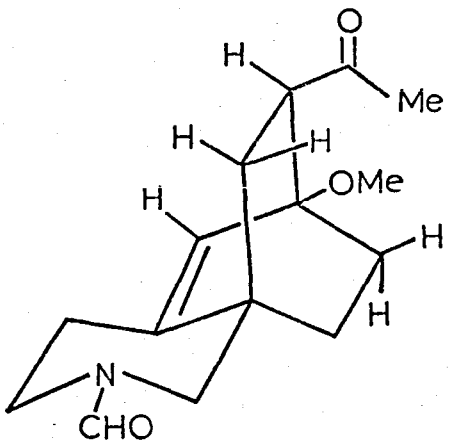
The heteroannular diene (312) can arise by further isomerisation of the homoannular diene (311) as shown below.



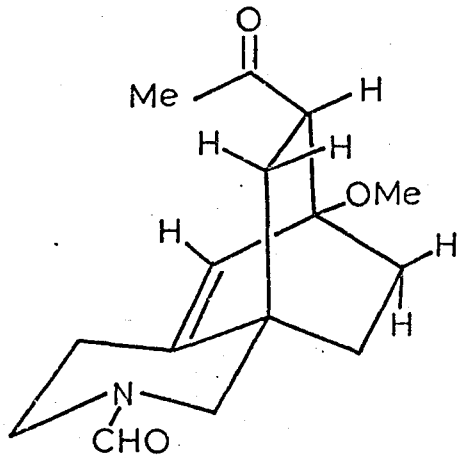
(311)

(312)

The isomerisation mixture containing ca. 75-80% of the conjugate diene (311) obtained as described above with potassium t-pentoxide in anhydrous DMSO was employed directly in Diels-Alder condensation with methyl vinyl ketone. The reactants were heated at 100°C on the steam bath in the presence of hydroquinone as stabiliser. After removal of excess dienophile in vacuo and column chromatography of the resultant residue over neutral alumina the epimeric Diels-Alder adducts (314) and (315) were obtained.

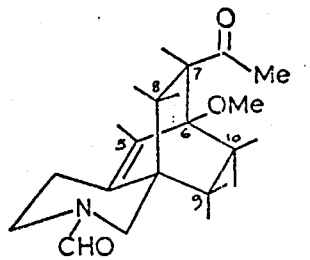


(314)



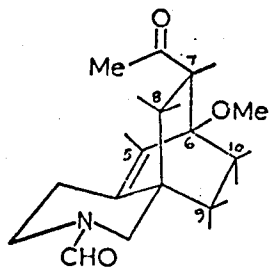
(315)

The exo-adduct (314) was eluted first from the column and crystallised : recrystallisation from diethyl ether afforded colourless rhombs (m.p.116-118°C). The endo-adduct (315) also crystallised (m.p.125-127°C). The endo-ketone was the most predominant product in a ratio endo : exo = 2.3:1. The infrared spectrum of the prepared adducts showed strong carbonyl peaks at 1660(amide C=O) and 1710cm^{-1} (acetyl C=O). The n.m.r. spectra of the N-formyl ketone adducts, Figs.7 and 8. display features in common with those discussed earlier for the N-methyl compounds. In particular the acetyl methyl resonance for the endo-ketone occurs at higher field (δ2.16) than that of the exo-ketone (δ2.28). This observed shielding is attributed to the anisotropy of the 4a,5 double bond. The C-5 olefinic proton in the exo-adduct (314) resonates at δ6.12 and that of the endo-adduct (315) at δ5.88. Shielding of the C-5 olefinic proton in the endo-adduct by the carbonyl group at C-7 occurred in a similar manner to that discussed earlier for the N-methyl analogues. The C-7 Hα in the exo-ketone resonated as a broadened quartet centred at δ2.92 ($J_{7\alpha,8\alpha}$ 11Hz and $J_{7\alpha,8\beta}$ 5Hz). The C-7 Hβ in the endo-ketone appeared as a triplet at δ3.07 ($J_{7\beta,8\beta} = J_{7\beta,8\alpha}$ 7.5Hz). The quartet for the C-7 Hα proton of the exo-ketone also showed fine splitting



(314)

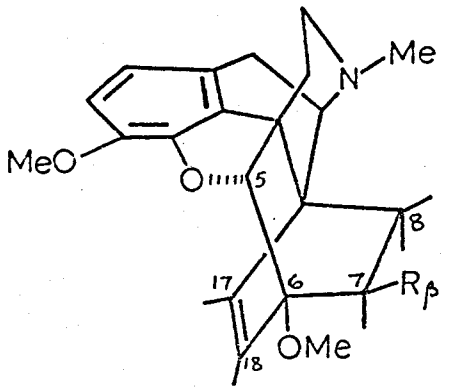
Fig.7.



(315)

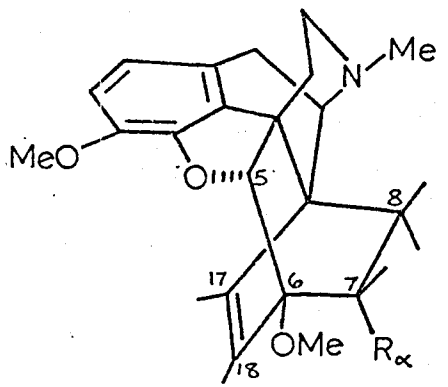
Fig.8.

TABLE 2 N.m.r. data for epimeric adducts of thebaine with methyl vinyl ketone and acrylonitrile compared with those for the adducts (314) and (315) from N-formyl-1,2,3,4,7,8-hexahydro-6-methoxyisoquinoline with methyl vinyl ketone.



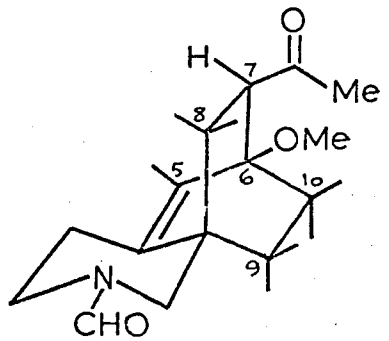
7β-epimer (exo)

from thebaine



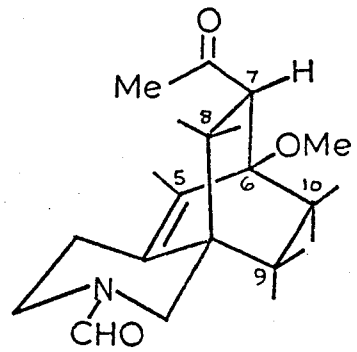
7α-epimer (endo)

from thebaine



7β (exo)

(314)



7α (endo)

(315)

Thebaine epimer	R	C-7Hα	C-7Hβ	C-18H	$J_{7\alpha,8\alpha}$	$J_{7\beta,8\beta}$	$J_{7\alpha,8\beta}$	$J_{7\beta,8\alpha}$	$J_{7\beta,18}$
7β	COMe	δ2.69	-	δ6.04	13.9Hz	-	δ5.0Hz	-	-
7α	COMe	-	δ2.90	δ5.85	-	9.7Hz	-	6.5Hz	<0.2Hz
7β	CN	δ2.79	-	δ5.90	11.2Hz	-	3.6Hz	-	-
7α	CN	-	δ2.85	δ5.93	-	9.5Hz	-	4.5Hz	<1.0Hz
Compound	Ketone			C-5H					$J_{7\alpha,10\alpha}$
314	exo	δ2.92	-	δ6.12	11.0Hz	-	5.0Hz	-	1.5Hz
315	endo	-	δ3.07	δ5.88	-	7.5Hz	-	7.5Hz	-

(J, 1.5Hz) due to long range coupling with the C-10 Hα proton. The n.m.r. of the N-formyl adducts thus show the general features in common with the other adducts synthesised so far.

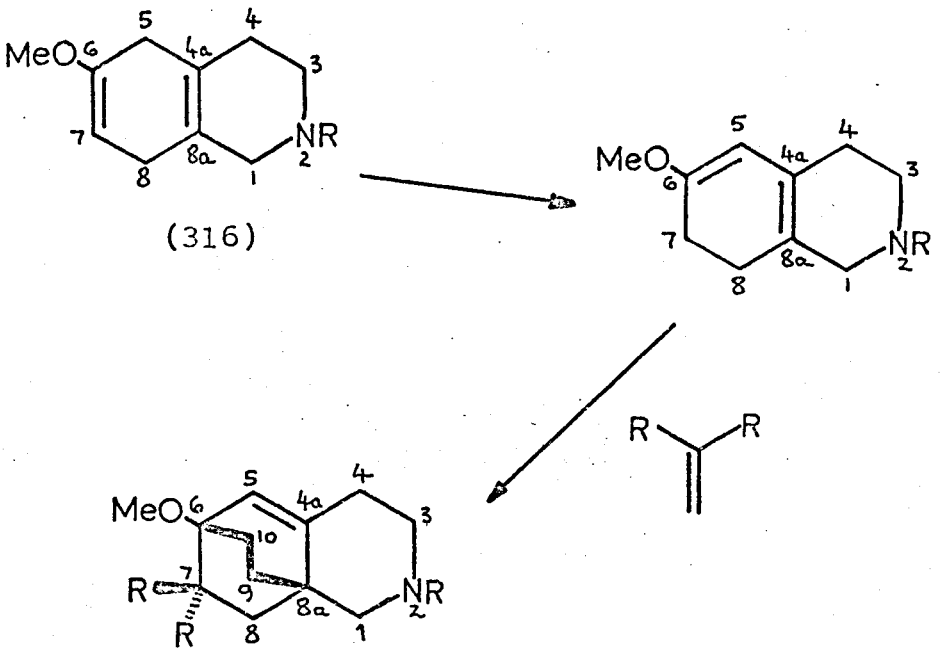
The estimated vicinal coupling constant J also affords a useful indication of stereochemistry, although the assignment of an exo or endo configuration on this basis must be undertaken with some reservation. For example, the claim that endo-endo vicinal coupling constants are much smaller than exo-exo coupling constants in norbornene derivatives has has been brought into question.[278] In the adducts of thebaine with methyl vinyl ketone and acrylonitrile,[86] which contain the bicyclo[2.2.2]octene system, endo-endo coupling constants are reported to be larger than exo-exo coupling constants[102] (see Table 2). This relationship has also been observed for Diels-Alder adducts prepared by our work and that of Crabb and Wilkinson.[249] e.g. $J_{7\alpha,8\alpha}$ = 11Hz for (314) whereas $J_{7\beta,8\beta}$ = 7.5Hz for (315) (see Table 2 and Table 1, pp.159 and 133).

PART 3

Synthesis of and Diels-Alder studies with 6-methoxy-2-substituted-1-benzyl-1,2,3,4,7,8-hexahydroisoquinolines

Preamble

Our successful synthesis of the 6-methoxy-6,8a-ethanoisoquinolines of general structure (317) is summarised in scheme 27.



(316)

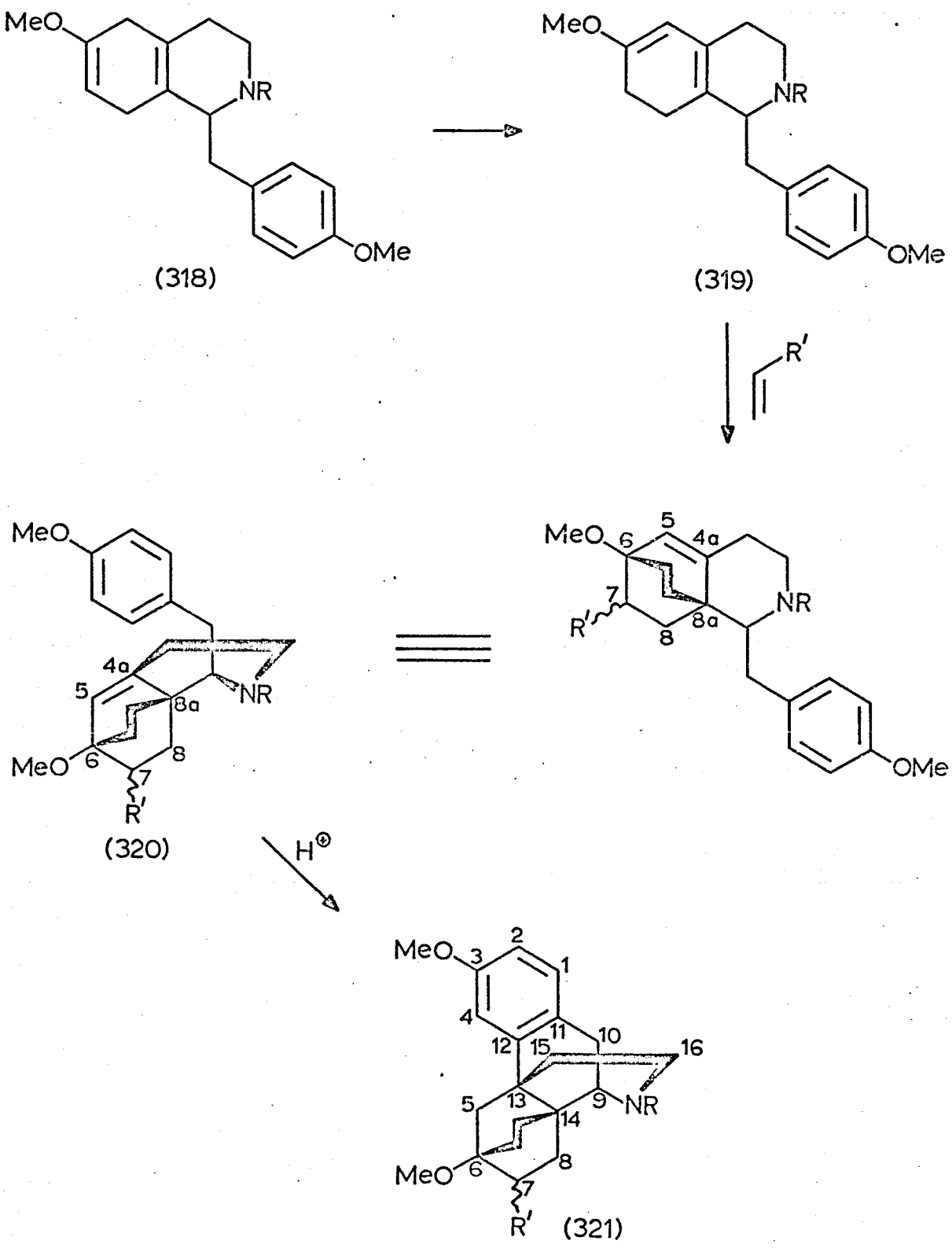
(317)

a) R=Me, R_1=H R_2=COMe
b) R=Me, R_1=COMe R_2=H
c) R=Me, R_1=H R_2=COPh
d) R=Me, R_1=COPh R_2=H
e) R=Me, R_1=Cl R_2=CN
f) R=Me, R_1=CN R_2=Cl
g) R=Me, R_1R_2 = C=O
h) R=CHO, R_1=H R_2=COMe
i) R=CHO, R_1=COMe R_2=H

Scheme 27

We wished to investigate extension of this synthetic scheme by incorporating a 1-benzyl substituent into the starting hexahydroisoquinoline (316, R=Me or CHO) to produce 1-benzylhexahydroisoquinolines (318). Base-catalysed

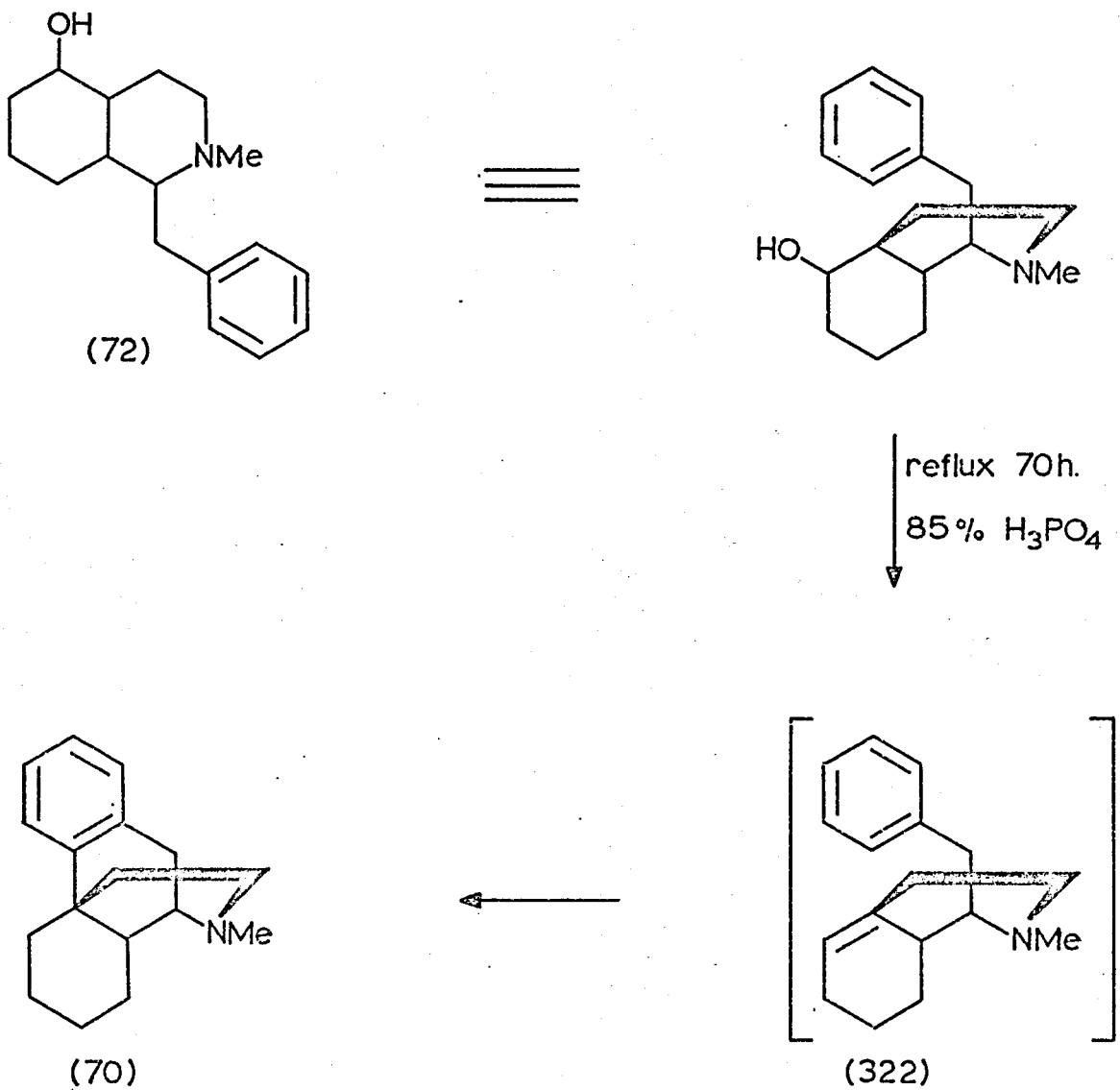
isomerisation of such compounds could afford 1,3 dienes of type (319) and Diels-Alder reactions of these could be studied. If adducts of type (320) could be obtained it would allow investigation of Grewe type acid-catalysed cyclisation to afford the novel 4,5-deoxy-6,14-ethanotetrahydrothebaines (321) (which are morphinan derivatives) as outlined in scheme 28.



Scheme 28

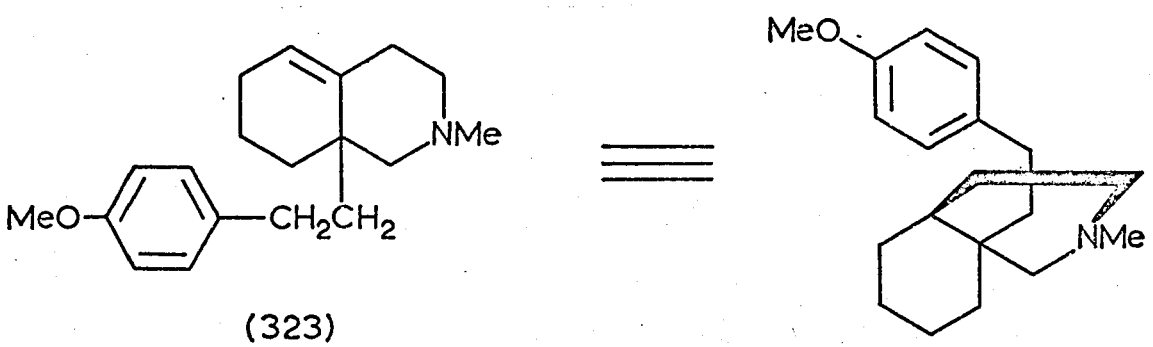
No precedent for Grewe cyclisation of this type, i.e; on to a bridged ring-A 1-benzylisoquinoline precursor has been reported (vide infra). Also cyclisation on to a 4a,5-double bond, as in (320), are less common than on to a 4a,8a-double bond. Sometimes the 4a,5-double bond is formed in situ.

Koelsch and Albertson[114] have reported the Grewe cyclisation of the 1-benzylisoquinoline (72), presumably the cyclisation proceeds via the Δ4a,5 compound (322) to afford the morphinan (70) in 10% yield.

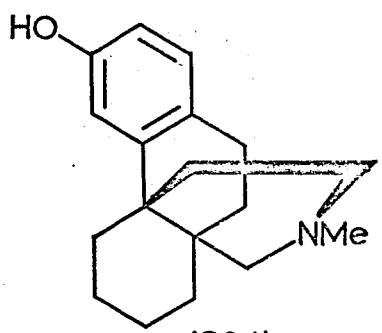


H.Kugita[279] has reported the synthesis of compounds in which the points of attachment of the hetero ring, its size and position of the nitrogen atom in the morphinan skeleton

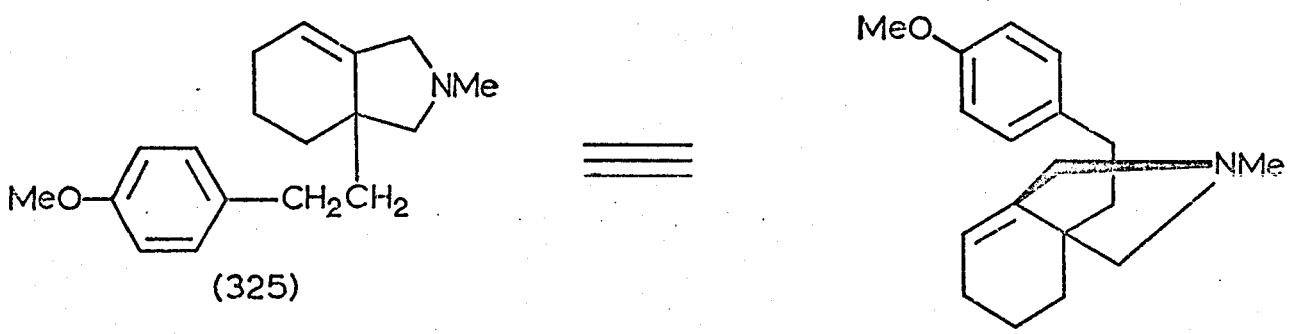
were modified. His synthetic scheme involved Grewe cyclisation of the compounds (323) and (325) containing 4a,5-type double bonds to afford the "modified" morphinans (324) and (326).



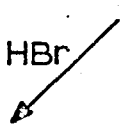
(323)

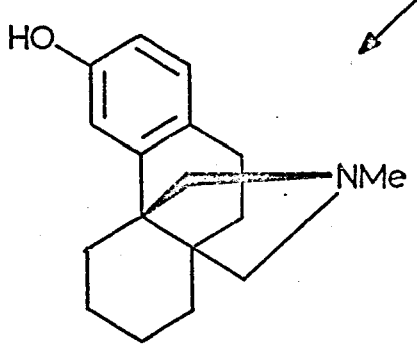


(324)



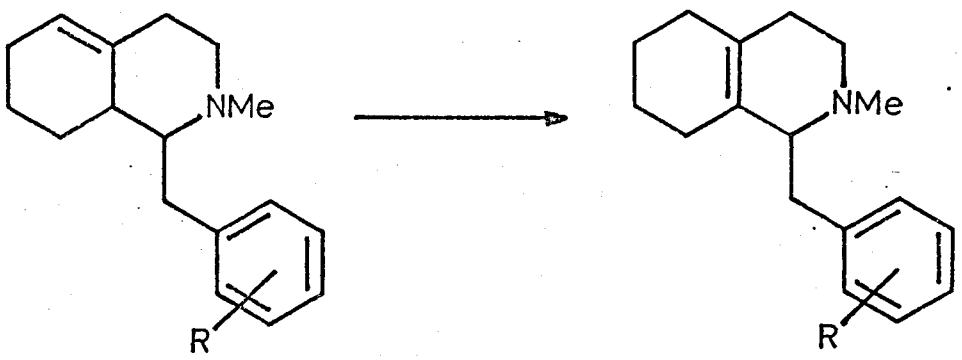
(325)





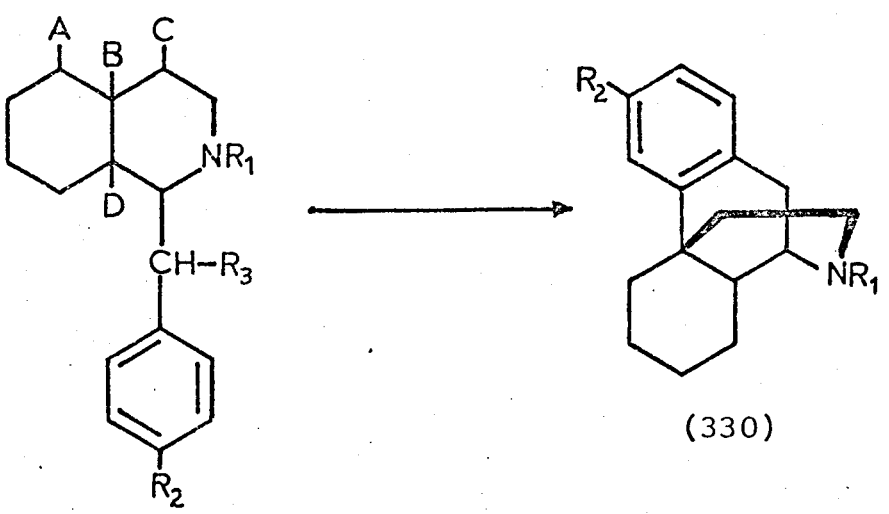
(326)

Thus morphinan cyclisation on to Δ4a,5 isoquinolines has been investigated, however, Grewe et.al.[122] have reported that the 1-benzyl compound (327) can be isomerised by hydrochloric acid into the 1-benzyl-2-methyloctahydroisoquinoline (328).



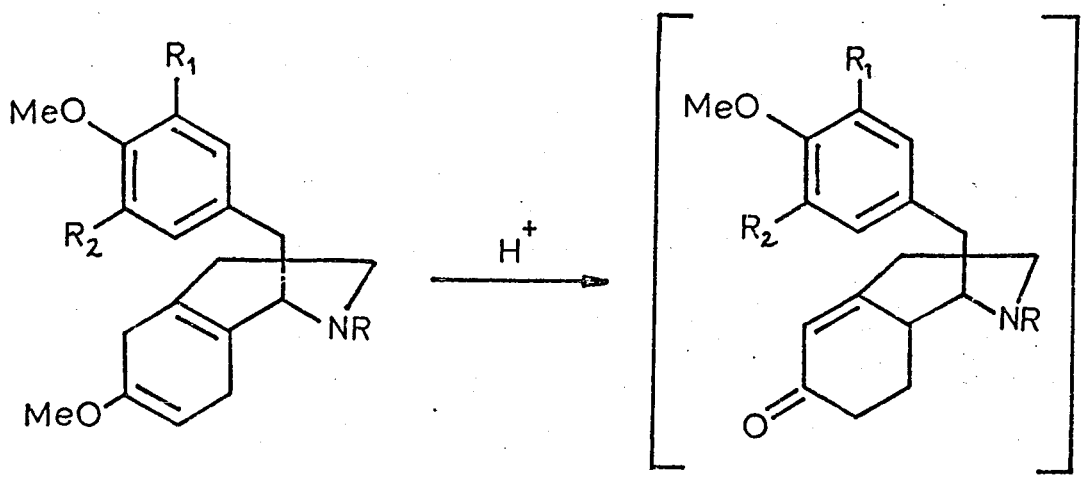
(327) (328)

A recent abstract of a Japanese patent[280] reports that compounds of formula (330) (where R_1=lower alk(en)yl, cycloalkyl, or aryl, and R_2 is lower alk(en)yl or alkoxy, cycloalkyl or aryl) are prepared by heating compounds of formula (329) [where R_3 is H, carbamoyl, (esterified carboxy or cyano, one of A,B,C and D is OH and the other three are H, or two of them form a double bond and the other two are H, provided that R_3 is not H when B and D form a double bond] at 70-120°C in the presence of 100-120% phosphoric acid. Pure (330) is claimed to be obtained in yields >80%.

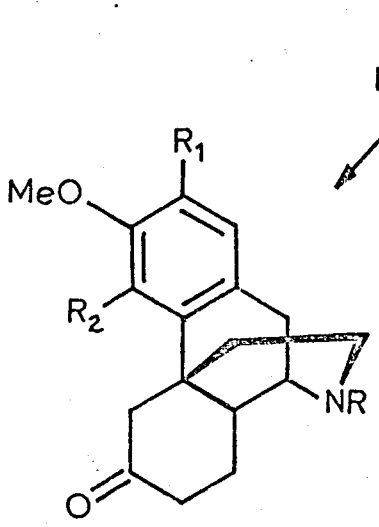


(329) (330)

As discussed earlier (see Introduction p.46) acid-catalysed ring closure of 6-methoxy-1-benzylhexahydro-isoquinolines of type (331) to 6-oxo-morphinans (333) has been effected and may proceed through the Δ4a,5-enone intermediate (332) (or the β,γ-unsaturated ketone)[132-137]



(331) (332)



(333)

Examination of Drieding models of the bridged ring-A 1-benzyl compounds (320) suggests that an ortho position of the aromatic ring of the benzyl moeity could approach the 4a-position in (320) for effective cyclisation

to be possible.

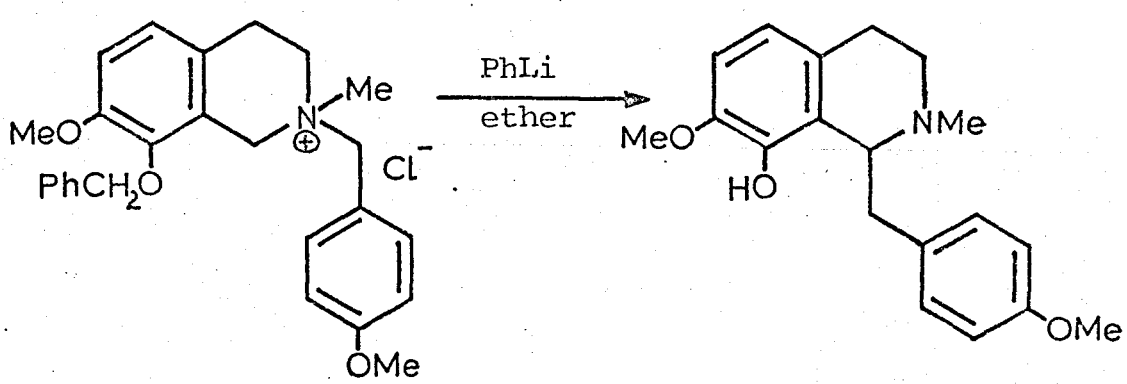
We thus set out to synthesise the 1,2,3,4,5,8-hexahydro-1-benzyl compounds (318) bearing in mind the possible further developments discussed above.

A Attempts to synthesise 6-methoxy-2-methyl-1-(4'-methoxybenzyl)-1,2,3,4,5,8-hexahydroisoquinoline via a Stevens rearrangement of an isoquinolinium salt.

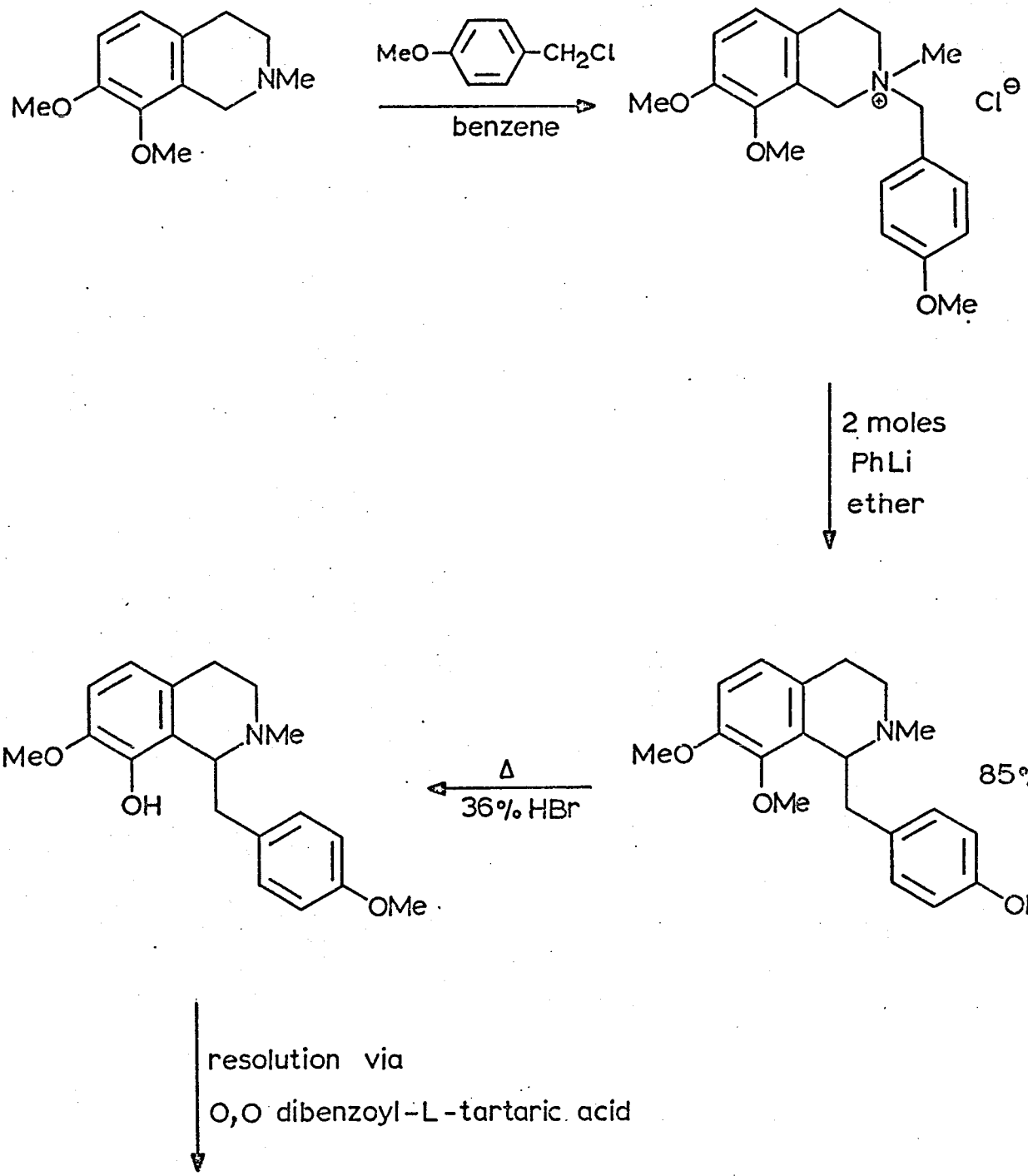
The base induced Stevens rearrangement of quaternary ammonium salts has been used with a variety of substituted N-benzyltetrahydroisoquinolines to produce 1-benzyltetrahydroisoquinolines. The yields may vary widely from 0 to 85% and in some cases a number of side products accompany the desired tetrahydrobenzylisoquinoline.[281]

G.Grethe et. al.[282] employed the Stevens rearrangement as the key step in the synthesis of the alkaloid petaline as depicted in scheme 29 . In this case the N → C rearrangement proceeded in 85% yield.

T.Kametani et.al.[283] also utilised the Stevens rearrangement in an alternative synthesis of petaline. They synthesised 8-benzyloxy-1,2,3,4-tetrahydro-7-methoxy-2-methyl-2-(4'-methoxybenzyl)isoquinolinium chloride (334) and employed phenyl lithium in ether to obtain norpetaline (335) in relatively low yield (16%)



(334) (335)

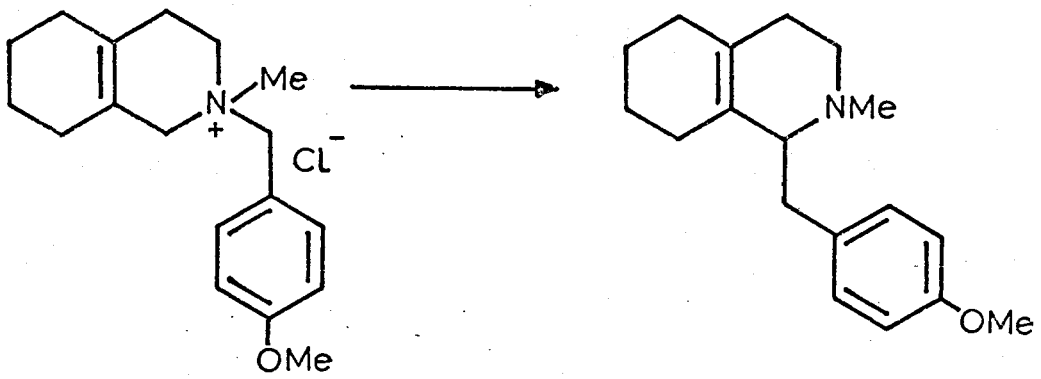


(-)-petaline iodide

Scheme 29

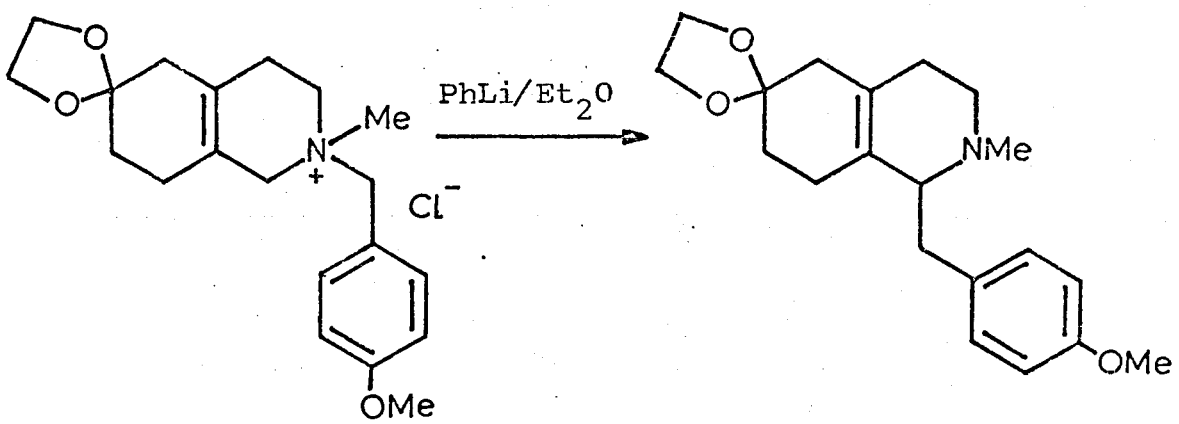
The alkaloid petaline has also been synthesised by different routes in this laboratory[284a] and elsewhere.[284b]

Closer to our own interests an American patent[285] describes the Stevens rearrangement of isoquinolinium salts of type (336) to give 1-benzyloctahydroisoquinolines of type (337) in yields ranging from 40-60% utilising various bases and solvent combinations.

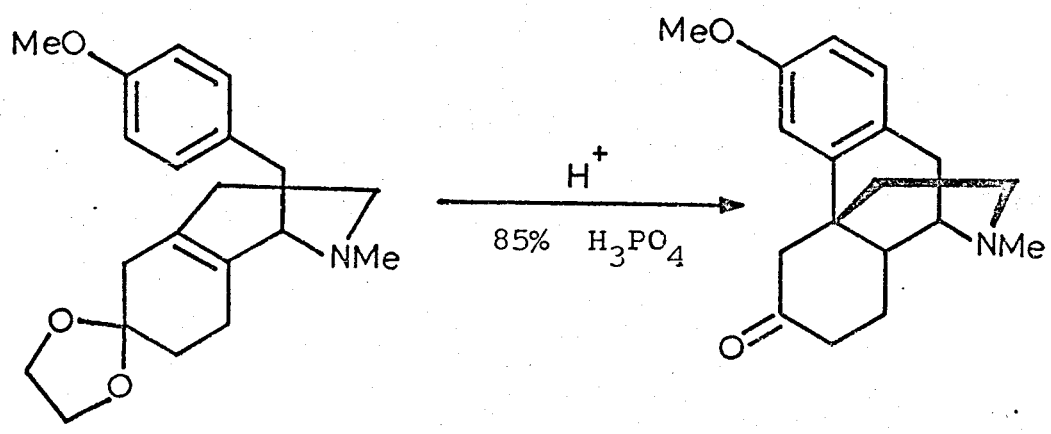


(336) (337)

R.Maeda and E.Ohsugi[286] in a synthesis of racemic-3-methoxy-6-oxo-N-methyl morphinan (340) utilised the Stevens rearrangement of the isoquinolinium salt (338) to obtain the desired precursor (339)(30%) for the morphinan closure as shown.



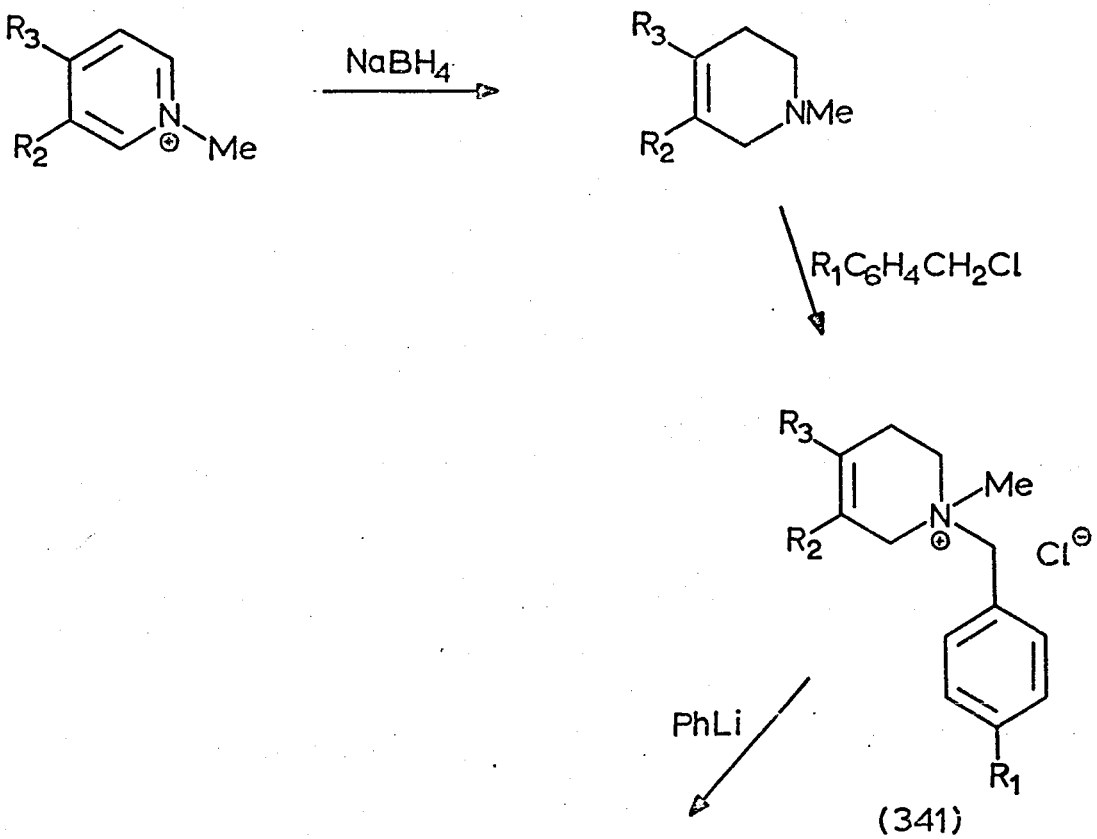
(338) (339)



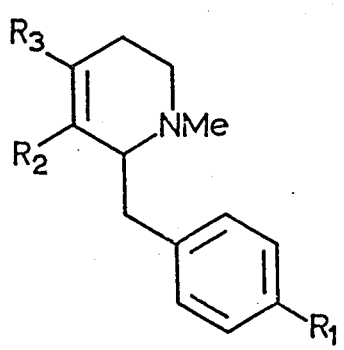
(339) (340)

The Stevens rearrangement of tetrahydropyridinium salts (e.g. 341) is also known. In their synthesis of benzomorphans Fry and May[287] utilised etheral phenyllithium to effect rearrangement of the tetrahydropyridinium salt (341) to give the tetrahydropyridine (342) which was subsequently cyclised with 48% HBr (Grewe cyclisation) to afford benzomorphans (344). It was noted that (342) is formed in the Stevens rearrangement rather than the isomeric (343) since the ylid intermediate leading to (342) is stabilised by resonance with the double bond. The acid-catalysed cyclisation of tetrahydropyridines to benzomorphans is discussed earlier (cf. p.93). Yokohama et.al.[288] and Block et.al.[289] have shown that powdered potassium hydroxide in toluene is a suitable environment for rearrangements of tetrahydropyridinium salts.

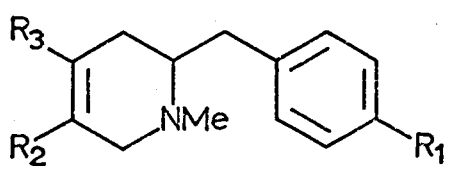
The production of side products in the Stevens rearrangement is well documented. In the Stevens rearrangement one alkyl group migrates from the quaternary nitrogen atom to the α carbon atom of a second alkyl group. The major competing reaction is the Sommelet-Hauser rearrangement[290] which involves migration to the ortho position of a benzyl quaternary ammonium salt. When structurally feasible, both rearrangements may occur simultaneously although experimental conditions markedly affect the competing pathways.



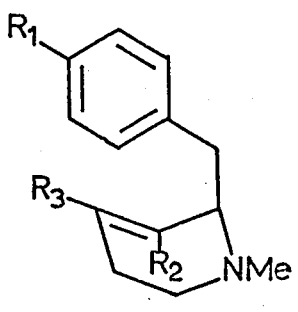
(341)



(342)

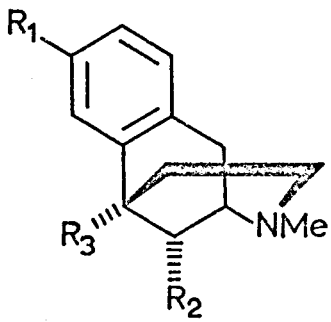


(343)



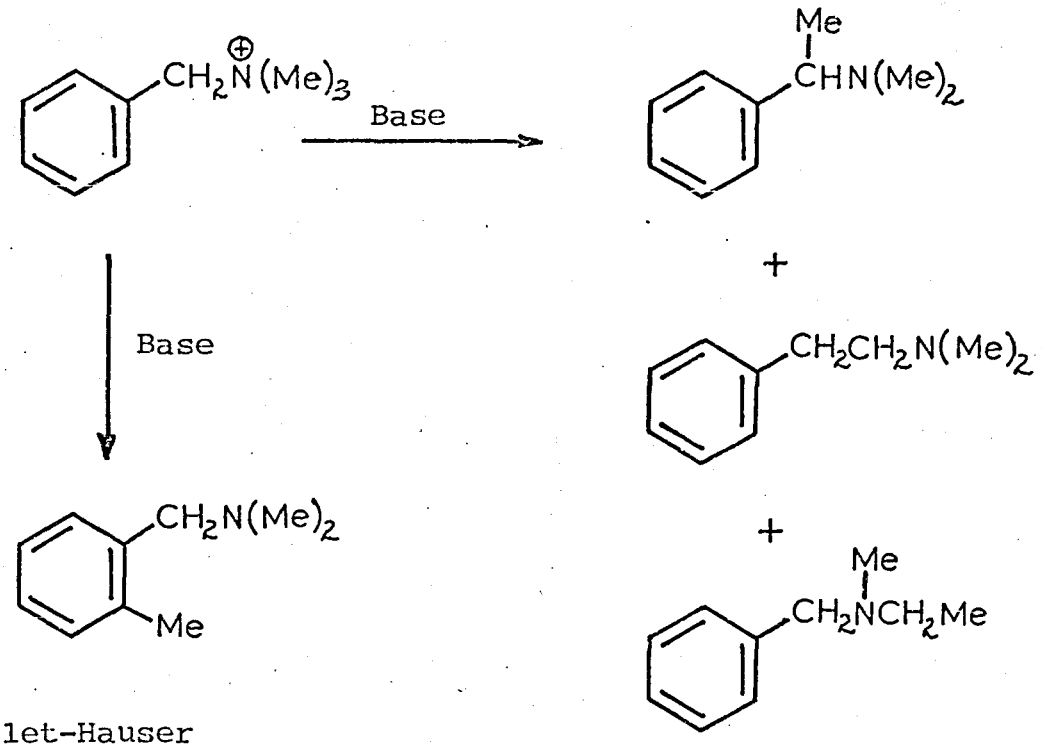
(342)

48% HBr



(344)

e.g.



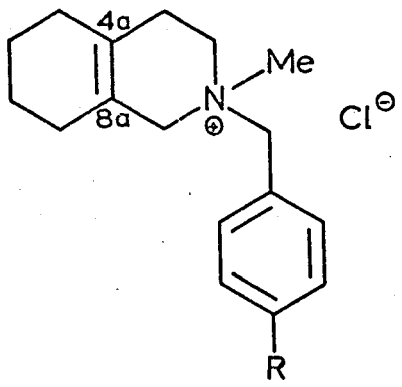
Sommelet-Hauser

Stevens rearrangement

In general, Stevens rearrangements occur most favourably in those quaternary ammonium salts that do not contain a β hydrogen atom and thus are not capable of undergoing the Hofmann elimination.

Maeda and Ohsugi[286] carried out the Stevens rearrangement of 2-methyl-2-benzyl-Δ-4a,8a-octahydroisoquinolinium chloride (345) by treatment with ethereal phenyl lithium. They found that the base induced reaction produced a mixture of four products as depicted in scheme 30.

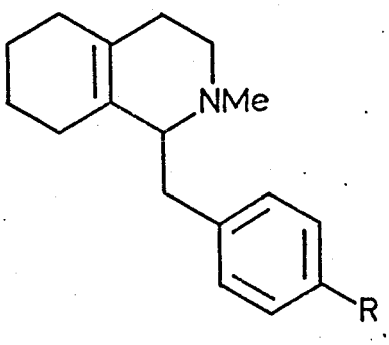
With a view to synthesising the required precursor (318) for the synthesis of the bridged ring-A 1-benzyl compounds (320) as outlined earlier in scheme 28, we investigated the synthesis and Stevens rearrangement of 6-methoxy-2-methyl-2-(4'-methoxybenzyl)-1,2,3,4,5,8-hexahydroisoquinolinium chloride (346). It was anticipated that the product obtained from a Stevens [1,2] process would be the hexahydro-1-benzyl compound (347). Stabilisation of the ylid intermediate leading to (347) being provided by resonance with



(345)

a. R = H
b. R = OMe

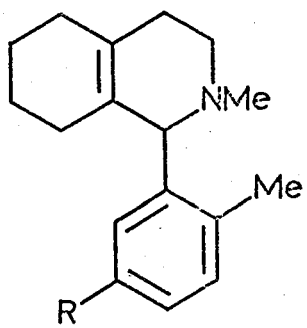
PhLi / ether



a. 19%
b. 35%

Stevens [1,2] process

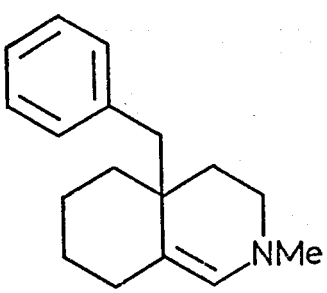
+



a. 19%

Sommelet type

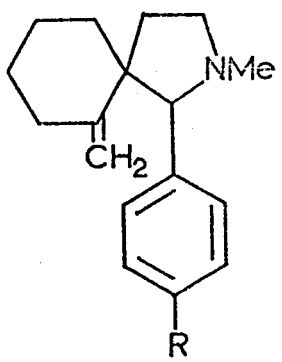
+



a. 5%

benzyl migration

+

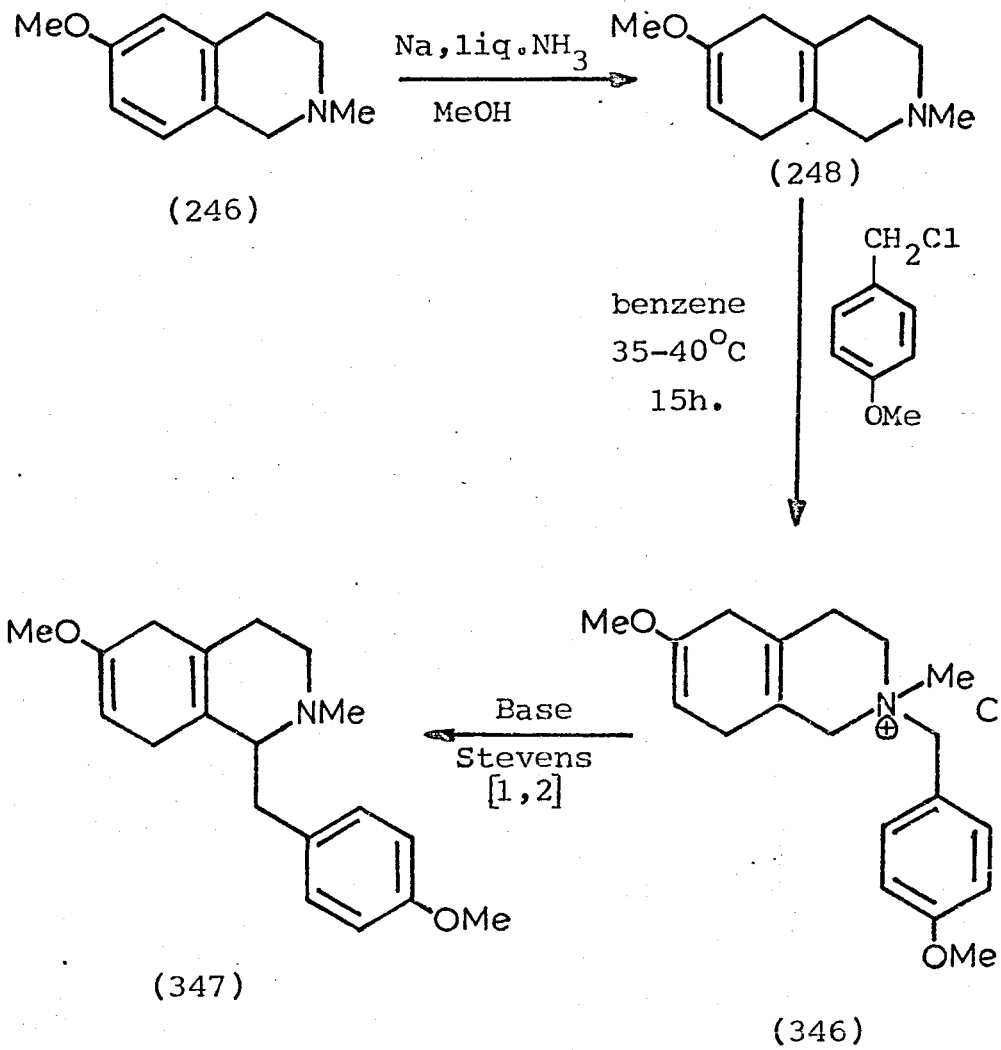


a. 1·5%

product from benzyl anion attack at C—4a

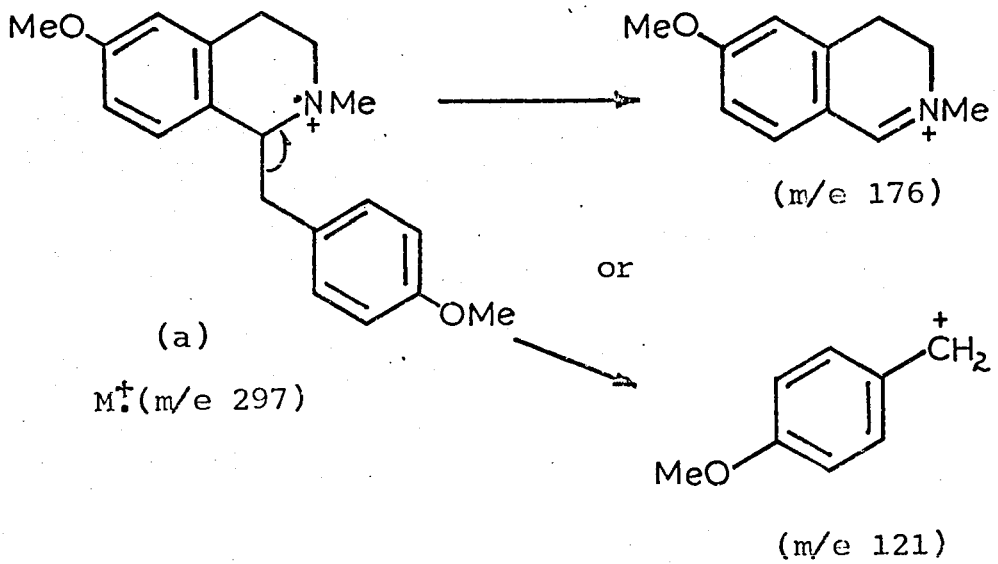
Scheme 30

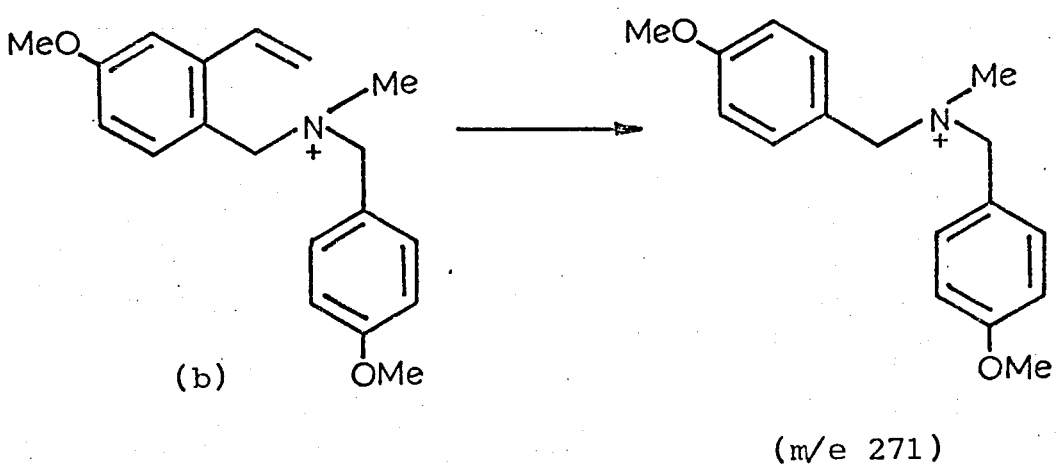
the 4a,8a double bond. Compound (346) was synthesised from 6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (246) as shown.



The isoquinolinium salt (346) was employed directly without prior purification in the Stevens rearrangement. We noted that the quaternary salt (346) tended to be hygroscopic. Previous workers have recommended the direct use of the quaternary salts without purification.[286] When the quaternary salt (346) was heated under reflux in anhydrous dimethylformamide with dry powdered potassium bicarbonate[285] in a nitrogen atmosphere a deep red-brown colour developed

after 30 minutes indicating the formation of carbanions. After 5h reflux t.l.c. analysis indicated that the product was a mixture of four products which could not be separated. Mass spectral analysis of the mixture showed the highest molecular ion at m/e 297 with a base peak at m/e 121 together with fragment ions at 271 and 176. The desired hexahydro-1-benzylisoquinoline (347) has molecular weight of 299; the molecular ion at m/e 297 suggested that dehydrogenation of ring-A may have occurred. The base peak at m/e 121 together with the fragment ion at m/e 176 could be rationalised as arising from fragmentation of (a). The fragment at m/e 271 could arise from the Hofmann elimination product (b) by loss of the ethylene side-chain. i.e.





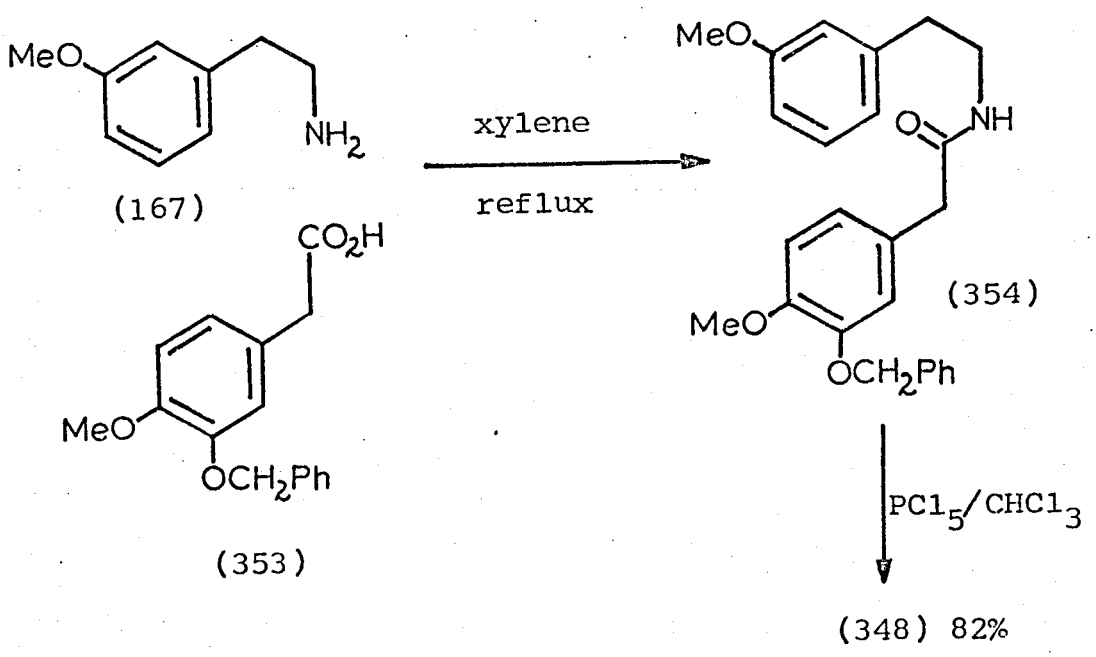
Purification of the mixture was attempted by vacuum distillation and column chromatography over neutral alumina, however, no pure characterisable products could be obtained.

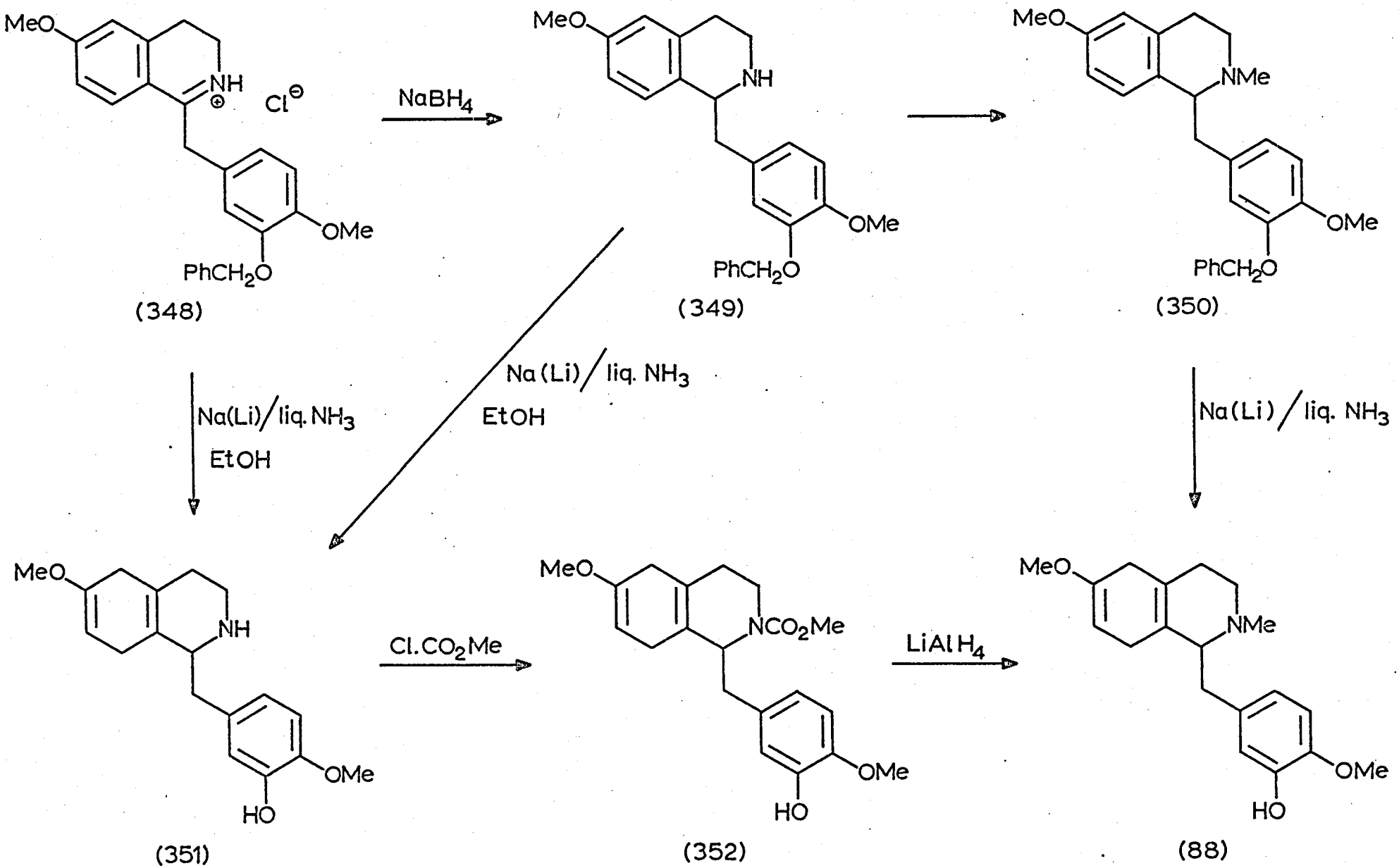
The reaction was repeated several times but from none of the reactions could a pure product be isolated, mixtures being given each time. The route was therefore abandoned : more success was obtained from the method described next.

B Synthesis of 1-benzyl-1,2,3,4,5,8-hexahydro-6-methoxy-isoquinolines via the partial Birch reduction of 1-benzyl-isoquinoline derivatives.

The synthesis of the 1-benzyl-1,2,3,4,5,8-hexahydro-6-methoxyisoquinolines of type (351) and (88) has been achieved by the partial Birch reduction of compounds of type (348), (349) or (350) as depicted in scheme 31 .[291] N-Methylation of the 1-benzyl-1,2,3,4,5,8-hexahydro compounds was achieved via the N-methoxycarbonyl derivative (352). The benzylic aromatic ring is not reduced in the Birch reduction because of the presence of a phenolic group, produced in situ by reductive cleavage of the $PhCH_2$ protecting group.

Grewe and Fischer[292] synthesised the 3,4-dihydro-compound (348) from 3-methoxyphenylethylamine (167) and 3-benzyloxy-4-methoxyphenylacetic acid (353) as depicted below:

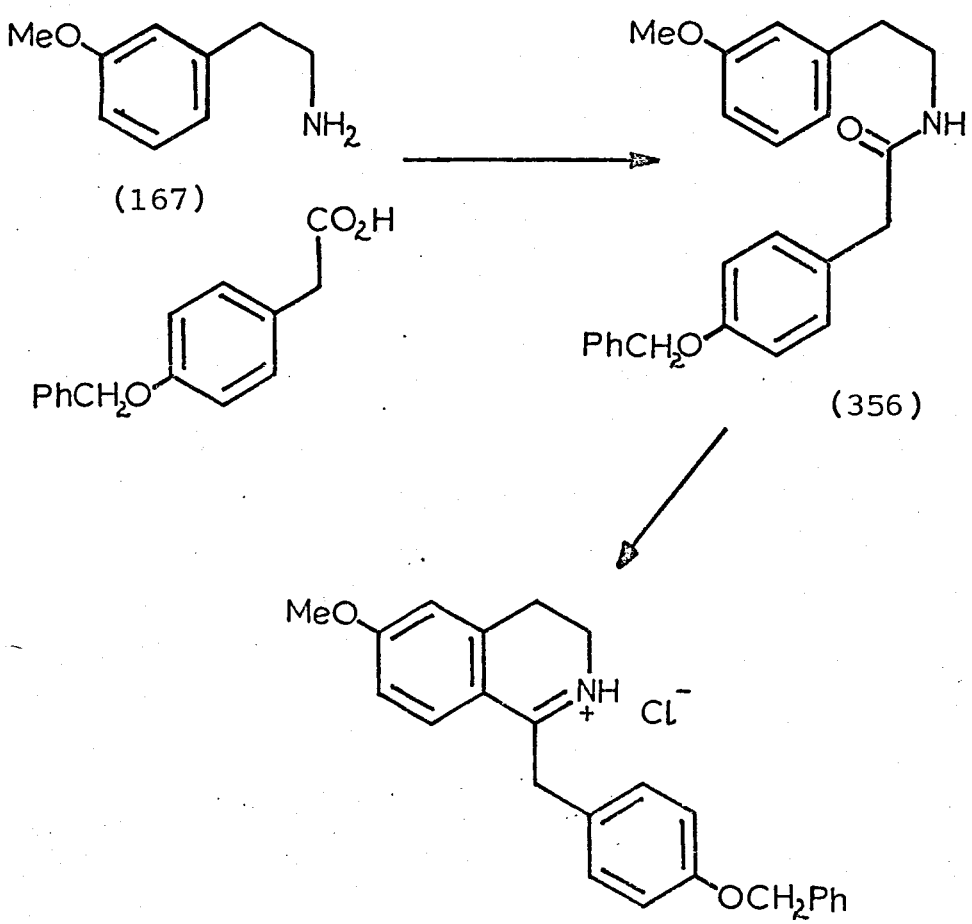



MeO
NH
Cl⊖
OMe
PhCH2O
(348)
NaBH4
(349)
NMe
(350)
Na(Li) / liq. NH3
EtOH
Na(Li) / liq. NH3
Na(Li) / liq. NH3
EtOH
(351)
Cl.CO2Me
NCO2Me
(352)
LiAlH4
(88)

Scheme 31

The Bischler-Napieralski cyclisation of the amide (354) was accomplished with phosphorus pentachloride in chloroform at room temperature.[292] The partial Birch reduction of 1-benzylisoquinoline derivatives has also been employed by Grewe et.al.[132], G.C.Morrison et.al.[133], De Graw et.al.[137] and H.C.Beyerman et.al.[134,135] in the total synthesis of morphinan derivatives (see Introduction p.46).

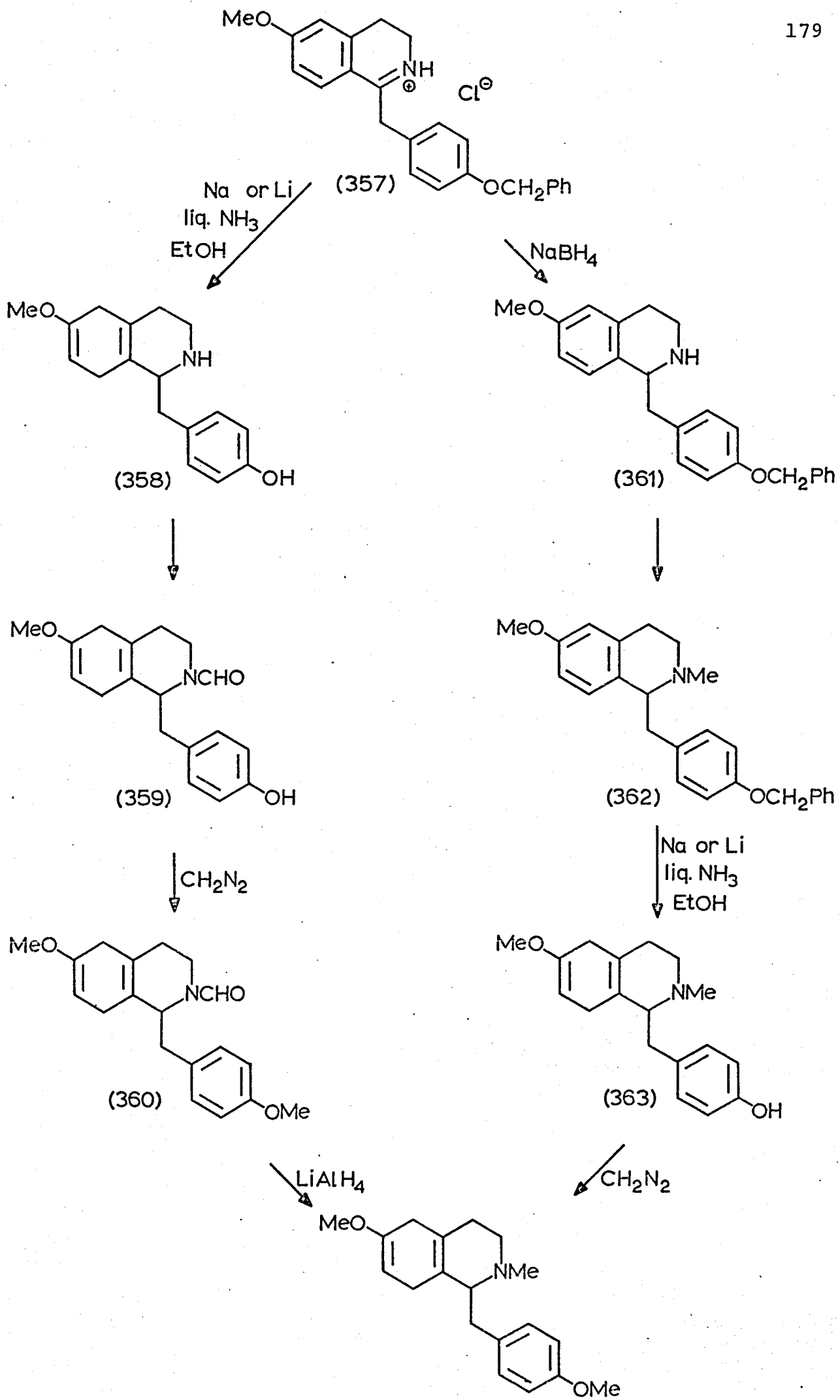
We set out to synthesise the previously unknown 1-(4'-methoxybenzyl)-1,2,3,4,5,8-hexahydroisoquinolines (247) and (360) by the routes shown in scheme 32 and scheme 33 .



(357)

Scheme 32

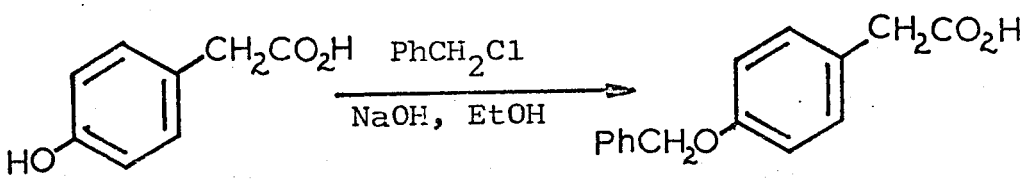
The 3,4-dihydroisoquinolinium compound (357) is serving as common intermediate for both synthetic routes.


MeO
NH
Cl⊖
(357)
OCH2Ph
Na or Li
liq. NH3
EtOH
NaBH4
(358)
OH
(361)
OCH2Ph
NCHO
NMe
(359)
(362)
CH2N2
Na or Li
liq. NH3
EtOH
(360)
OMe
(363)
OH
LiAlH4
CH2N2

Scheme 33

(1) Synthesis of 1-Benzyl-3,4-dihydroisoquinolines.

4-Benzyloxyphenylacetic acid (355) was synthesised by benzylation of commercially available 4-hydroxyphenylacetic acid with benzyl chloride in ethanolic sodium hydroxide in 80% yield.



(355)

The amide (356) was prepared by a number of methods:-

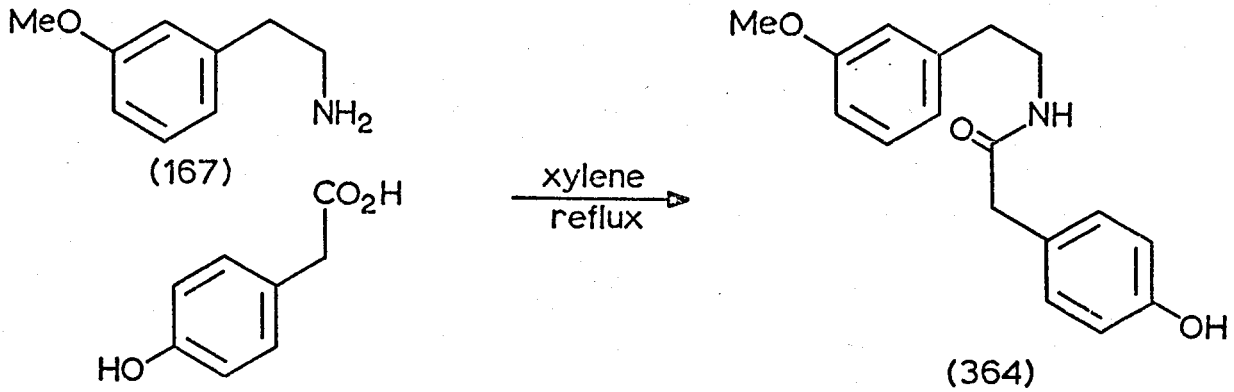
(a) Direct condensation of 3-methoxyphenylethylamine (167) with 4-benzyloxyphenylacetic acid (355) in refluxing xylene with constant separation of the water produced during condensation in an atmosphere of nitrogen.[210,292]

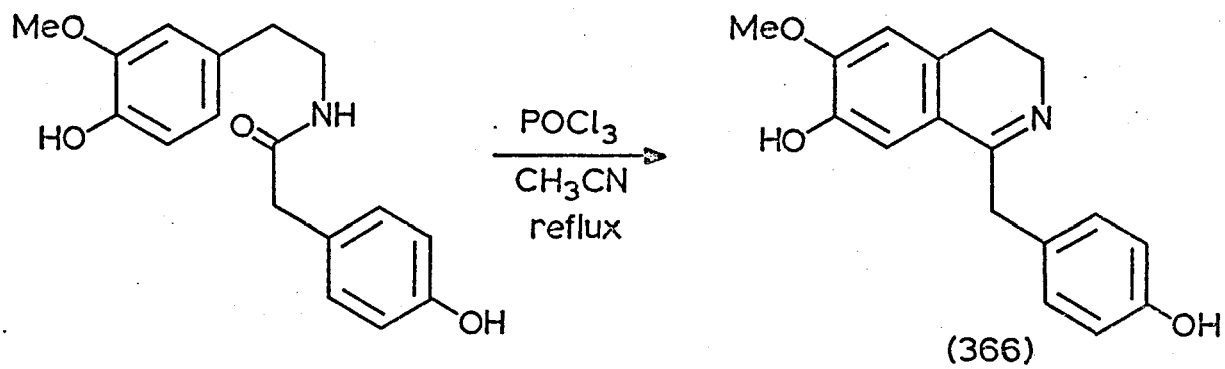
(b) Condensation of 3-methoxyphenylethylamine hydrochloride with 4-benzyloxyphenylacetyl chloride (prepared from the acid and thionyl chloride) in the presence of triethylamine in chloroform.[293]

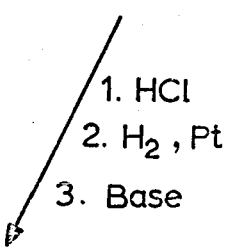
(c) Condensation of the amine (167) with the phenylacetic acid (355) in the absence of solvent in a nitrogen atmosphere at 190-200°C.[294]

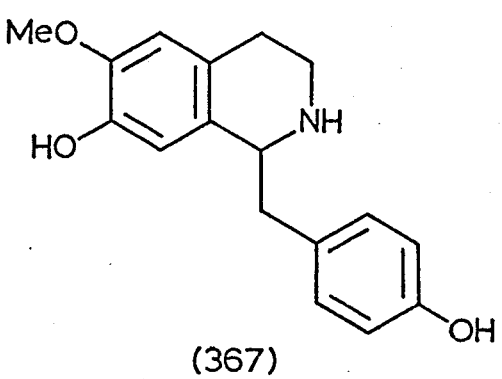
Procedures (a) and (c) proved to be the most convenient and the crystalline amide (356) (m.p. 96-96.5°C) was obtained in 90% and 85% yield respectively. Method (b) gave 69%.

We also synthesised the unprotected phenolic amide (364) (m.p. 125-126°C) by condensation of 3-methoxyphenylethylamine (167) with 4-hydroxyphenylacetic acid. Teitel and Brossi had reported the Bischler-Napieralski cyclodehydration of the closely related unprotected phenolic amide (365) with phosphoryl chloride in refluxing acetonitrile to afford the 3,4-dihydro-compound (366) which was progressed to (±)-coclaurine (367) in 61% overall yield.[222]


MeO
NH2
(167)
CO2H
HO
xylene
reflux
MeO
NH
O
OH
(364)

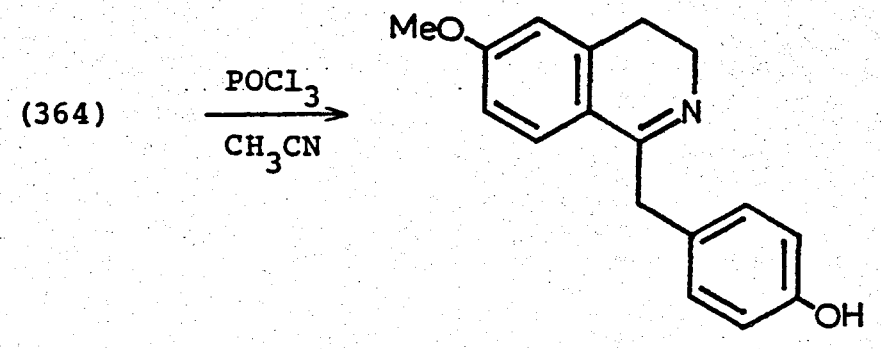

MeO
HO
NH
O
OH
POCl3
CH3CN
reflux
MeO
HO
N
OH
(366)


1. HCl
2. H2 , Pt
3. Base


MeO
HO
NH
OH
(367)

(±)- Coclaurine

However, Bischler-Napieralski cyclodehydration of (364) with phosphoryl chloride in refluxing acetonitrile gave only poor yields of the 3,4-dihydroisoquinoline (368) which was characterised as its hydrochloride salt [m.p.156 -158°C.



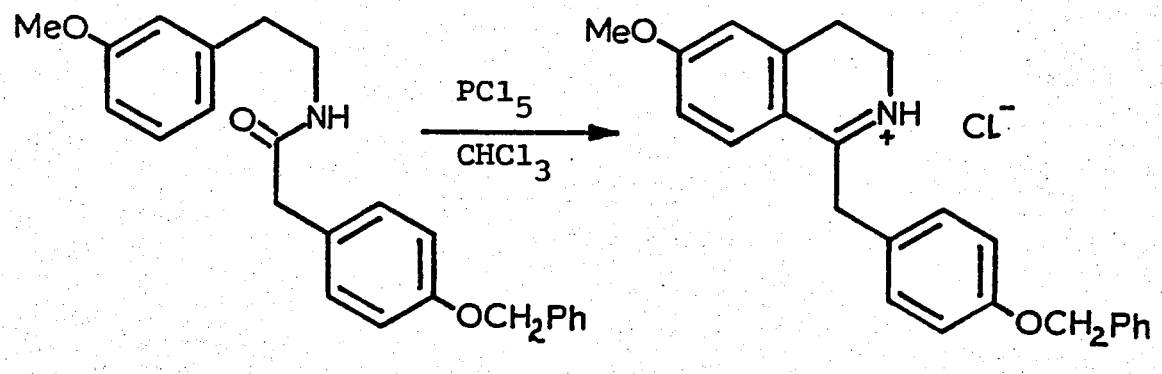
(368)

We found that protection of the phenolic hydroxyl in (364) as a benzyl ether ie. amide (356) provided for high yield syntheses of the 3,4-dihydroisoquinolinium hydrochloride (357) as discussed below.

Phosphorus pentachloride in chloroform was found to be the reagent of choice for the Bischler-Napieralski cyclisation[196] of the benzyl protected amide (356). This reagent combination has been employed extensively in the literature for the cyclisation of analogous compounds.[294-297] Of the literature analogues available, the work-up procedure differs. We tried a number of work-up methods to obtain the highest yield of the important intermediate 3,4-dihydro compound (357).

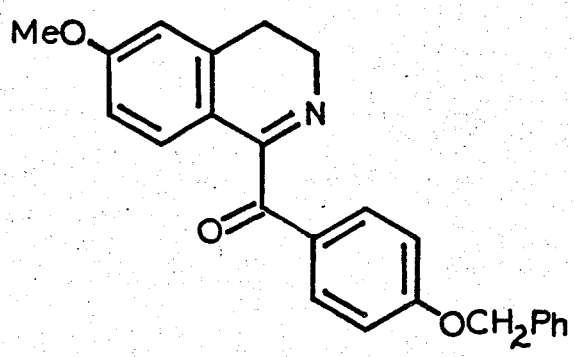
1-Benzyl-3,4-dihydroisoquinoline formation using $PCl_5/CHCl_3$.

a) Following the procedure of Grewe and Fischer[292] for cyclisation of the related amide (354) which utilised PCl_5 in chloroform we obtained the required 3,4-dihydroisoquinolinium hydrochloride (357) in 80% yield (m.p.181-183°C). The n.m.r. spectrum was consistent with structure (357).



(356) (357)

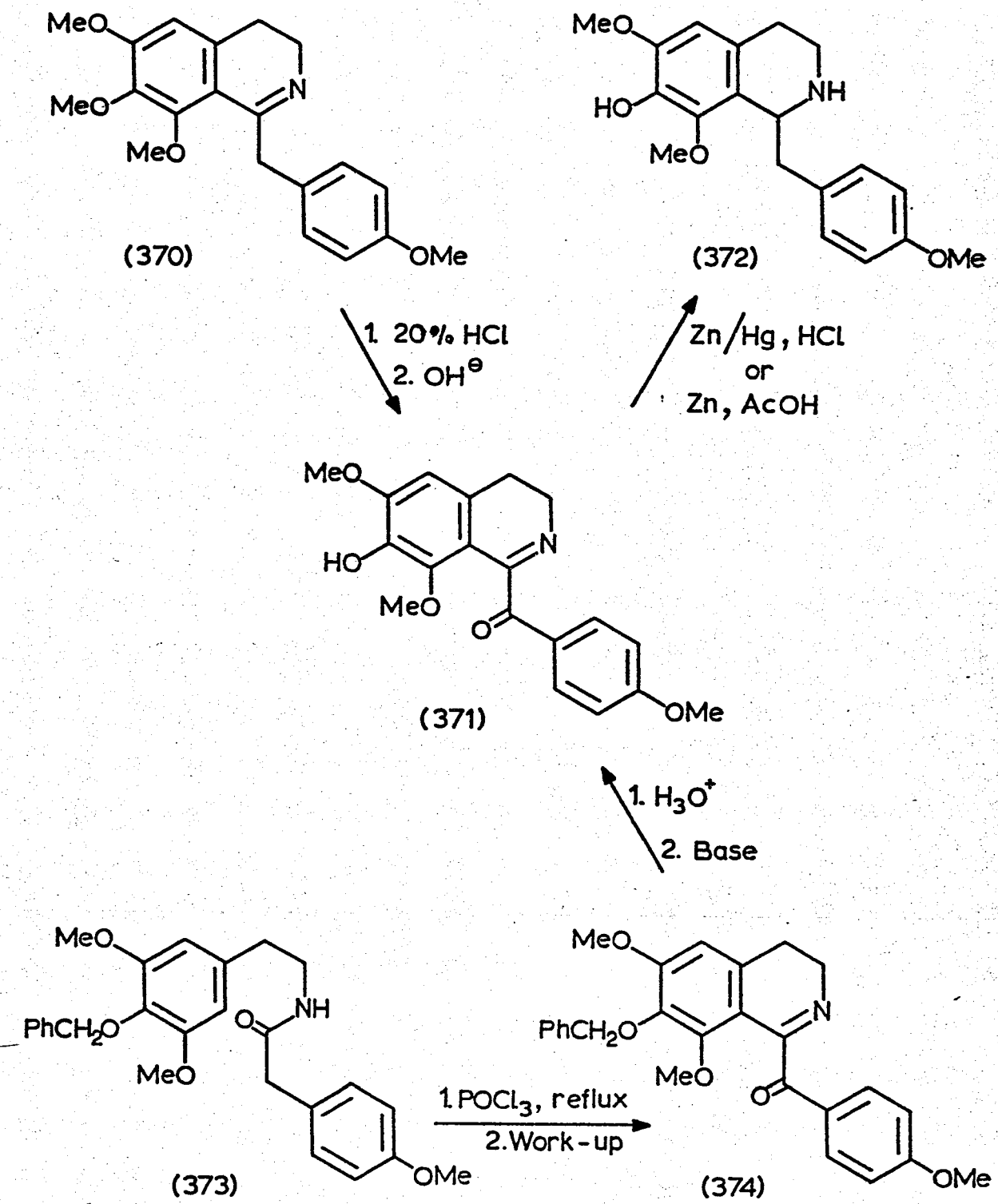
If the reaction mixture was not taken to the hydrochloride but was basified and worked-up in an attempt to isolate the free base, the compound isolated (m.p.109°C) showed a strong carbonyl absorption at 1660cm^{-1}. The n.m.r. spectrum of the crystalline base was consistent with the 1-benzoyl-3,4-dihydroisoquinoline structure (369).



(369)

Compound (369) probably arises during the work-up procedure. It is well known that the benzylic position of aromatic and 3,4-dihydroisoquinolines is very susceptible to oxidation.[298] Kametani and co-workers[299] working on the selective demethylation of the imine (370) with 20% hydrochloric acid and subsequent basification obtained a product (371). This had a free phenolic group at C-7 and oxidation of the

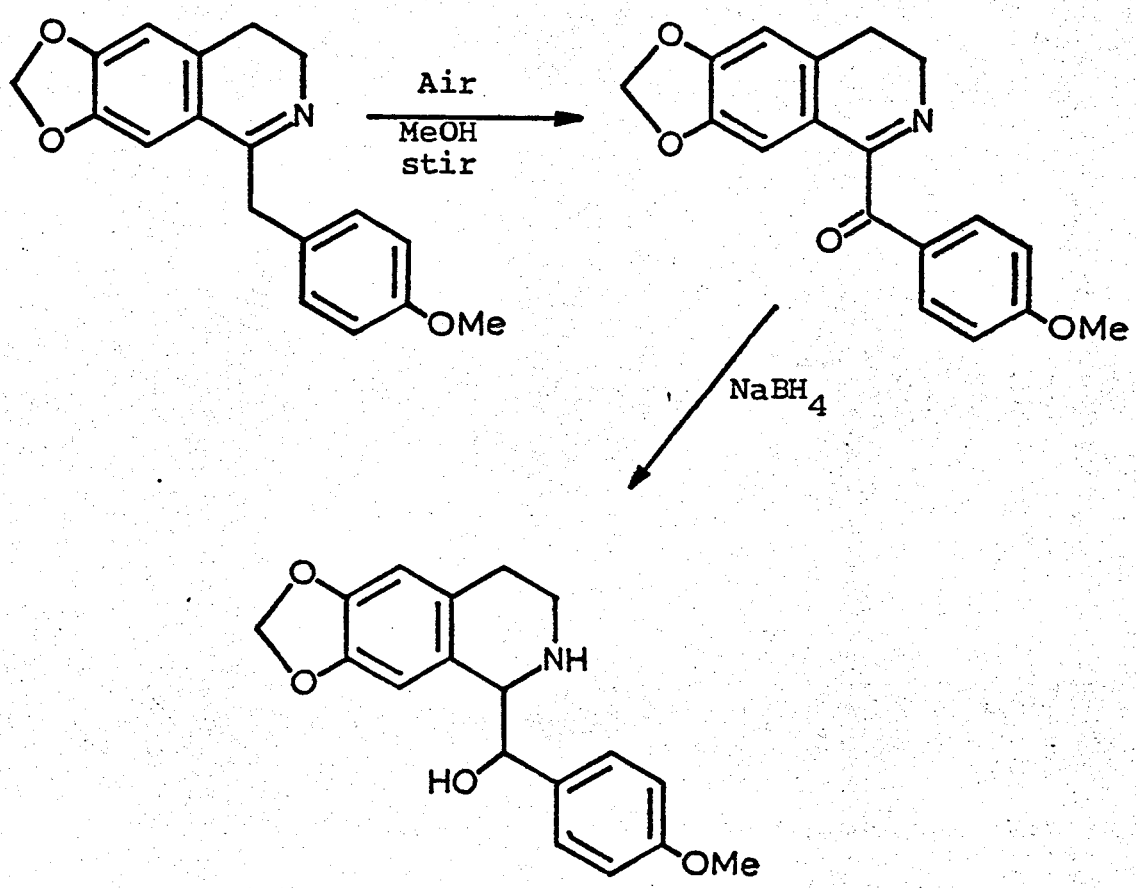
α-methylene function had also occurred. The ketone (371) was transformed into a tetrahydrobenzylisoquinoline (372) by Clemmensen reduction or by zinc in acetic acid. Alternatively, Bischler-Napieralski cyclisation of the amide (373) followed by hydrolysis of the benzyloxy group in (374) also gave the ketone (371) as shown in scheme. 34 .



Scheme 34.

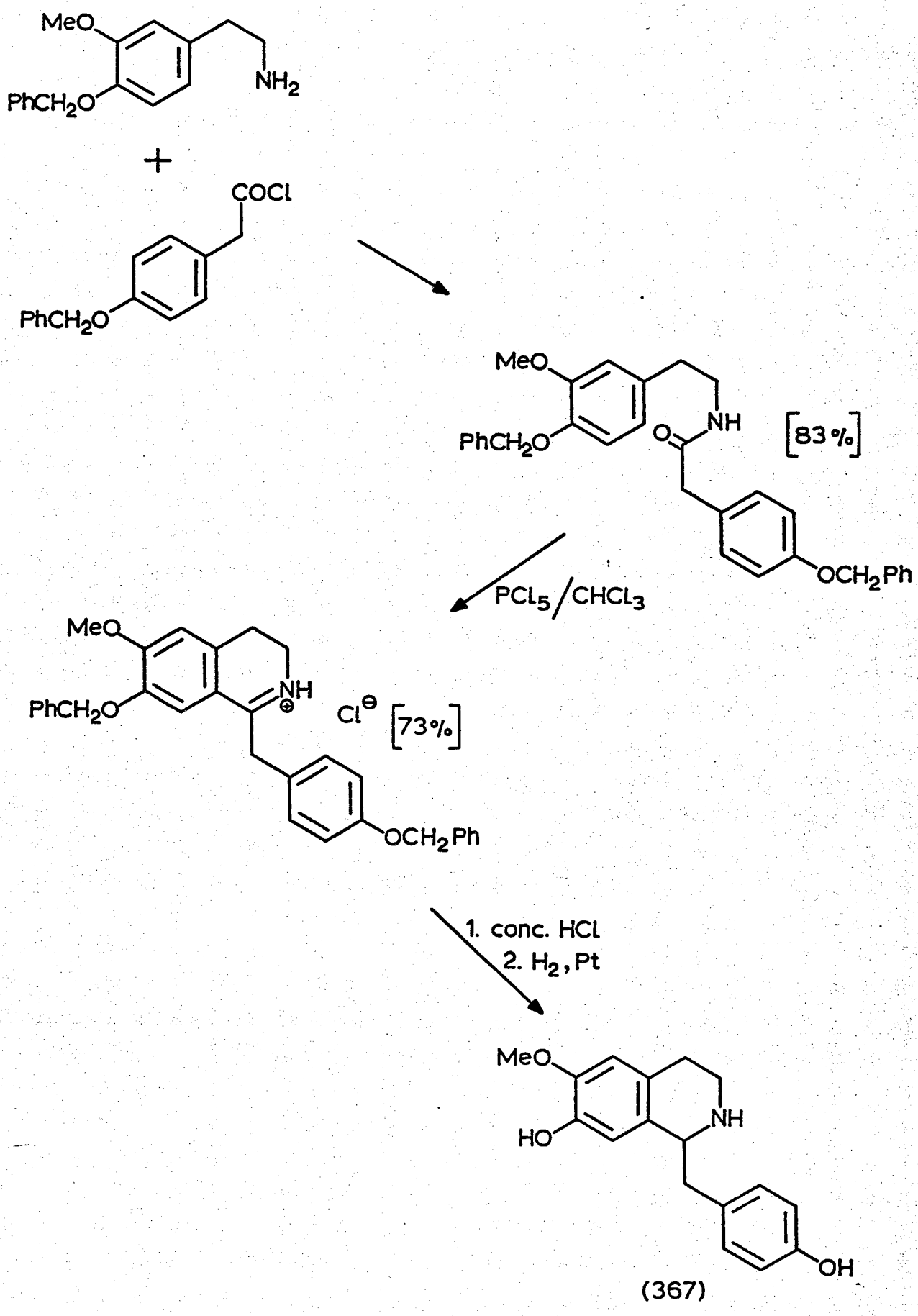
Oxidation of the α-methylene was claimed to probably occur during work-up.[290,299] It has been shown that if a 3,4-dihydroisoquinoline is stirred for 1-3 weeks in air, an imino ketone is obtained which may be cleanly reduced to an imino alcohol with sodium borohydride.[300]

e.g:



b) Other procedures.

In their synthesis of racemic coclaurine (367) K.Kratzl and G.Billek[297] employed the synthetic route shown below:

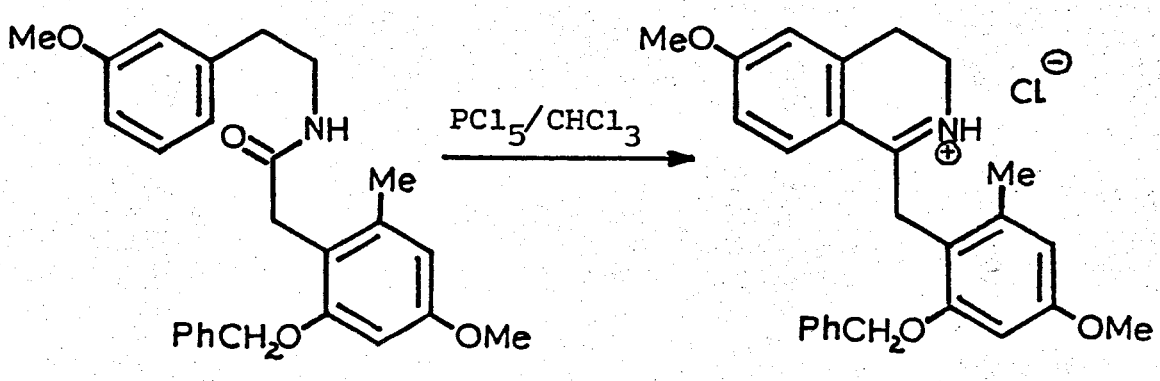

MeO
PhCH2O
NH2
+
COCl
PhCH2O
MeO
PhCH2O
NH
O
[83%]
OCH2Ph
PCl5/CHCl3
MeO
PhCH2O
NH
Cl⊖
[73%]
OCH2Ph
1. conc. HCl
2. H2, Pt
MeO
HO
NH
OH

(367)

The work-up of the Bischler-Napieralski cyclisation differed from that of Grewe and Fischer[292] in that after allowing the amide to stand for 24h with $PCl_5/CHCl_3$ the solution was poured into excess anhydrous ether and the resultant precipitated phosphorus complex collected by filtration and decomposed to the isoquinolium hydrochloride with ice-cold absolute methanol. Grewe and Fischer[292] decomposed the intermediate phosphorus complex by the addition of absolute methanol to the chloroform solution followed by removal of solvents *in vacuo* and subsequent addition of ethanol and 2N aqueous hydrochloric acid to obtain the crystalline hydrochloride product.

Upon repeating the procedure of Kratzl and Billek we obtained the 3,4-dihydroisoquinolinium hydrochloride (357) in 81% yield.

At this time a paper appeared in the literature by H.C.Beyerman *et.al.*[135] in which the synthesis of the 3,4-dihydroisoquinolinium hydrochloride (376) was described by cyclodehydration of the amide (375) with phosphorus pentachloride in chloroform.



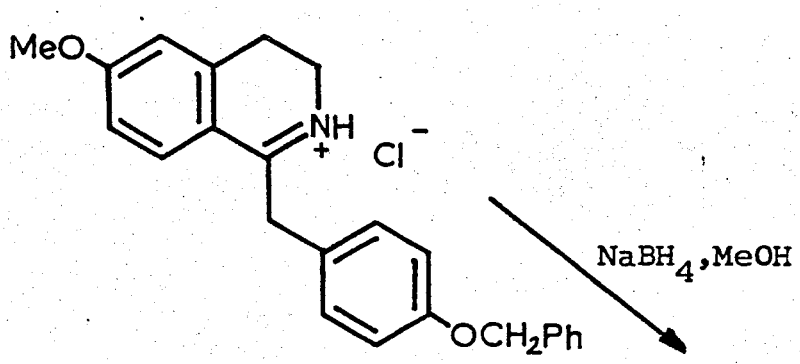
(375) (376)

Beyerman employed essentially the same method as Grewe and Fischer[292] except that concentrated hydrochloric acid was used *in lieu* of aqueous 2N HCl to induce crystallisation of the isoquinolinium hydrochloride salt (376) from the ethanolic product solution. Employing the

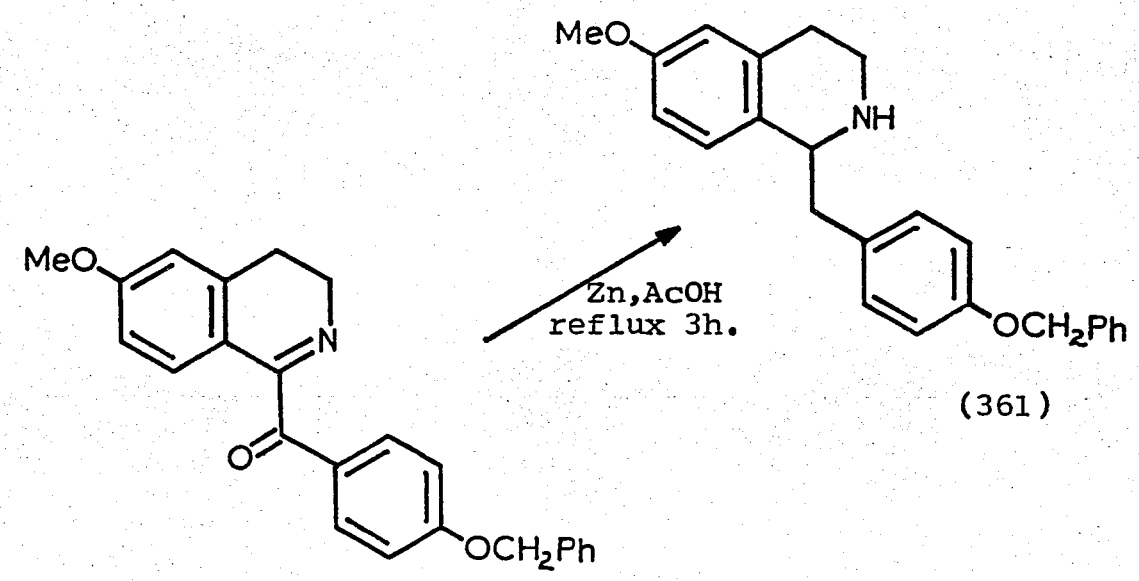
procedure of Beyerman et.al.[135] for the related compound (375) we obtained the 3,4-dihydro compound (357) in 95% yield.

(2) Synthesis of 1-Benzyl-1,2,3,4-tetrahydroisoquinolines: Observations in the N.m.r. spectrum.

Sodium borohydride reduction of the 3,4-dihydroisoquinolinium compound (357) proceeded smoothly and the racemic 1,2,3,4-tetrahydro compound (361) was obtained in 94% yield. Compound (361) was also obtained in 52% yield from the previously synthesised imino-ketone (369) by treatment with zinc dust in refluxing acetic acid.[299]



(357)

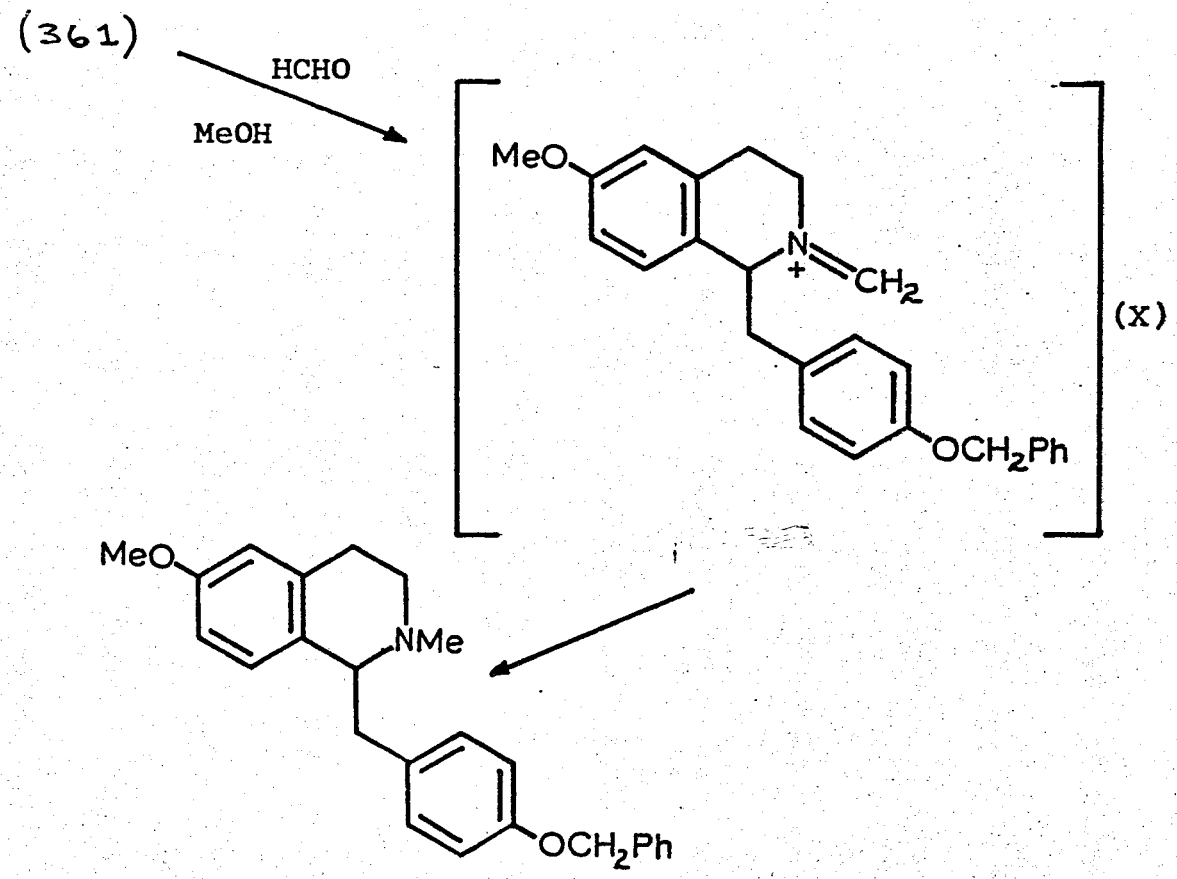


(361)

(369)

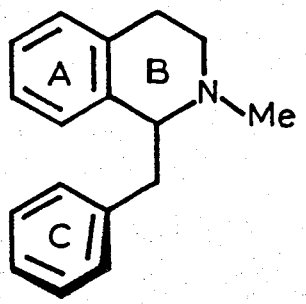
Treatment of the secondary base (361) (m.p.131-132°C) with formalin and sodium borohydride[301] afforded the N-methyl

compound (362) (m.p.69-71°C) presumably via the intermediacy of the quaternary Schiff base (X)

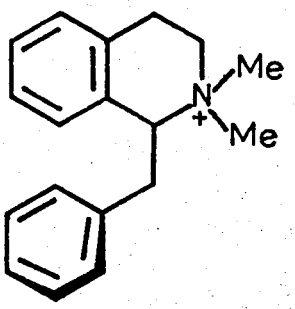


(362)

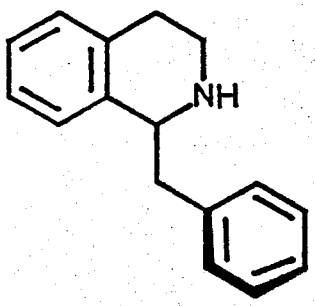
As a result of the work carried out on the n.m.r. spectra of 1-benzyltetrahydroisoquinolines an interesting conformational effect has been described [302-308] which indicates that although in the tertiary and quaternary bases the more stable conformation is the one shown in (I) and (II) where the benzyl group is below the benzene ring of the tetrahydroisoquinoline moeity, in the secondary bases conformation (III) with the benzyl group situated in the opposite direction is the most stable.



(I)



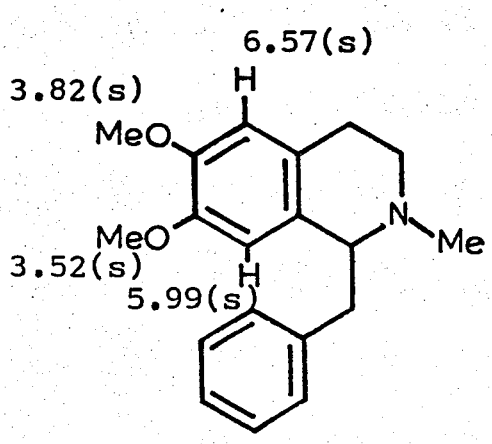
(II)

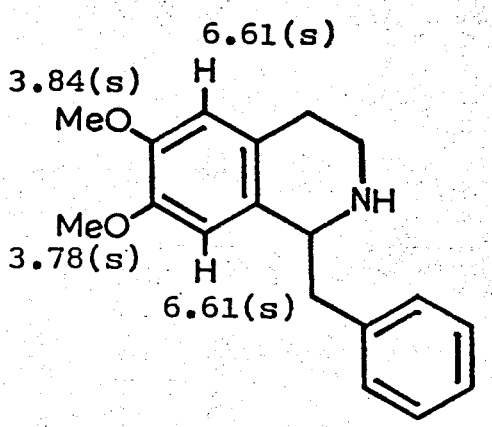


(III)

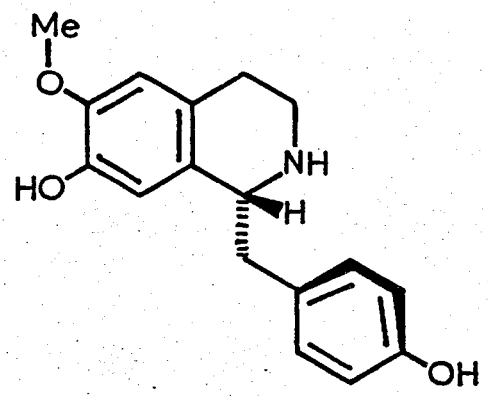
This situation is detected by the marked influence (upfield shift) of the ring current of the benzene nucleus C of the tertiary and quaternary bases on the aromatic proton at C-8 and on the protons of the methoxyl group (if any) located at C-7. Upfield shifts of about 0.52ppm are found for the proton at C-8 when compared with the proton at C-5, and of about 0.32ppm for the methoxyl protons at C-7 if they are compared with those of a similar group placed at C-6. These shifts are not observed in the case of secondary bases (III) or when the benzyl group is absent.[302-308]

e.g:



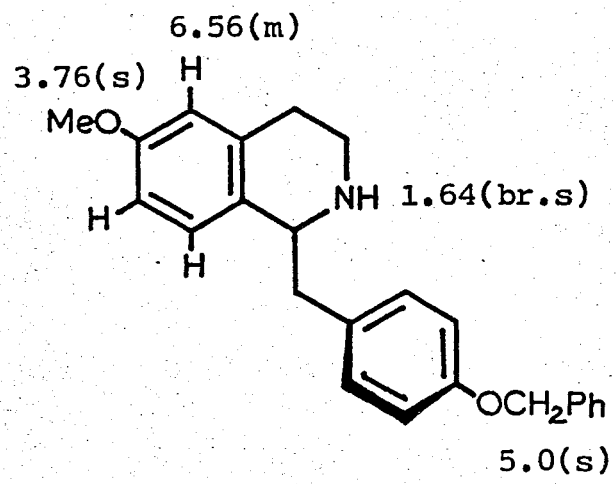


An X-ray study of the hydrobromide of D(+)-coclaurine has confirmed its structure to be (377) in the solid.[309]

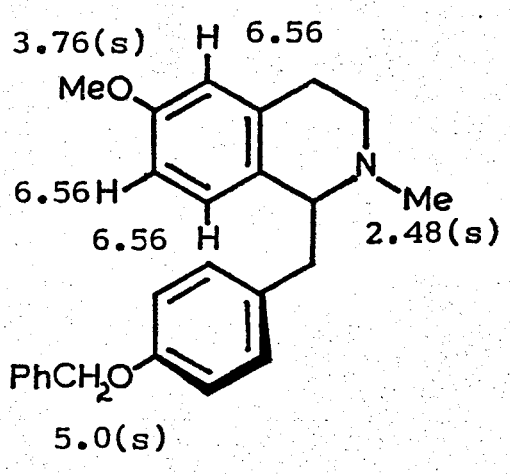


(377)

Comparison of the n.m.r. spectra of our secondary base (361) Fig.9 and the tertiary base (362) Fig.10 showed agreement with these observations. The conformation of the benzyl group in (361) and (362) is as depicted below.



(361)



(362)

The secondary base (361) exhibits a complex pattern for the aromatic protons, the signal at δ6.56 is assigned to the proton at C-5 of ring-A. The proton at C-7 appears as a

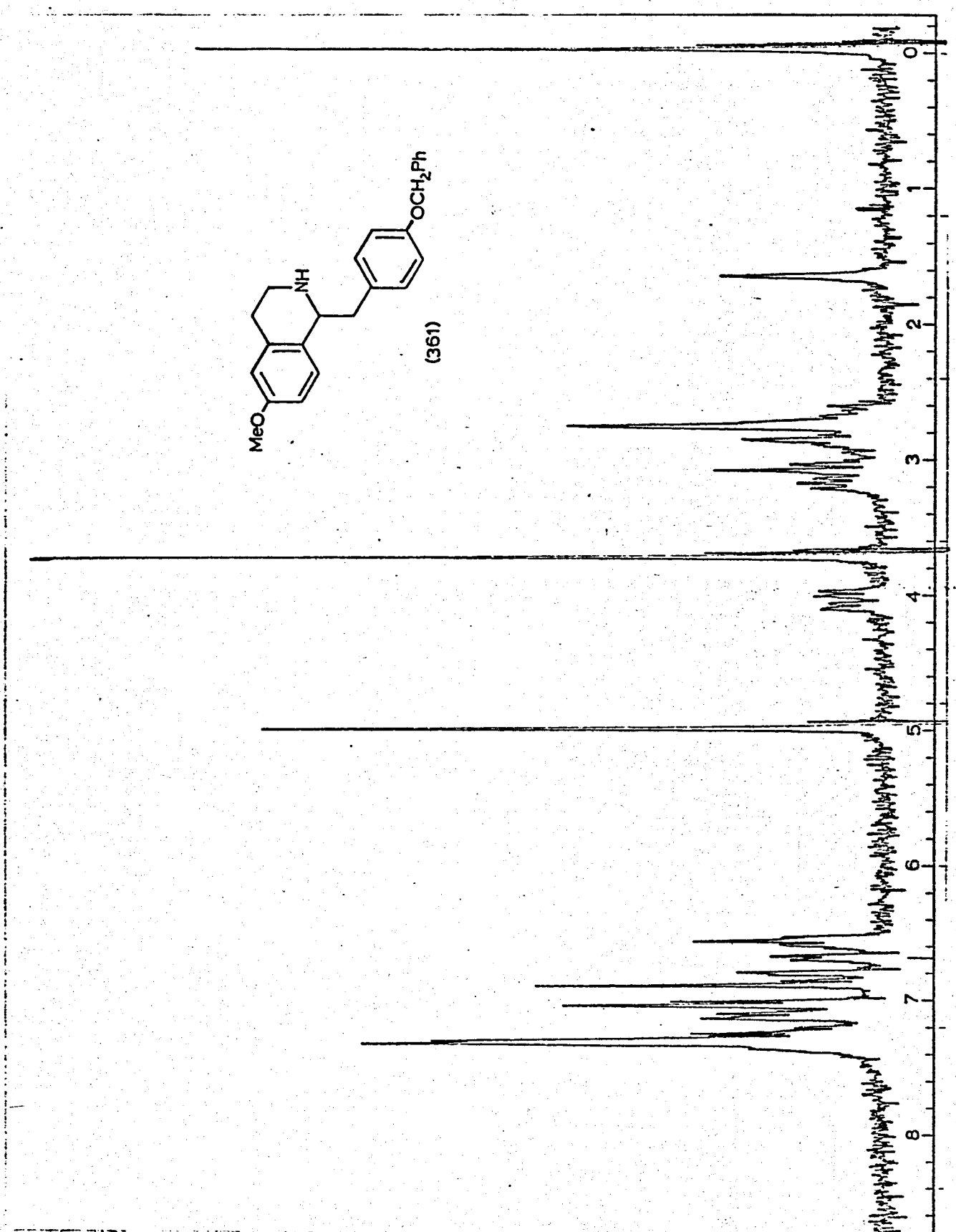


Fig.9.

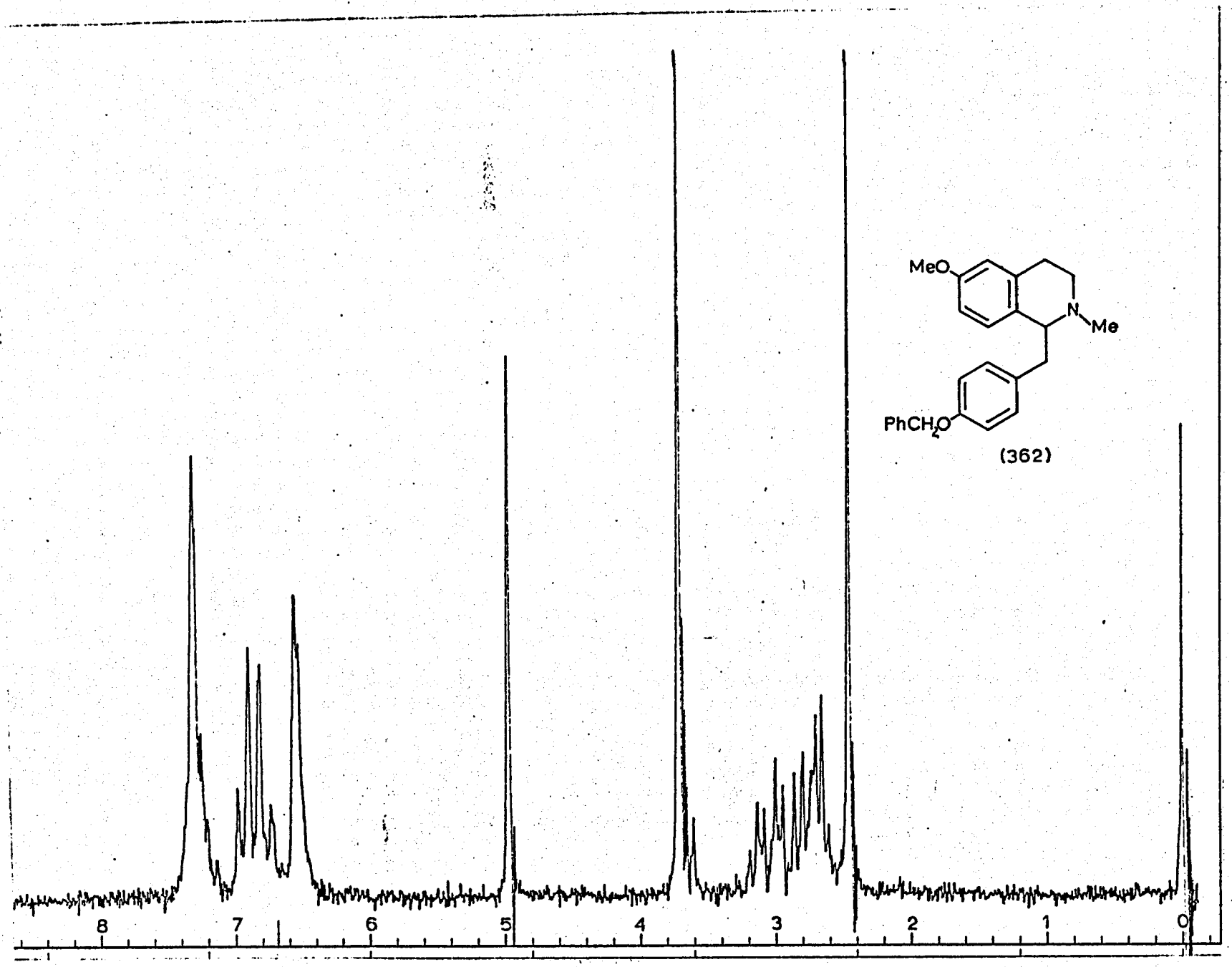
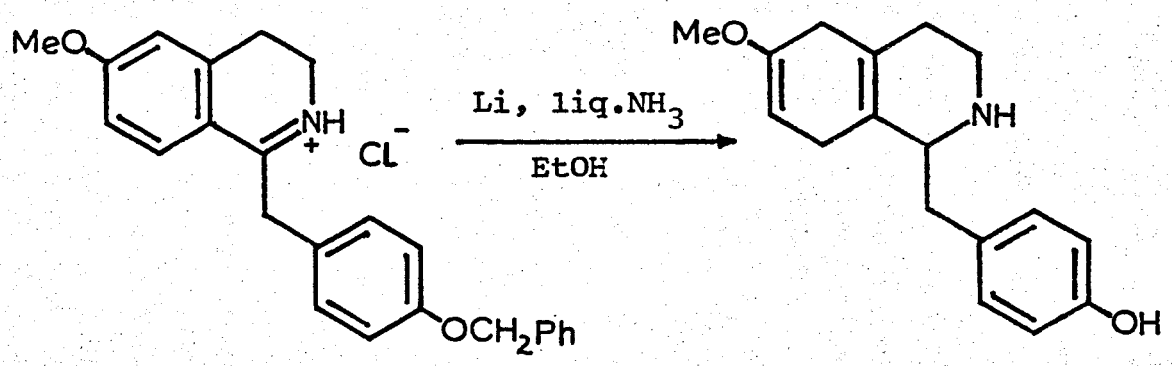


Fig.10.

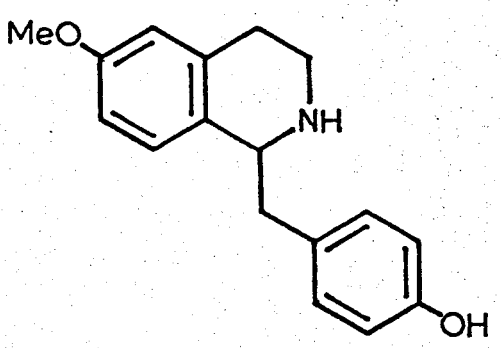
doublet (J_o 10Hz) centred at δ6.65 further split by meta coupling (J_m 3Hz) with C-5. The signal due to the proton at C-8 is obscured by the other aromatic proton resonances. The aromatic region of the spectrum is simplified in the case of the N-methyl compound (362) and all three protons of ring-A appear as a broad signal at δ6.56. Ring-C of the 1-benzyl group producing a marked shielding effect on the protons at C-7 and C-8 in conformation (362). The A_2B_2 quartet for the aromatic protons of ring-C is clearly distinguishable at δ6.88 and protons of the benzyloxy protecting group as a broad signal at δ7.30 ppm.

(3) Birch reduction of 3,4-dihydro and 1,2,3,4-tetrahydro-1-benzylisoquinolines.

Compound (357) was subjected to a Birch reduction.[182,310] Upon repeating the procedure used by Grewe et.al.[291] to obtain (351)(cf. earlier p.176) we found that together with the required 1,2,3,4,5,8-hexahydroisoquinoline (358) there was also formed the 1,2,3,4-tetrahydroisoquinoline (378) as a by product. The presence of (378) was suggested by the n.m.r. spectrum.

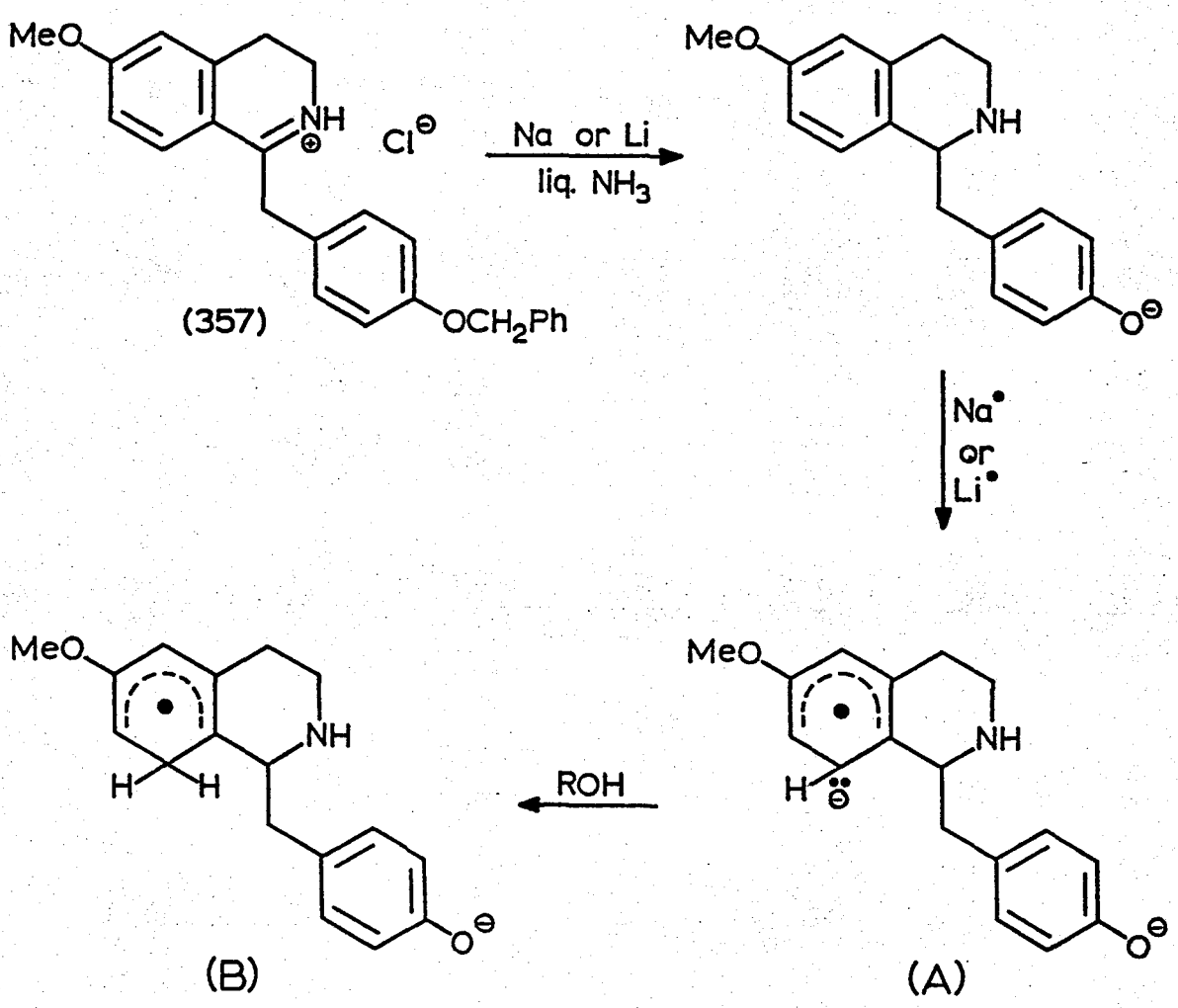


(357) (358)



(378)

Repeated recrystallisation from ethanol afforded the required compound (358) in a pure state. In the alkaline medium the benzyl ether is cleaved during the Birch reduction yielding a phenolate anion, which prevents further reduction of the 1-benzyl group on the isoquinoline moeity. The 1,2 double bond of the latter is also reduced. A mechanistic interpretation[275] of the Birch reduction to the diene (358) is given in Fig. 11. Addition of an electron to the aromatic nucleus produces the anion radical (A)[311] in which the greatest free charge density is meta- to the methoxyl group.[312] Protonation gives the radical (B) and addition of a second electron forms the mesomeric anion (C). The conditions under which Birch reduction occurs favour kinetically controlled addition of the second proton to the position of greatest free charge density, ie. the centre of the pentadienate anion[313], to give the unconjugated diene (D).



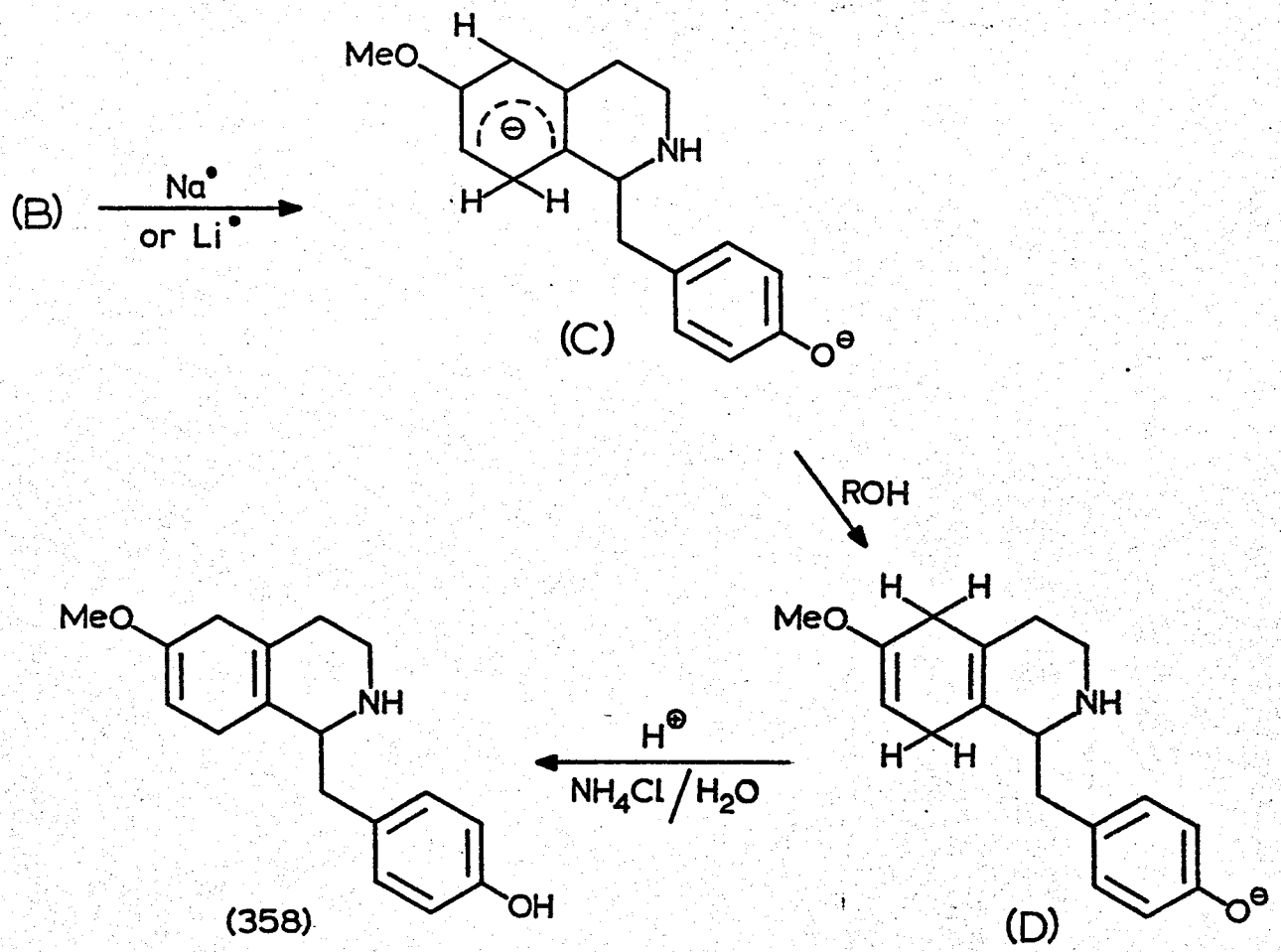
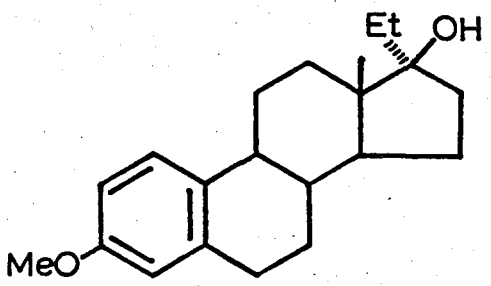


Fig 11

In the Birch reduction, the proton donor is an alcohol which is a much stronger acid than the conjugate acid (D) of the anion (C). When no alcohol is present, the more weakly acidic ammonia molecule acts as proton donor and gives the thermodynamically controlled addition product.[178] Unconjugated dihydroanisoles, formed by Birch reduction, can be isomerised to conjugated products by potassamide or sodamide in liquid ammonia.[178,228,315] The methoxyl group then becomes fully- rather than cross-conjugated with the diene system in the ring.[275]

Wilds and Nelson[187] have attributed the apparent superiority of lithium as the alkali metal in the Birch reduction to its greater reduction potential (-2.99v) in liquid ammonia compared to that of sodium (-2.59v) and potassium (-2.73v).

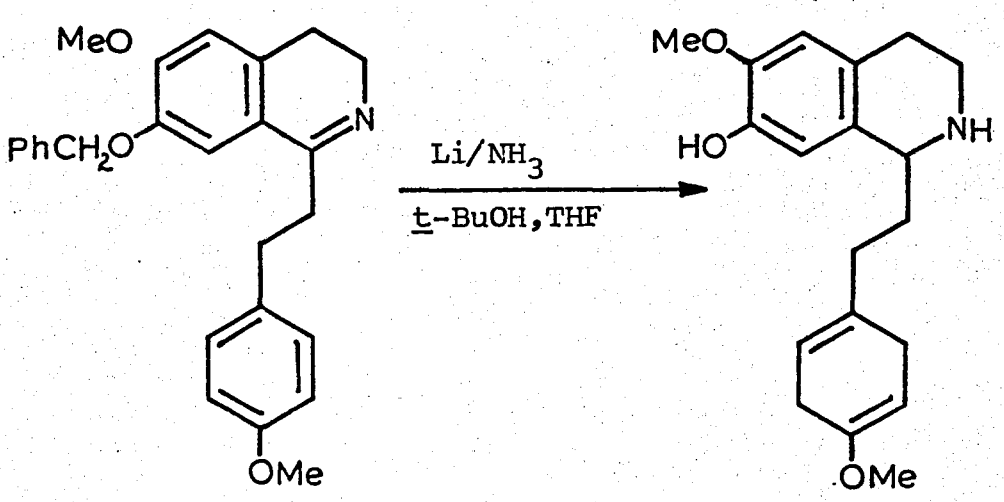
Since the Birch reduction of our 3,4-dihydro-compound (357) by the method of Grewe et.al.[291] did not give complete reduction we modified our conditions to those of H.L.Dryden et.al.[316] They found that under the normal Birch reduction conditions viz. liquid ammonia-ether and lithium or sodium with ethanol as proton donor, incomplete reduction of estradiol derivatives (e.g. 379) occurred due to the low solubility of the compounds in the reaction mixture.



(379)

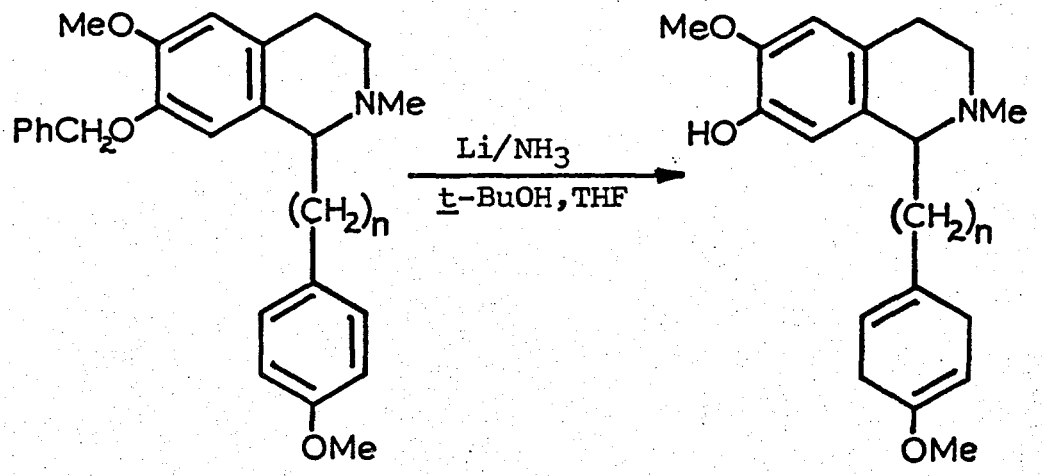
The typical Birch reduction mixture consists of a deep blue liquid phase covered by a layer of lithium-ammonia "bronze" and, in the hope of obtaining a more homogeneous mixture, Dryden et.al.[316] sought an additional cosolvent which might favour solution of the lithium as well as the steroid. They found that not only did lithium react relatively slowly with an ammonia-THF- t-butyl alcohol mixture (2:1:1) but that such a mixture readily dissolved 17-ethyl-estradiol-3-methyl ether (379). The mixture also appeared to retain more lithium in the lower phase than ammonia-THF alone.

In 1973 W.V.Curran[317] utilised the Dryden modifica-



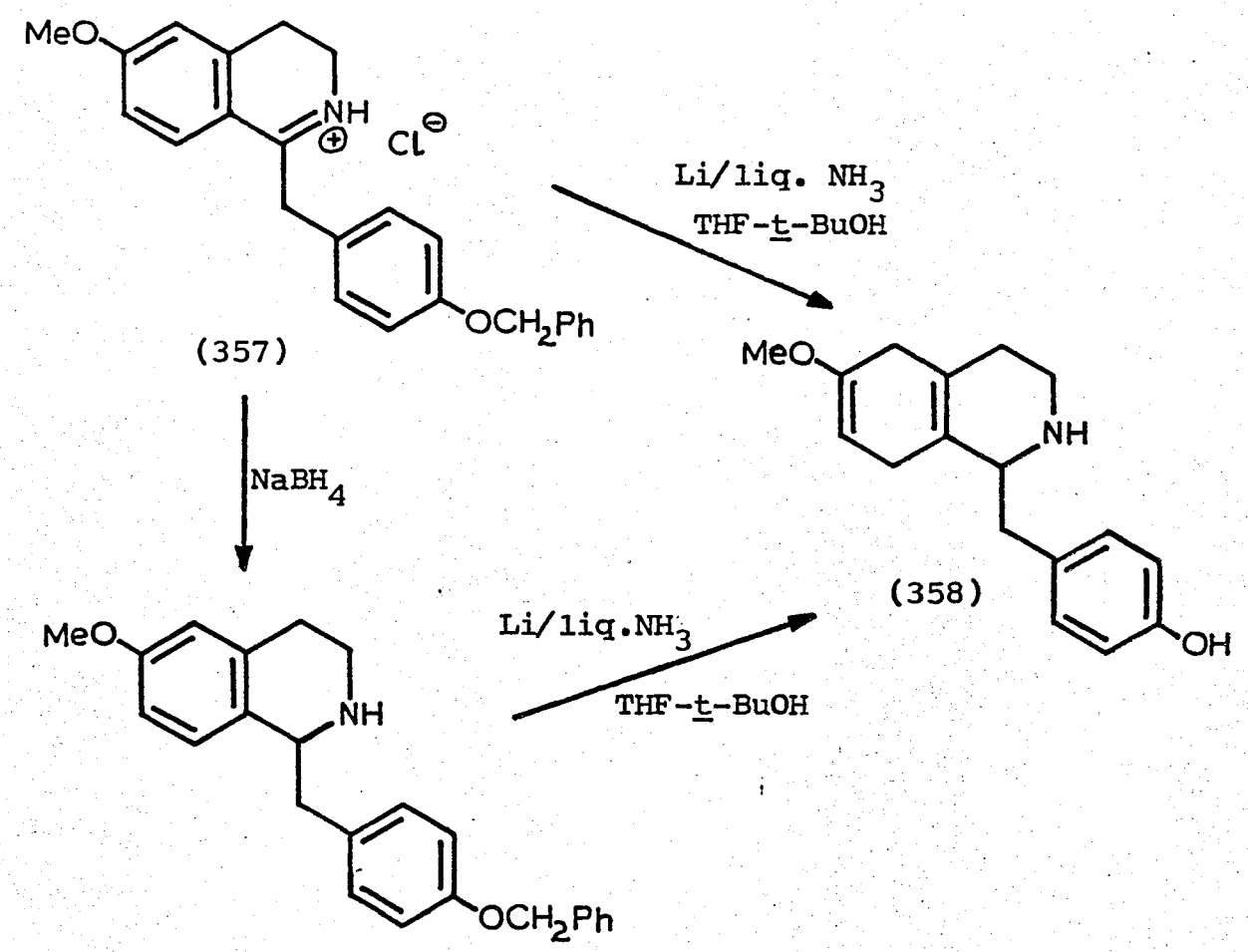
(380) (381)

tion of the Birch reduction to obtain the enol ether (381) from the dihydroisoquinolines (380) in 83% yield. Curran also obtained the enol ether (383) from the tetrahydroisoquinolines (382) in 78% (n=1) and 60% (n=2) yield by the same procedure.



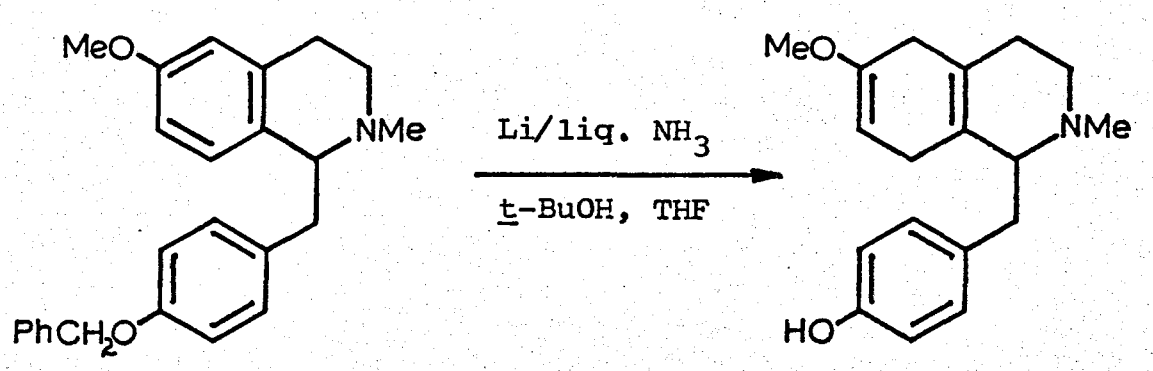
(382) (383)

We found that by use of lithium metal in liquid ammonia in the presence of THF and t-butanol as co-solvents that the 3,4-dihydroisoquinolinium hydrochloride (357) could be effectively and reproducibly reduced to the hexahydro compound (358) in yields of 80-87%. Birch reduction of the 1,2,3,4-tetrahydro compound (361), obtained as described earlier, by the Dryden procedure also afforded the hexahydro base (358) in 78% yield. Compound (358) (m.p. 199-201°C) showed a bathochromic shift to longer wavelength in its ultraviolet absorption spectrum in the presence of alkali indicating that it was phenolic.[318] The infrared spectrum of (358) showed bands at 1695 and 1665cm^{-1} assigned to the double bonds of the dihydroanisole system[188a,291] and a sharp band at 3290cm^{-1} due to the secondary amine NH. In the n.m.r. the signal for the C-7 olefinic proton appeared as a broad signal not fully resolved at δ4.66. The C-1 methine proton resonated as a broadened quartet at δ3.25 coupled to the adjacent α-methylene protons. The distinguishing features in the n.m.r. of the hexahydro compound (358) and the by product (378) obtained by the procedure of



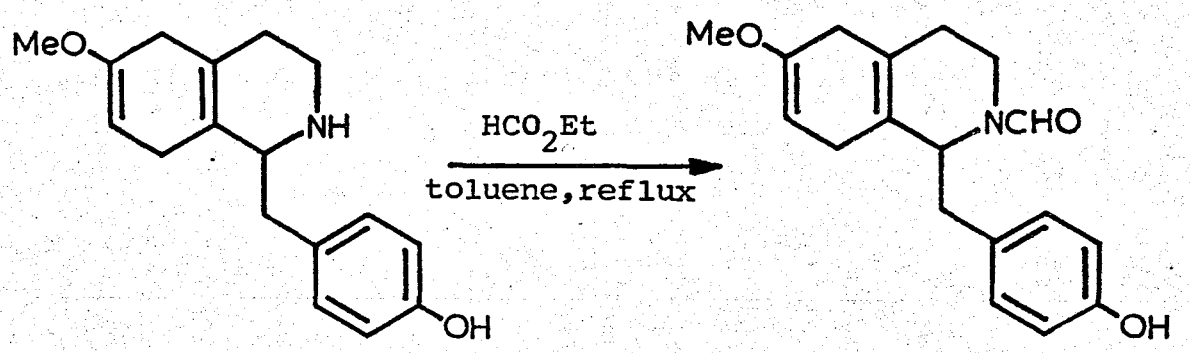
Grewe et.al.[291] are the position of the methoxyl resonances δ3.5 in (358) and 3.8 in (378), the C-1 methine proton at δ3.25 in (358) and at lower field 4.05 in (378) (due to the deshielding effect of the adjacent aryl ring). The aromatic region of the spectrum of (358) is a simple A_2B_2 quartet but (378) shows a more complex pattern.

Birch reduction of the tertiary base (362) with lithium in liquid ammonia with THF and t-butanol co-solvents, afforded the hexahydro-N-methylisoquinoline (363) in 81% yield.



(362) (363)

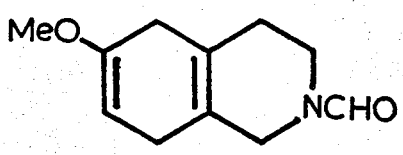
Selective formylation of the secondary amine function of the hexahydro compound (358) was next investigated. Treatment of (358) with formic acid and dicyclohexylcarbodiimide, a reagent combination employed in the peptide field for N-blocking of amino acids, afforded the N-formyl derivative (359) in low yield. More satisfactorily the secondary base (358) was formylated smoothly with ethyl formate in refluxing toluene and the N-formyl compound (359) was isolated in 92% yield (m.p.204-205°C).



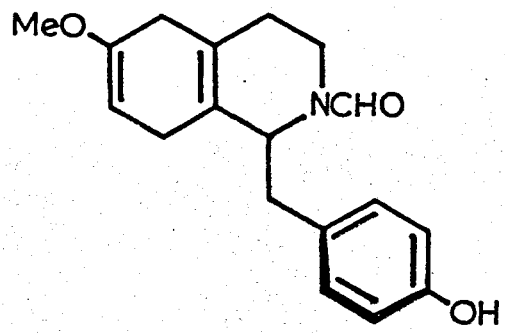
(358) (359)

The n.m.r. spectrum of (359) clearly shows the presence of two relatively stable rotational isomers in the ratio 2:1. The n.m.r. spectrum of the unsubstituted N-formyl-6-methoxy-1,2,3,4,5,8-hexahydroisoquinoline (306)

(cf. Discussion Pt.2 p.152) shows the formyl rotamers as two signals at δ8.07 and 8.14 in the ratio 5:4. In the case of the 1-benzyl compound (359) the formyl protons of the rotamers occur at δ7.4 and 7.9 in the ratio 2:1.



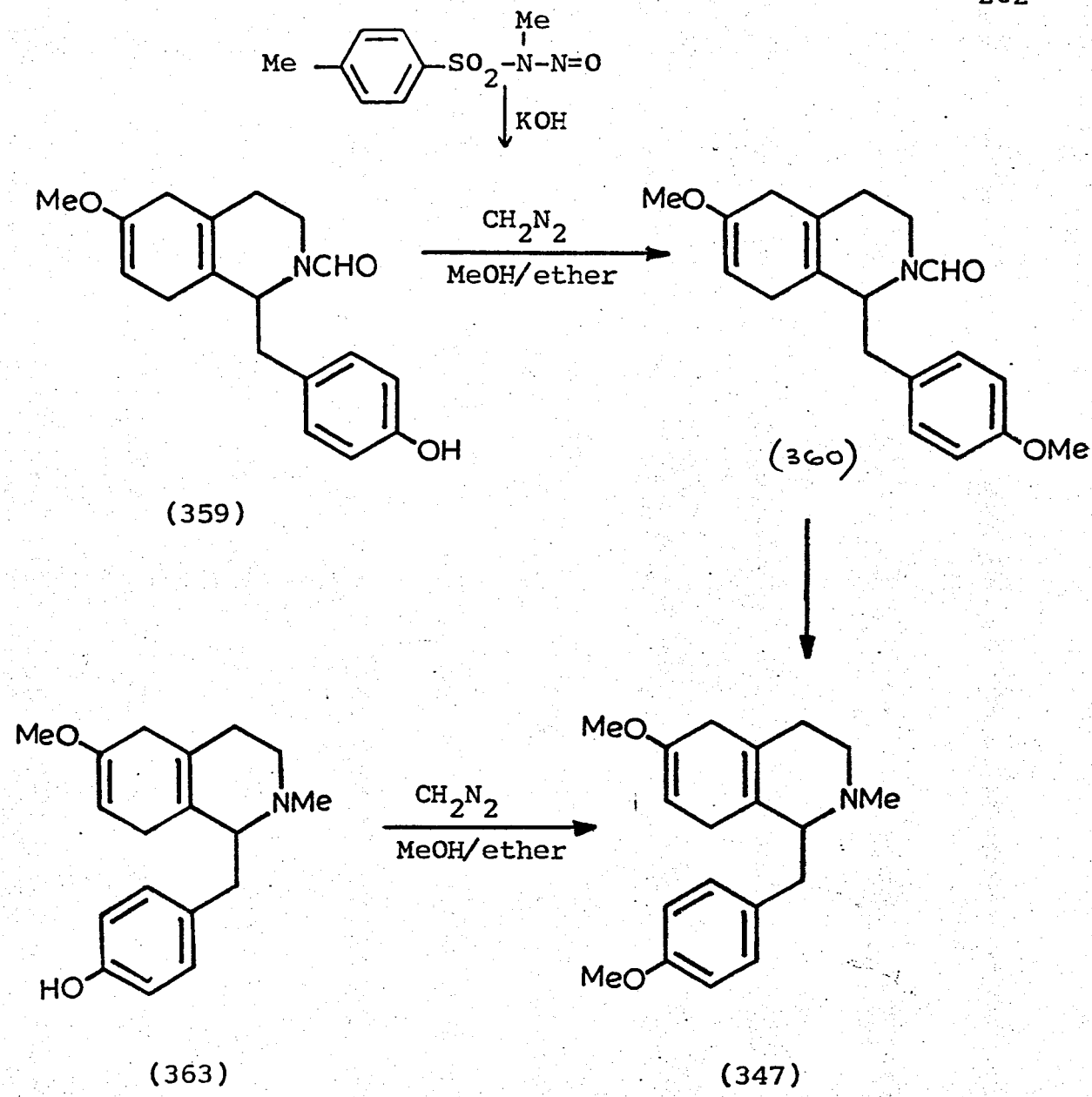
(306)



(359)

The results suggest that the 1-benzyl ring is spending the majority of its time away from ring A and shielding the formyl group. This is borne out by the move to higher field of both formyl rotamer signals, one shifting more than the other due to its closer proximity of the flat surface to the benzyl aromatic ring.

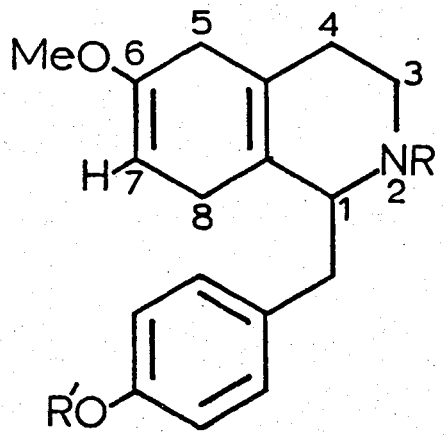
Treatment of the N-formyl compound (359) with excess ethereal diazomethane (generated from p-tolysulphonylmethyl-nitrosamide "Diazald") in absolute methanol afforded the O-methylated analogue (360) (m.p. 121-122°C) in 90% yield. Similarly the N-methyl compound (363) afforded the O-methylated tertiary base (347) (m.p. 84-85°C) in 80% yield. The N-methyl compound (347) could also be obtained by lithium aluminium hydride reduction of the N-formyl compound (360).



(359) (360)

(363) (347)

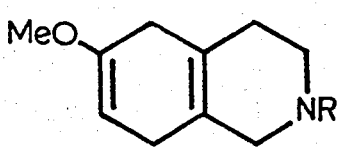
The preferred conformation of the 1-benzyl group is as shown and is borne out by the observed shift to higher field of the vinyl protons at C-7 in the N-methyl compounds (363) and (347) as compared with the N-formyl compounds (359) and (360) and the secondary base (358), see Table 3.



Compound	R	R'	C-7 olefinic proton resonance
358	H	H	4.66
359	CHO	H	4.70
360	CHO	Me	4.70
363	Me	H	4.52
347	Me	Me	4.50

Table 3.

This completes the total synthesis of the 1-benzyl analogues of the previously discussed N-formyl and N-methyl hexahydroisoquinolines (316; R=Me and R=CHO).



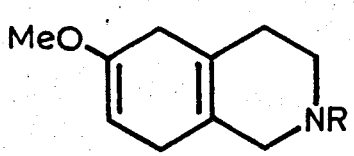
(316)

The compounds obtained were present as racemic (±) mixtures as no resolutions were carried out. We next investigated the base-catalysed isomerisation and Diels-Alder condensation of the 1-benzyl-hexahydroisoquinolines (347) and (360).

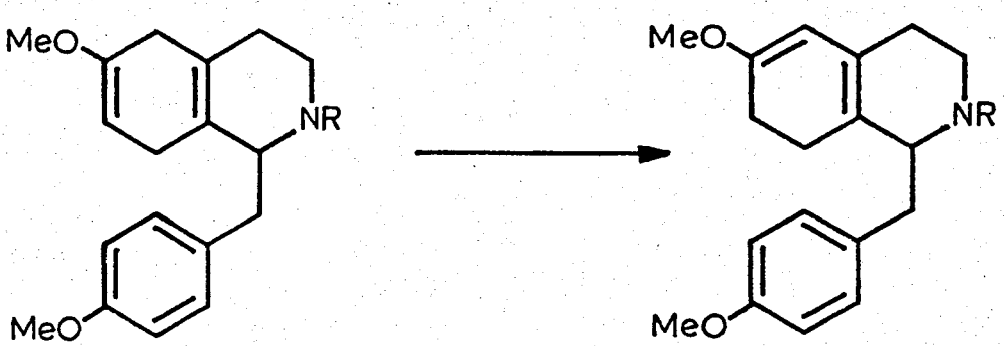
C Base-catalysed isomerisation and Diels-Alder studies of 1-benzyl-1,2,3,4,5,8-hexahydroisoquinolines.

As outlined earlier, (cf. Discussion p.117) the base-catalysed isomerisation of 1,2,3,4,5,8-hexahydro-6-methoxy-2-methylisoquinoline has been reported by Crabb and Wilkinson.[234] We have isomerised the 2-methyl-6-methoxyisoquinoline (316, R=Me) in the same manner and subsequently condensed the conjugated diene obtained with various dienophiles to afford 6,8a-ethano-bridged compounds. We have also studied the isomerisation and Diels-Alder condensation with a 2-formyl analogue (316, R=CHO) employing a different procedure for the isomerisation from that reported by Crabb et.al.[234] for the N-methyl compound, viz potassium t-pentoxide in DMSO.

It was anticipated that base-catalysed isomerisation of the novel hexahydro-1-benzyl compounds (347), (318, R=Me)



(316)

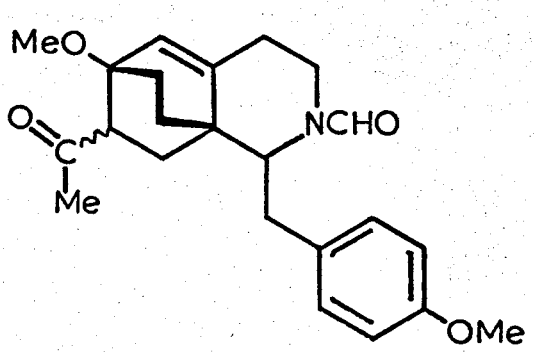


(318) (319)

and (360), (318; R=CHO) would proceed in a similar manner to the hexahydroisoquinolines (316; R=Me and R=CHO) to afford conjugated dienes (319; R=CHO and R=Me).

The isomerisation of the N-formyl-1-benzyl compound (360) was studied by use of the same conditions as those employed by us for the hexahydro-2-formylisoquinoline (306)(316; R=CHO) with potassium t-pentoxide in anhydrous DMSO. The production of the conjugated diene was monitored by extracting aliquots and quenching with water; the diene was extracted with chloroform, dried and evaporated and the n.m.r. spectrum and the infrared spectrum recorded. The u.v. spectrum was not a satisfactory method of determining the amount of conjugated diene present as its absorption was masked by the absorption of the aryl group of the 1-benzylisoquinoline moeity. The n.m.r. of the isomerisation mixture showed two peaks in the olefinic region at δ4.70 and 4.75, the former broader peak being due to the C-7 proton of the unconjugated compound (318; R=CHO) and the latter sharper peak was assigned to the C-5 proton of the diene (319; R=CHO). The spectrum also showed two sharp methoxy absortions at δ3.62 and 3.58, the former assigned to the conjugated diene methoxyl and the latter was in accord with the unconjugated diene methoxyl on the dihydroanisole system. From the n.m.r. integrals the relative proportions of dienes (318;R=CHO) : (319;R=CHO) was 36% : 74%.

The isomerisation mixture containing the conjugated diene (319; R=CHO) was heated under reflux with methyl vinyl

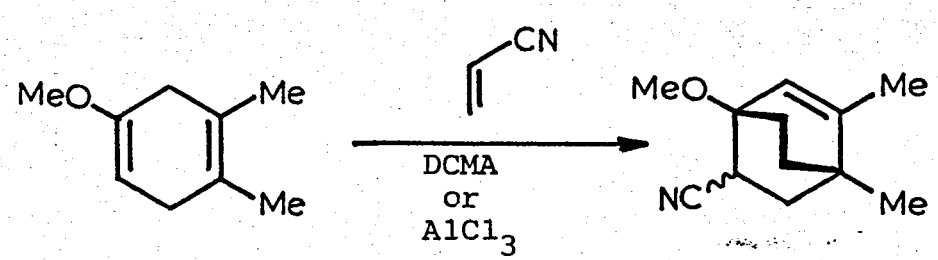


(384)

ketone in the presence of a trace of hydroquinone as stabiliser for periods of 3-24h. However, after exhaustive column chromatography and thin layer chromatographic separation no Diels-Alder adduct (384) could be isolated.

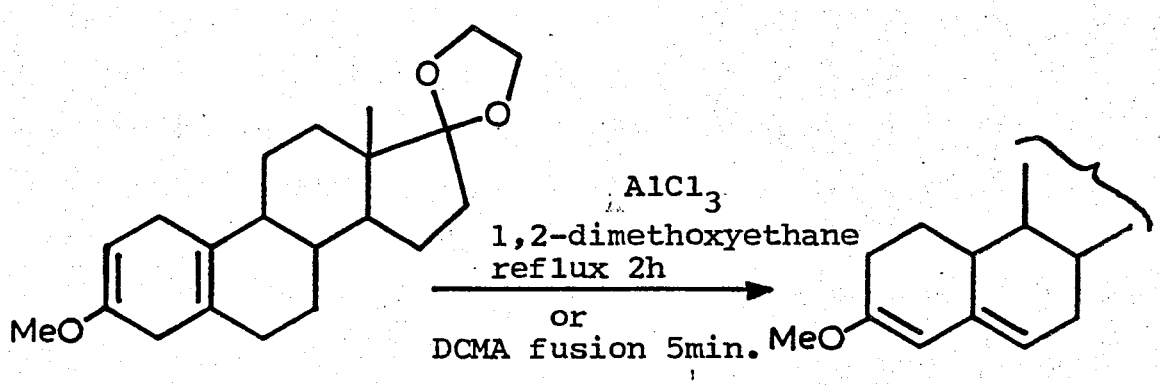
Polymerisation of the dienophile appeared to occur together with aromatisation of the conjugated diene and no pure products were isolated. The Diels-Alder reaction was repeated in refluxing benzene and toluene for similar reaction times but again no Diels-Alder adduct was obtained. We thus investigated alternative conditions for the reaction.

Literature reports of the equilibration of the various 1-methoxy-1,4-dienes (obtained by metal-liquid ammonia reduction of anisole derivatives) with the more stable 1,3-dienes include the use of potassamide in liquid ammonia through salt formation involving the 6-position of the dihydroanisole system.[182] It has also been shown that conjugation can be brought about by electron accepting substances such as dienophiles[231]; in particular dichloromaleic anhydride (DCMA) is an effective catalyst.[319] The Lewis acid aluminium chloride and the Bronsted (protic) acid p-toluenesulphonic acid (PTSA) have also been observed to be active in the same manner.[320] A.J.Birch and K.P.Dastur[320] used the initial 1,4-diene directly with a dienophile and a catalyst, rather than the equilibrium mixture obtained via a base-catalysed isomerisation. For example, the Diels-Alder reaction of 1-methoxy-4,5-dimethylcyclohexa-1,4-diene (385) with acrylonitrile and DCMA or aluminium chloride under reflux gave the adduct (386) in 74% yield.



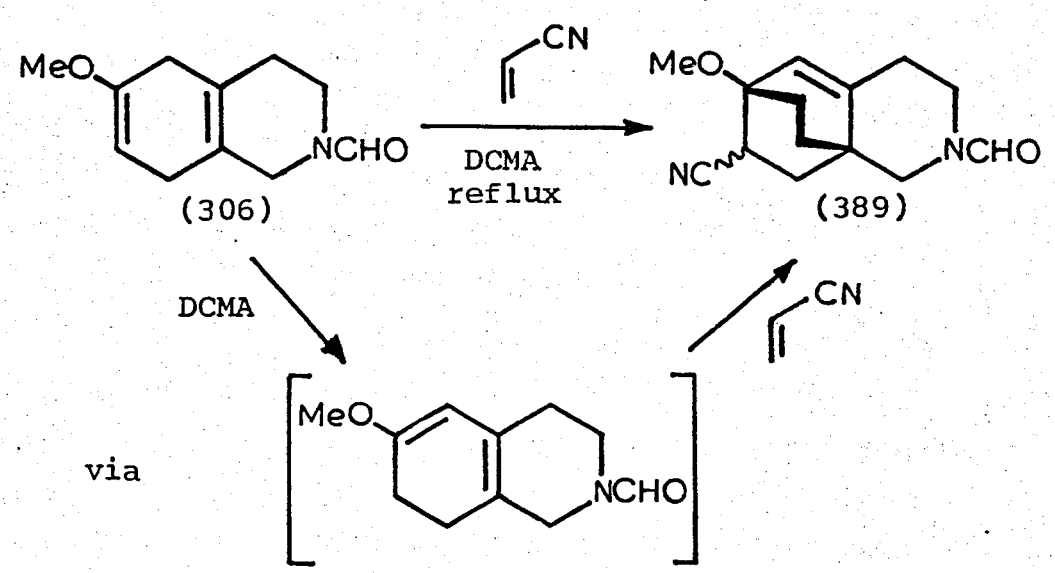
(385) (386)

The reaction was found to be generally applicable to dihydroanisoles of type (385). However, it was observed that 17,17-ethylenedioxy-3-methoxyoestra-2,5(10)-diene (387) did not undergo Diels-Alder condensation under similar conditions since it yielded predominantly the exocyclic 3,5(6)-diene (388).[320]



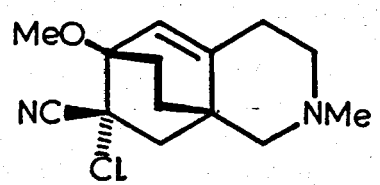
(387) (388)

We employed dichloromaleic anhydride (DCMA) with the 2-formyl-hexahydroisoquinoline (306) and acrylonitrile under reflux as a model reaction. After 15 hours refluxing the Diels-Alder adduct (389) was obtained as a mixture of epimers in the ratio <u>exo</u> : <u>endo</u> <u>ca</u>. 5 : 3.



(306) (389)

Although the adducts were not obtained analytically pure the infrared spectrum of the viscous oil obtained, after column chromatography over neutral alumina, showed a strong nitrile absorption at 2240cm^{-1} together with the formyl group carbonyl at 1660cm^{-1}. The n.m.r. spectrum showed a sharp methoxy singlet at δ3.43, and olefinic proton resonances at 5.93 (exo nitrile) and 614 (endo nitrile) shielding of the C-5 olefinic proton in the exo-nitrile being analogous to that described earlier for the exo-nitrile-endo-chloro-adduct (291)(cf. p.143).



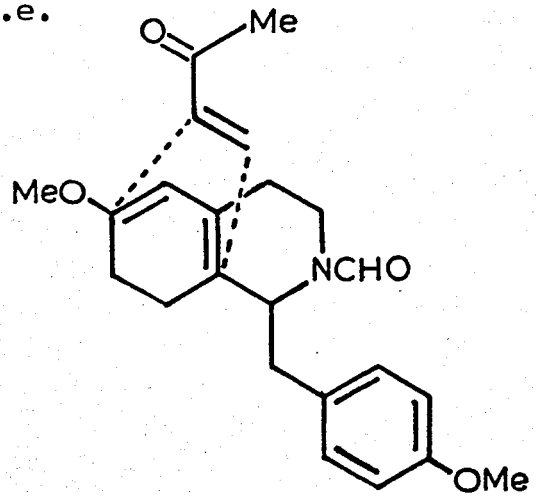
(291)

Since the use of DCMA proved promising we applied the same technique to the 1-benzyl-2-formyl compound (360), however even after extensive reflux periods (6-48h) with acrylonitrile, spectral and t.l.c. analysis of the product showed it to be starting material and no Diels-Alder adduct could be isolated.

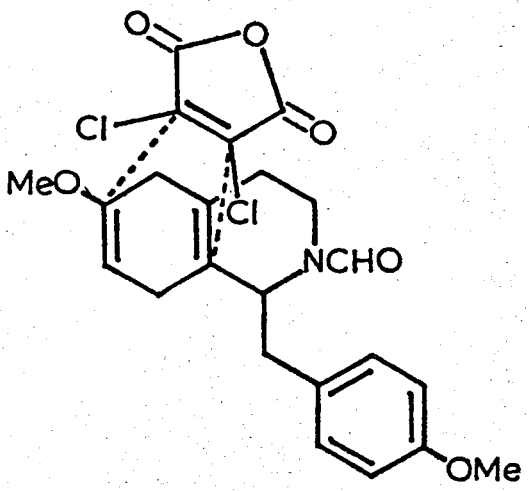
The conjugated diene (360) was also heated under reflux in 1,2-dimethoxyethane with DCMA to see if conjugation could be effected, however, spectral examination of the product showed it to be starting material and conjugation had not occurred.

It would appear that the 1-benzyl group could be exerting some steric interference to approach of dienophile in the conjugated diene (390). In the case of the DCMA catalysed reaction, the 1-benzyl group could be preventing the dichloromaleic anhydride from approaching sufficiently close to permit a charge-transfer complex to form prior to isomerisation.

i.e.



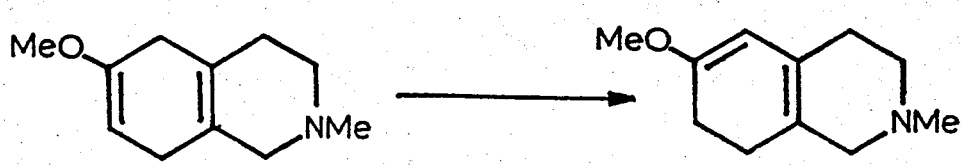
(390)



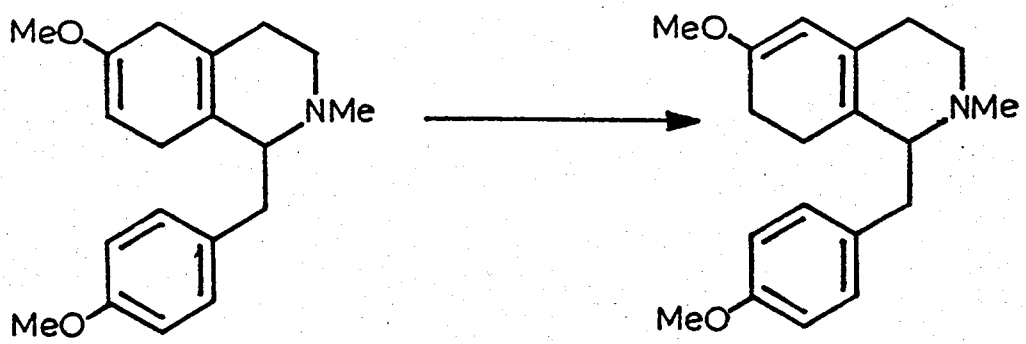
(360)

The DCMA *in situ* isomerisation and Diels-Alder reaction was also attempted with methyl acrylate as dienophile, however, spectral examination of the product indicated extensive aromatisation of ring-A had occurred and no Diels-Alder adduct was formed.

The base-catalysed isomerisation of the *N*-methyl-1-p-methoxybenzyl compound (347) was investigated employing potassium *t*-pentoxide in *t*-pentyl alcohol at 100°C, the conditions employed by Crabb and Wilkinson[234] for the hexahydroisoquinoline (248). However, after 4h at this temperature n.m.r. spectral analysis indicated that a 50:50 mixture of the conjugated diene (391) and the unconjugated diene (347) was present and no improvement utilising these isomerisation conditions could be obtained. We found that when the unconjugated diene (347) was heated with potassium *t*-pentoxide in dry DMSO for 1h at 60-65°C the conjugated diene (391) was obtained in high yield (*ca*. 90%).



(248) (250) 75%



(347) (391)

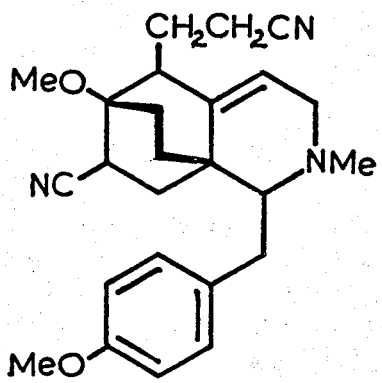
The infrared spectrum of the isomerisation mixture showed strong bands at 1675 and 1620cm^{-1} attributed to unconjugated and conjugated dienes respectively. The n.m.r. spectrum showed a sharp singlet at 4.58 due to the olefinic proton at C-5. The C-7 proton of the non-conjugated diene (347) was still just visible at δ4.5. This mixture containing the conjugated diene (391) was employed directly in subsequent Diels-Alder condensations. When the diene (391) was heated under reflux with methyl vinyl ketone, N-phenyl maleiimide in refluxing toluene, or methyl acrylate, for periods of 6-24h spectral analysis of the products indicated unchanged starting materials and no cycloadducts could be isolated. However, when the diene (391) was heated under reflux with acrylonitrile for 36h and the dark viscous product chromatographed over neutral alumina a dark green viscous oil was obtained. T.l.c. indicated that the product was a mixture which could not be separated nor obtained analytically pure.

The n.m.r. spectrum of the mixture showed three absorptions attributable to olefinic hydrogens in the ratio ca. 1 : 0.5 : 1, at δ4.7, 5.2 and 5.45. The total integral for these was equivalent to one proton assumming the aromatic signal integral to be four protons. The olefinic signals at δ4.7 and 5.2 were distinctly sharp ($w_{\frac{1}{2}}$∿4Hz) whereas the signal at δ5.45 was a broadened triplet (J 7Hz). Also evident in the n.m.r. were sharp singlets assigned to

methoxy groups at δ3.80, 3.58 and 3.56 together with singlets at 2.32 and 2.28 attributed to NMe groups.

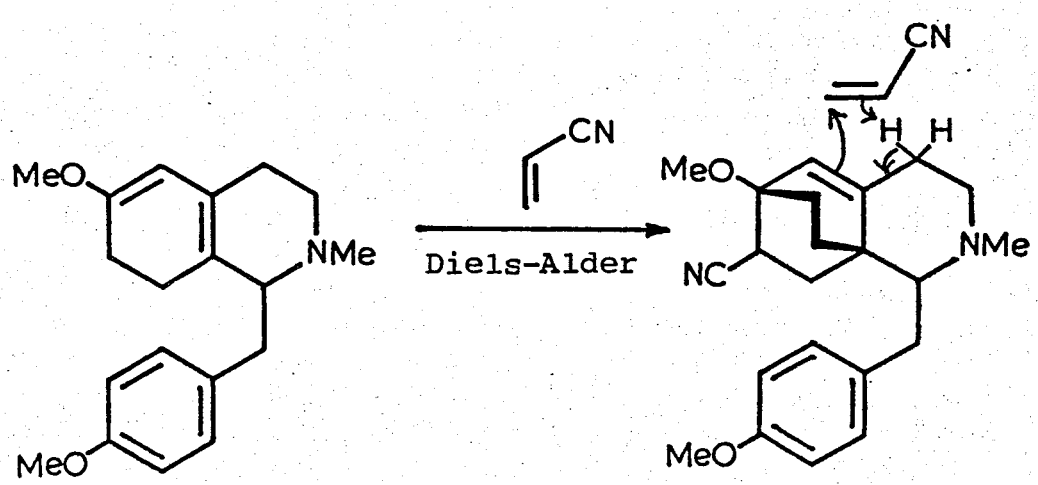
The infrared spectrum showed a sharp nitrile absorption at 2,250cm^{-1} together with C=C stretching frequencies at 1640 and 1610cm^{-1}.

The mass spectrum showed a molecular ion with accurate mass 405.2407, which corresponds to $C_{25}H_{31}N_3O_2$ (requires 405.2416).A possible structure in agreement with these data is (392)

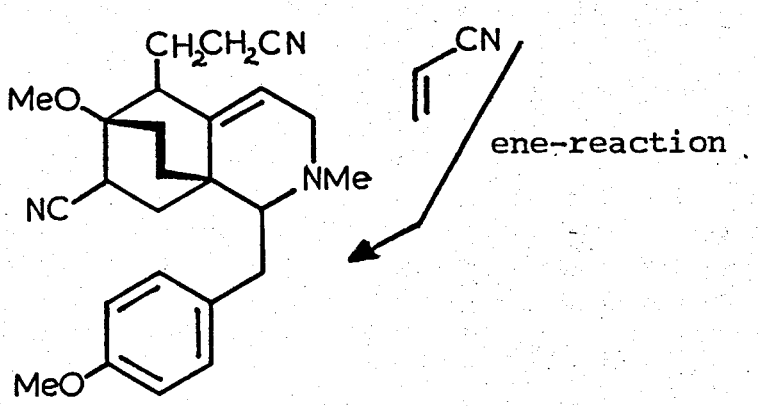


(392) M.Wt. 405.

This could arise by a Diels-Alder addition followed by an ene reaction[321] as shown:-



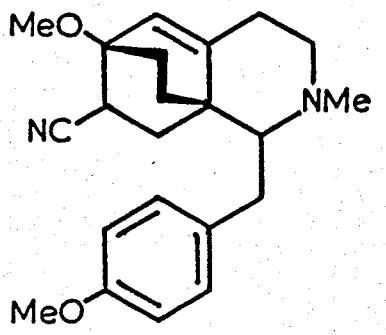
(391)



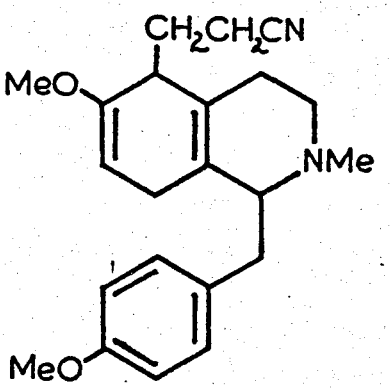
(392)

The structures of the other products remain more speculative. A peak in the mass spectrum of the mixed products occurs at $^{m}/e$ 352. An accurate mass measurement of this has not proved possible but the adjacent fragment ion at m/e 351 shows an accurate mass of 351.2077 corresponding to a molecular formula of $C_{22}H_{27}N_2O_2$ (requires 351.2072).

If it can be assumed that this latter fragment is an $[M-1]^+$ ion, i.e. the ion at m/e 352 represents a molecular ion, then two further structures can be advanced to correspond with such a value viz (393) and (394).

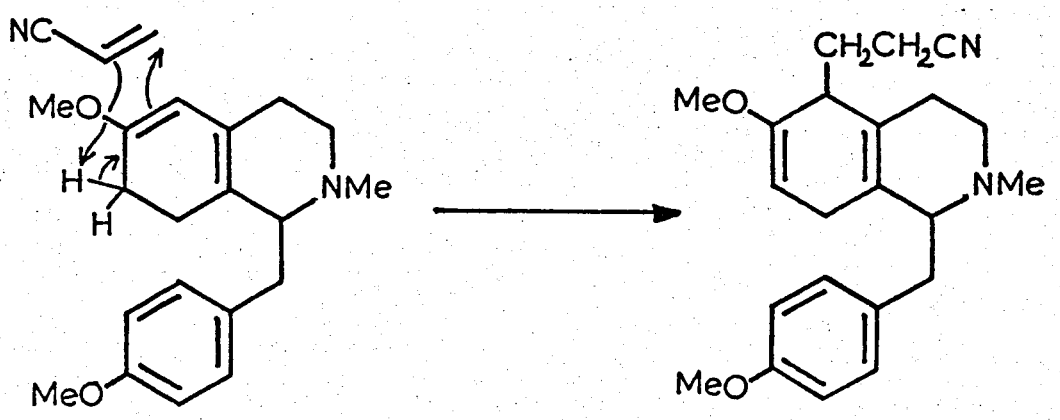


(393)



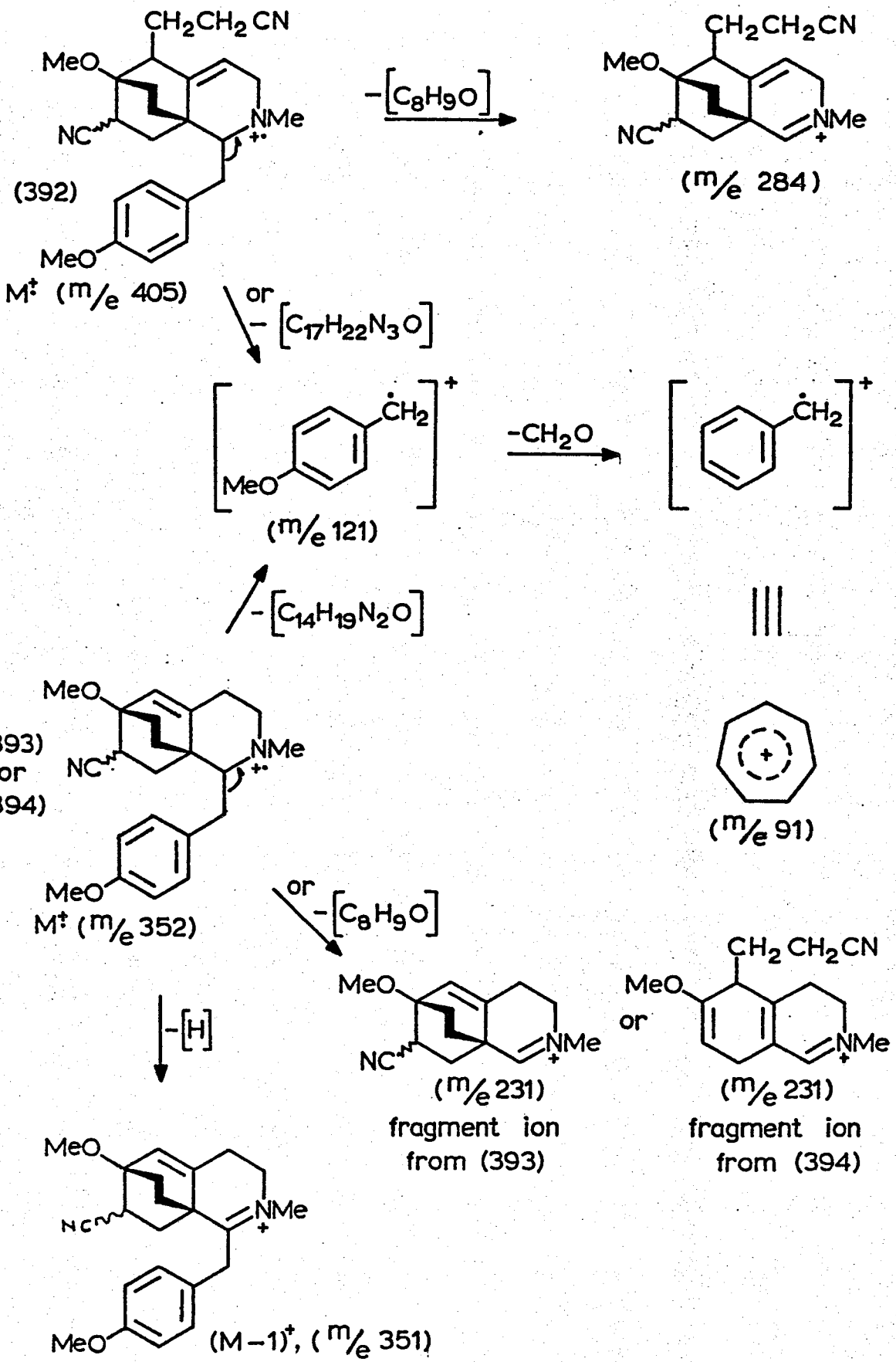
(394)

The former would be the precursor of (392), the latter (394) is available from an ene reaction of the starting conjugated diene as shown:-



(391) (394)

Although there is no hard evidence that the ion at m/e 352 represents a molecular ion it is not apparent how such a fragment could arise from (392). Other principal fragments in the mass spectrum can be interpreted as follows:

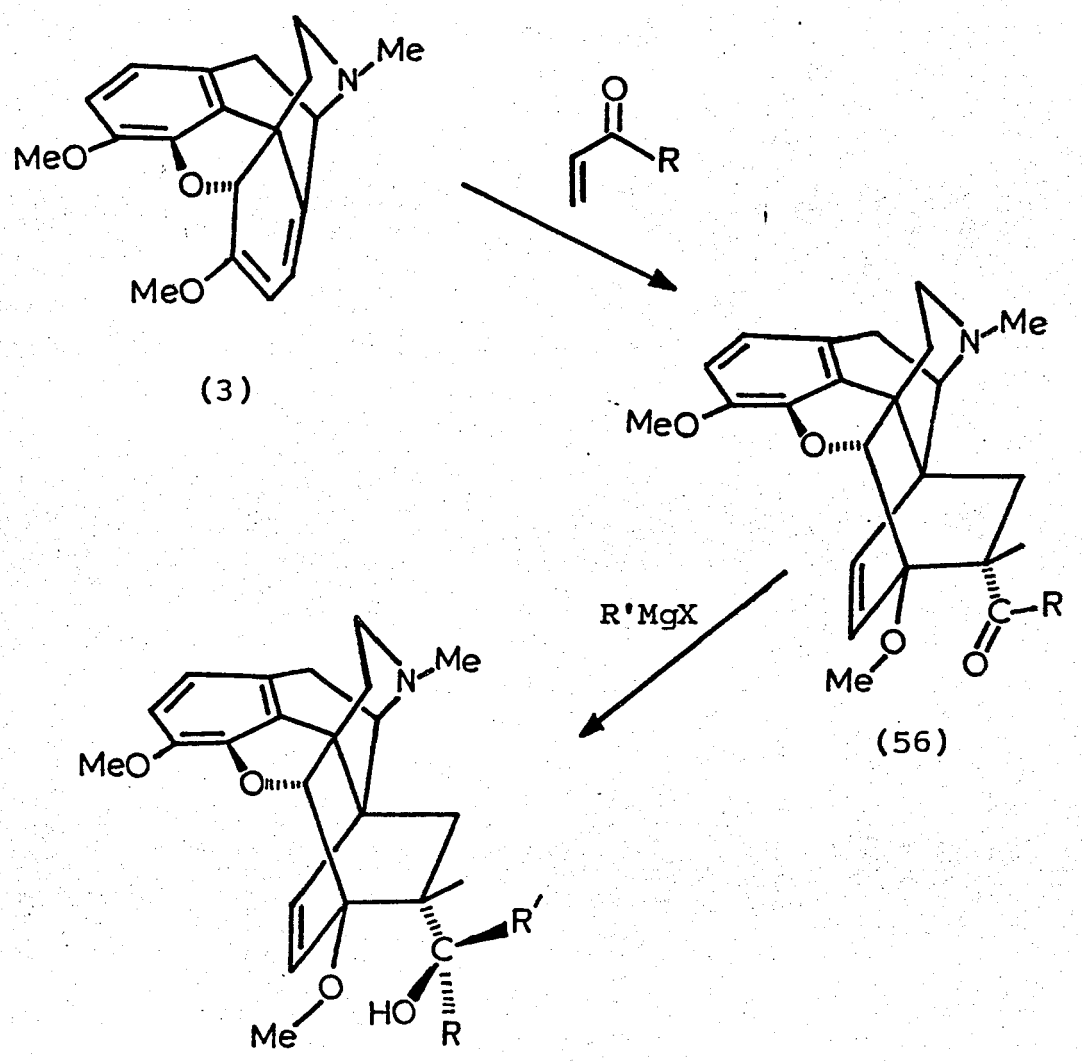


PART 4

Reactions of Ring-A Bridged Isoquinolines.

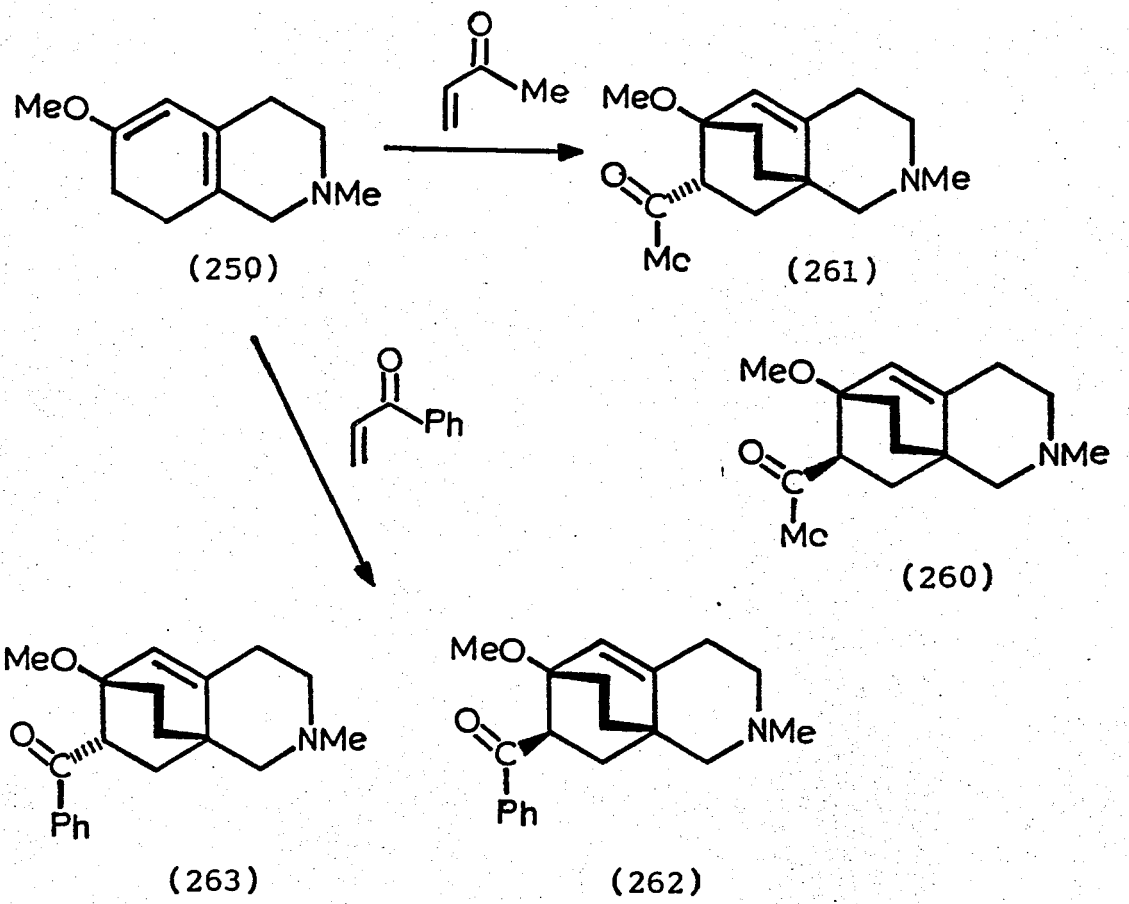
Preamble

The alkaloid thebaine (3) condenses readily with methyl vinyl ketone[86] and phenyl vinyl ketone[314] to afford the 7α- ketones (56, R=Me) and (56, R=Ph) respectively. In the case of the condensation with methyl vinyl ketone a small amount of the 7β- epimer is also obtained (ca. 0.5% yield). Subsequent Grignard reactions of the 7α- ketones to give 7α- carbinols (57) have been studied by Bentley et.al.[108] Many of the derived carbinols are highly potent analgesics.[108,109]



As described above we found the 6-methoxy diene (250)

reacts with methyl vinyl ketone to produce a mixture (ratio ca. 3:2) of the endo-ketone (261) [stereochemically analogous to the modified ring C of the 7α- thebaine adduct] and the exo-ketone (260). With phenyl vinyl ketone the diene (250) produces a mixture (ratio ca. 7:3) of the endo-ketone (263) and the exo-ketone (262).
ie:



(250) (261) (260) (263) (262)

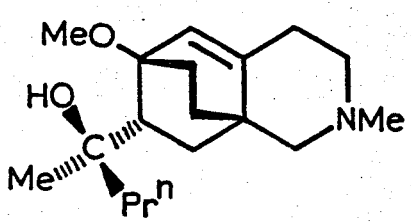
We investigated two aspects of the chemistry of these bridged ring adducts; firstly the modification of substituents by Grignard reactions and, secondly, reactions of the derived carbinols which resulted in skeletal rearrangements i.e. a modification of the ring system itself.

A Modification of Substituents.

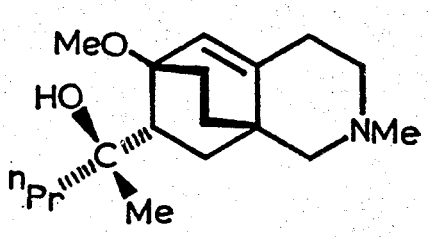
The reactions of the prepared methyl ketone adducts (260) and (261) with Grignard reagents was investigated. The Grignard reaction will introduce a new asymmetric centre at C-11 and thus could provide diastereoisomeric alcohols.

1) Reactions with n-propylmagnesium halides.

The reaction of the M.V.K. derived ketones (260) and (261) with n-propylmagnesium iodide was investigated since the n-propyl carbinol, derived from the adduct of thebaine with methyl vinyl ketone is a potent analgesic.[108] Grignard reaction of the endo-ketone (261) with n-propyl-magnesium iodide in benzene and diethyl ether in a similar manner to that employed for the related thebaine ketone[108] afforded only low yields of a single tertiary carbinol (395) or (396) : starting ketone was recovered unchanged. However, when the Grignard reaction was carried out with n-propyl-magnesium bromide in tetrahydrofuran higher yields of the same tertiary carbinol were obtained.



(395)

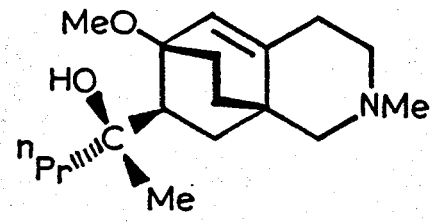


(396)

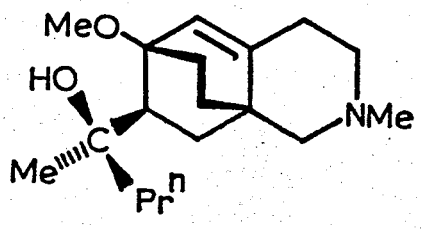
The pure tertiary carbinol formed colourless crystals (m.p. 87-88°C) after column chromatography over neutral alumina and recrystallisation from light petroleum.

Grignard reactionoof the exo-ketone (260) with n-propylmagnesium bromide in refluxing tetrahydrofuran again afforded a single tertiary carbinol, together with starting

material. Chromatographic separation over neutral alumina gave the carbinol as a viscous oil (b.p. 132-134°C/0.03mm. Hg). The two alternative diastereoisomers that may be produced are (397) and (398)



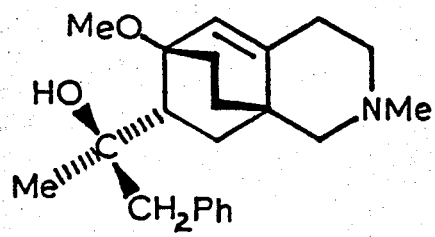
(397)



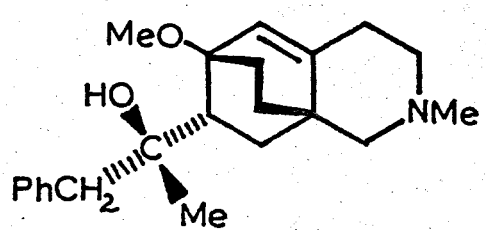
(398)

2) Reaction with benzylmagnesium bromide.

Reaction of the endo-ketone (261) with excess benzylmagnesium bromide in refluxing tetrahydrofuran also produced only one of the two possible diastereoisomeric tertiary carbinols, (399) or (400).



(399)



(400)

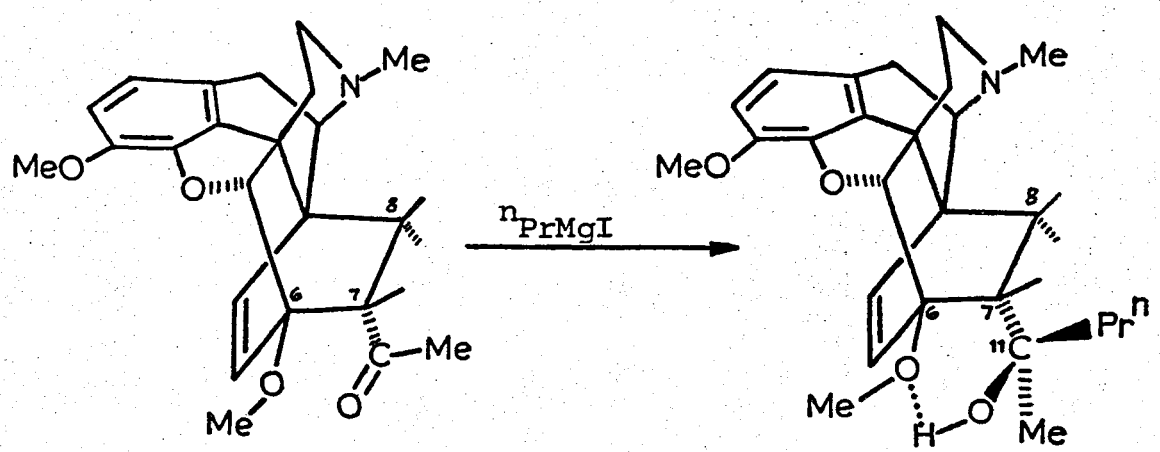
Bibenzyl ($PhCH_2CH_2Ph$) was isolated as a by-product. The benzyl carbinol was isolated by column chromatography over neutral alumina and was obtained as a viscous oil which formed a methiodide (m.p. 212-213°C). Reaction of the exo-ketone (260) with benzylmagnesium bromide in refluxing tetrahydrofuran again afforded one tertiary carbinol only,

obtained as a viscous oil after column chromatography over neutral alumina. The exo-benzyl carbinol also formed a methiodide (m.p. 233-234°C).

3) Structural assignment of the C-11 carbinols.

The four Grignard reactions described above had each yielded only one tertiary carbinol.

These results are in close analogy with the findings of Bentley et.al.[108] in their studies of Grignard addition to the methyl vinyl ketone Diels-Alder adduct (401) of thebaine. They found a remarkably high degree of stereoselectivity, obtaining normally a high yield of an almost pure diastereoisomer of the tertiary carbinol.[108] For example, with n-propylmagnesium iodide the only tertiary carbinol obtained was the diastereoisomer (402), together with two minor products viz a secondary carbinol (from Grignard reduction) and a rearrangement product.[108]

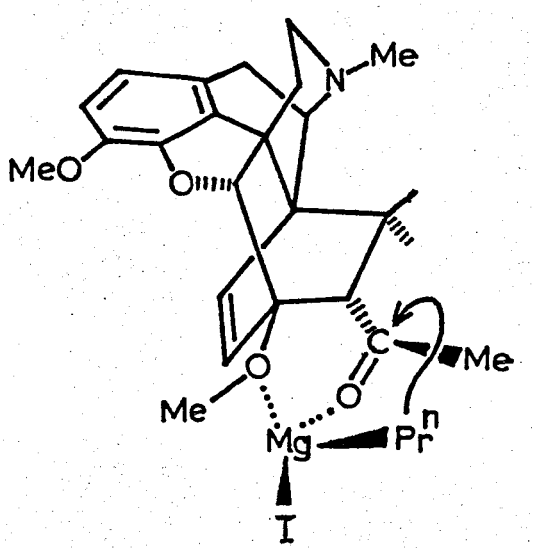


(401) (402)

Carbinols with the configuration at C-7 and C-11 shown in (402) each showed the presence of intramolecular hydrogen bonding with the C-6 methoxy oxygen.[102,108] In the infrared spectrum of (402) OH stretching appeared at 3497 cm^{-1} and in the n.m.r. the hydroxyl proton absorption was at δ4.80.[102,108] This may be contrasted with the values of 3597cm^{-1} and δ2.20 for the equivalent absorptions by the non-hydrogen bonded OH in the secondary alcohol

corresponding to (402) where Pr^n is replaced by H.[102,108] Bellamy[322] lists free OH absorptions as appearing within the range 3650-3590cm^{-1} and intramolecular H-bonded OH absorption 3570-3450cm^{-1} (concentration independent). It is well known that in the n.m.r. hydrogen bonding shifts OH proton absorption to lower field, e.g. ca δ5 (free OH ca δ2).[323] In structure (402) the hydrogen bonding permits the more bulky Pr^n and less bulky Me groups to adopt positions reasonably free from non-bonded interactions.

The asymmetric induction process giving diastereoisomers of type (402) is explained by Bentley et.al.[108] as being a consequence of the formation of a six-membered intermediate in which the magnesium atom is co-ordinated with both the carbonyl and methoxy oxygens, as shown in (403). An inspection of models then shows that "top-side" approach of Pr^n to the carbonyl carbon, as shown in (403), to give (402), is less hindered than approach from below (the vicinity of the 6,14-etheno bridge).[108]



(403)

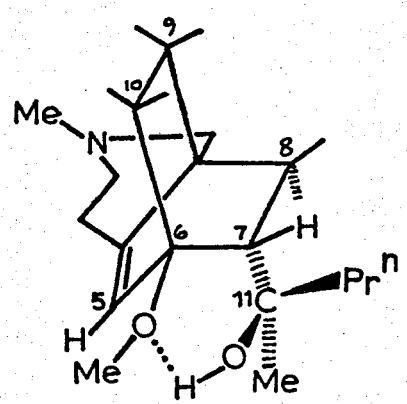
An examination of the spectra of our carbinols suggests an analogous situation obtains. Models indicate that the stereochemical constraints offered by the bicyclo[2,2,2]octene moeity in our compounds will be similar to those resulting from the bicyclo[2,2,2]octene

moeity in (401).

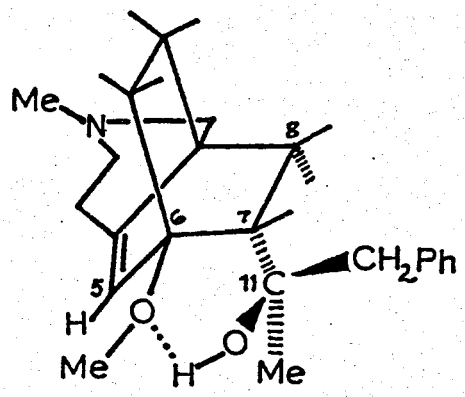
The spectroscopic data obtained from our C-11 tertiary carbinols is summarised in Table 4. (The 100MHz n.m.r. spectra of the n-propyl carbinol (395) and the benzyl carbinols (399) and (405) are shown in Fig.12, Fig.13 and Fig.14.

It can be seen that in each case the hydroxyl group is clearly H-bonded, such bonding being intramolecular as it is concentration independent (in CCl_4). I.r. OH absorption is between 3480-3490 cm^{-1} and n.m.r. δ4.70-δ4.93 for the four carbinols.

Applying therefore the same principal as discussed above for the thebaine series[102,108] we propose the following structures for the endo-carbinols (395), and (399).

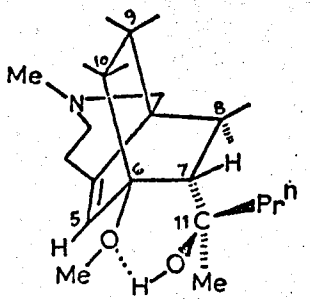


(395)



(399)

For the Grignard reactions with the exo-ketones asymmetric induction could develop through a magnesium complex as shown (404). In this case models reveal that the less hindered approach by the n-Pr group (or CH_2Ph) is from beneath, see (404). Approach from the top-side would involve encounter with the C-10 methylene group of the 6,8a-ethano bridge.


Me
N
9
10
7
8
6
7
H
5
H
O
Me
11
C
Pr^n
O
H
Me

(395)

C-6 MeO
NMe
C-11 Me
OH
C-5H
C-7Hβ
8
7
6
5
4
3
2
1
0

Fig.12.

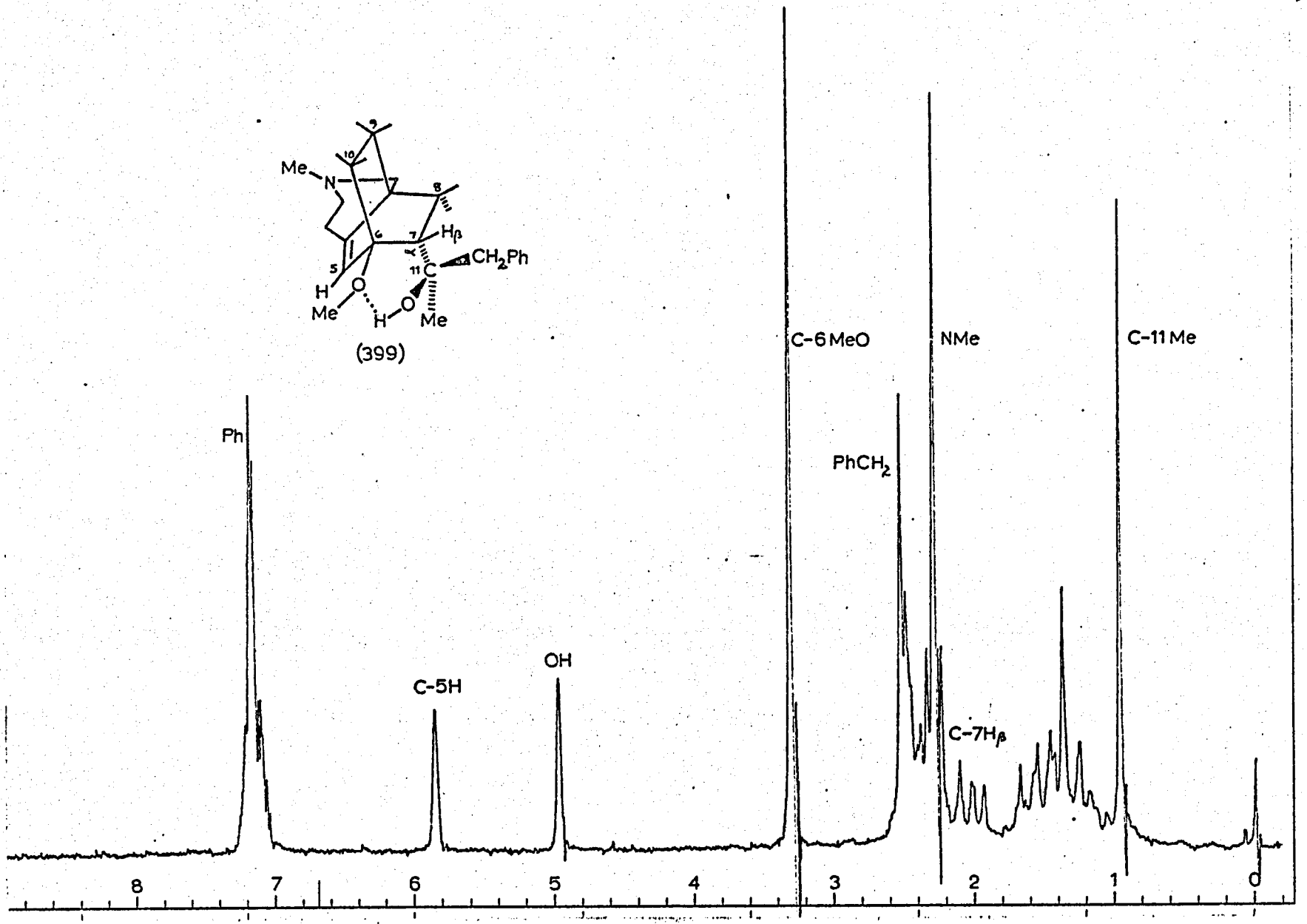

Me
N
H
O
Me
H
O
Me
Hβ
CH2Ph
(399)
Ph
C-5H
OH
C-6 MeO
PhCH2
NMe
C-7Hβ
C-11 Me
8
7
6
5
4
3
2
1
0

Fig.13.

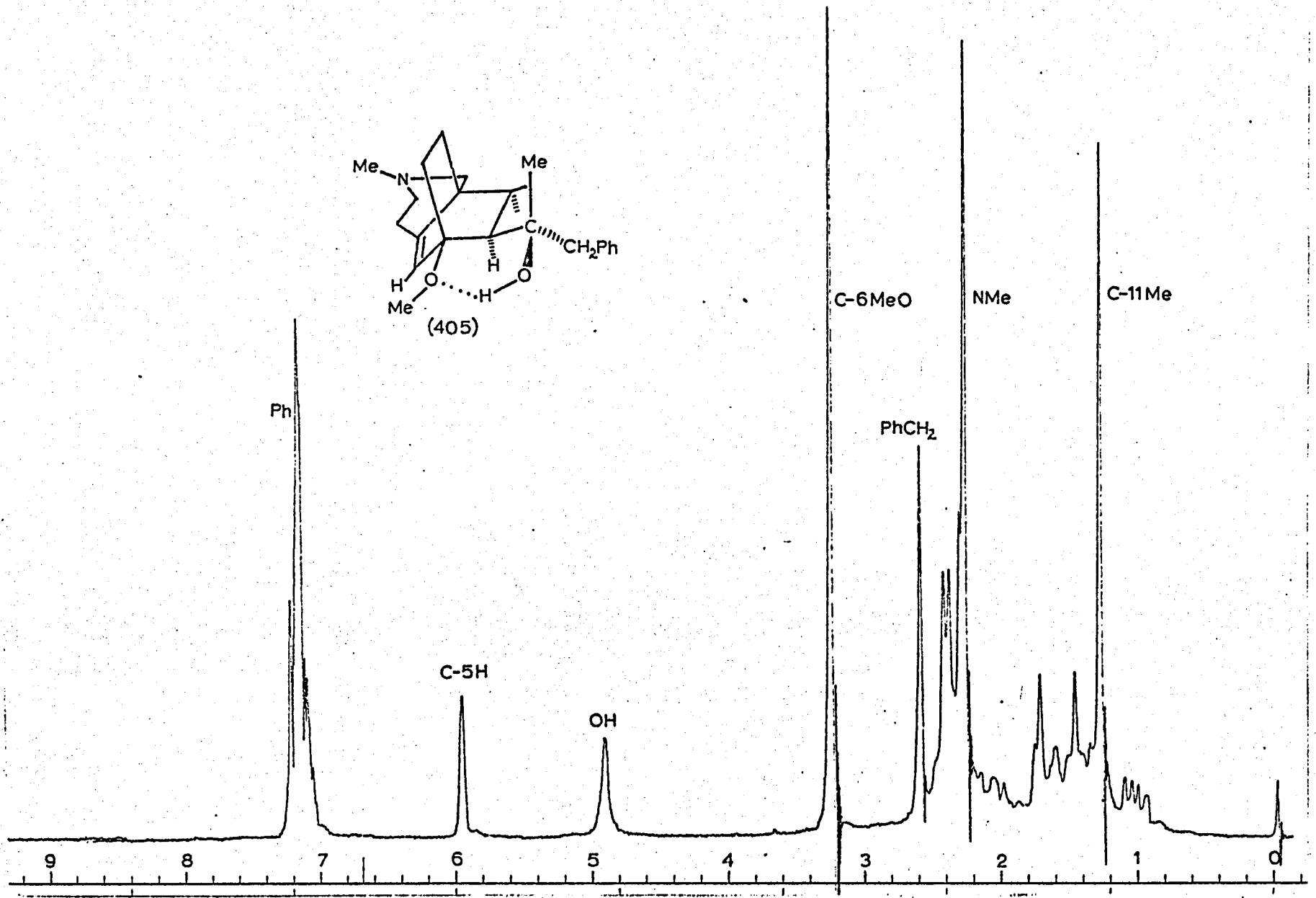
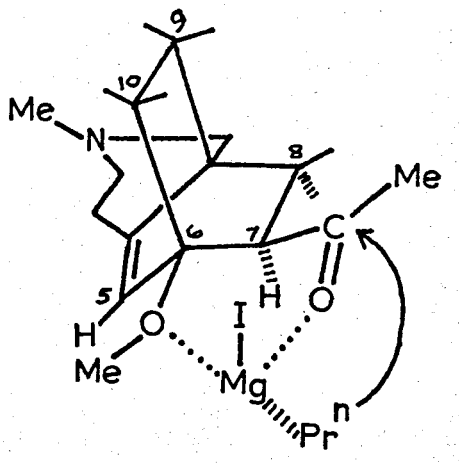

Me
N
Me
C
CH2Ph
H
H
O
O
H
Me
(405)
Ph
C-5H
OH
C-6MeO
PhCH2
NMe
C-11Me
9
8
7
6
5
4
3
2
1
0

Fig.14.

Table 4

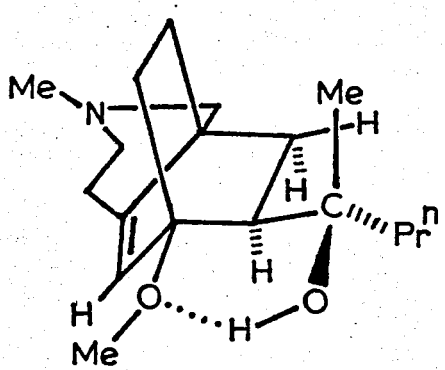
Spectral Data for the C-11 tertiary carbinols obtained by reaction of a Grignard reagent with the endo or exo-adducts of methyl vinyl ketone with 6-methoxy-2-methyl-1,2,3,4,7,8-hexahydro-isoquinoline (250).

Ketone	Grignard reagent	Carbinol, %	OH stretch ν_{max} cm^{-1} (CCl_4)	OH δ	C-5H δ	C-11Me δ	N-Me	$\underline{CH_3}CH_2CH_2$	$PhCH_2$
endo	n-PrMgBr	(395) 86	3480	4.76	5.85	0.90	2.30	0.85	-
endo	$PhCH_2MgBr$	(399) 83	3490	4.93	5.84	0.95	2.25	-	2.50
exo	n-PrMgBr	(397) 85	3480	4.70	6.10	1.30	2.35	0.86	-
exo	$PhCH_2MgBr$	(405) 81	3490	4.90	5.96	1.30	2.32	-	2.62

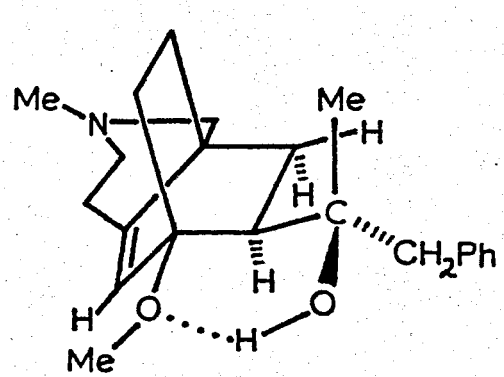


(404)

We therefore propose structures (397) and (405) for the exo-carbinols from n-PrMgBr and $PhCH_2Br$ respectively.



(397)



(405)

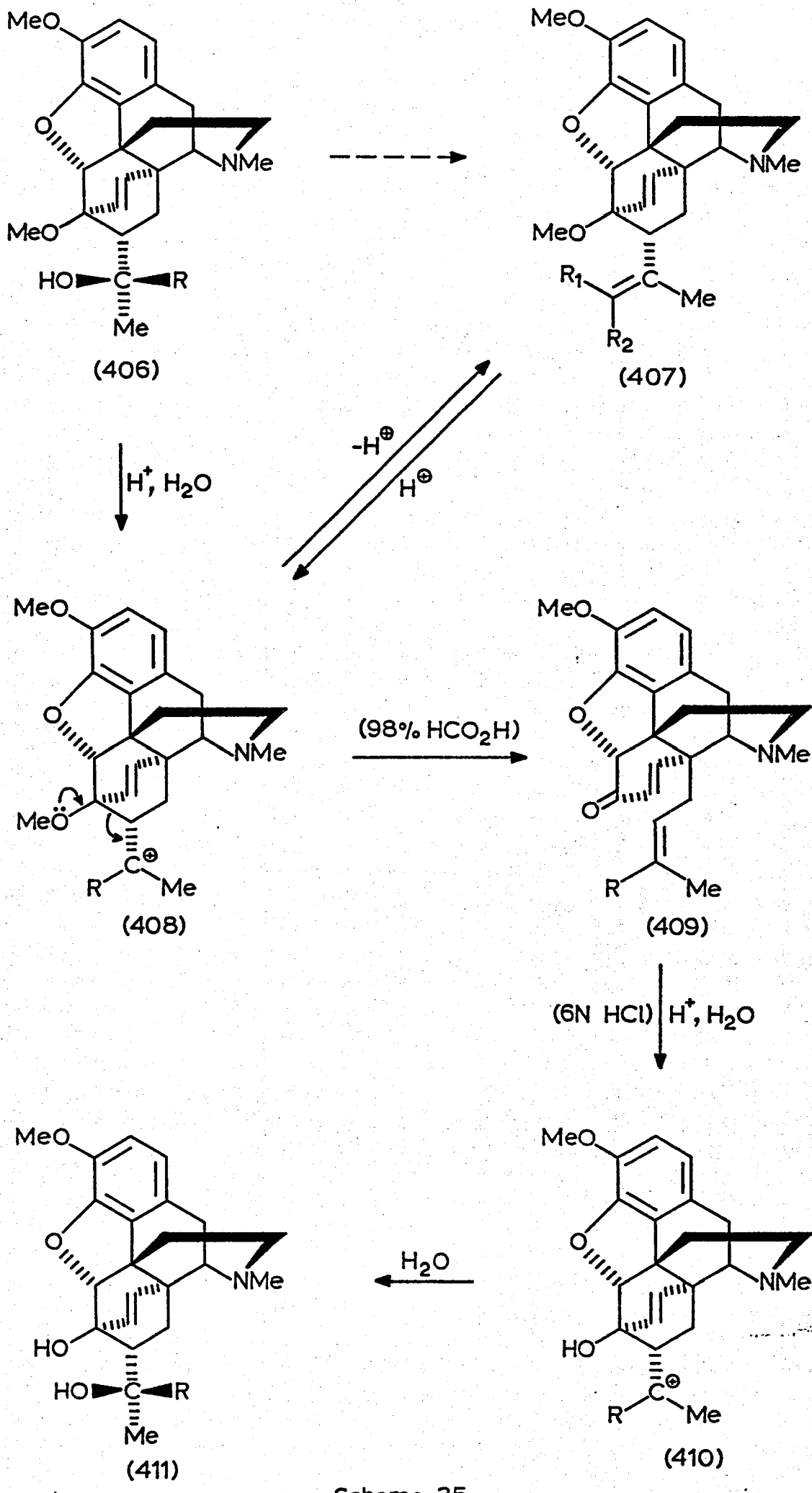
Support for the suggested configuration at C-11 is provided by the chemical shift of the C-11 methyl group of the exo-carbinols (397) and (405) (Table 4). In (397) the C-11 methyl group appears at δ1.30 and in (405) also at δ1.30 compared with δ0.90 and δ0.95 for the similar methyl group in the endo-carbinols (395) and (399). The lower field resonance of the C-11 methyl group in (397) and (405) is probably due to its lying almost exactly in an extension of the plane of the σ-bonds of the 4a,5-double bond, i.e. in a deshielding region. In contrast the C-11 methyl group in the endo-carbinols (395)

and (399) lies almost underneath the 4a,5-double bond σ-bond plane, i.e. in its shielding region.

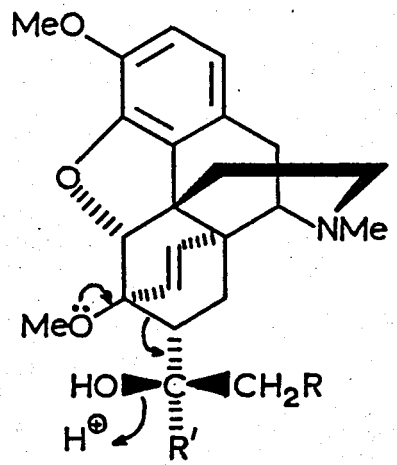
Following our findings Crabb and Wilkinson[324] reported obtaining some analogous carbinols by a similar method. In particular they made the 6-ethoxy analogues of (395) and (397). They too observed high stereoselectivity. Their conclusions regarding stereochemistry support ours although their reasoning, in one instance, does not. They postulate the relative deshielding of the C-11 Me in the ethoxy analogue of (397) is due to its proximity to the ethano-bridge and they ignore the effect of the 4a,5-double bond.[324]

B Modification of the ring system : formation of Azapropellanes

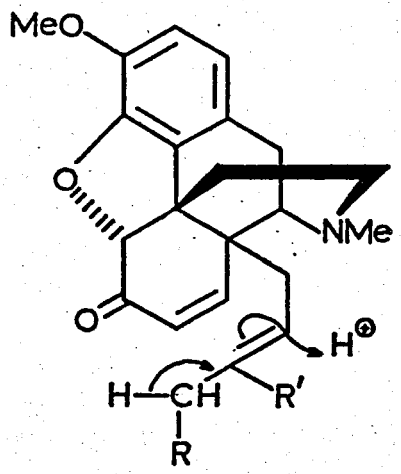
The alcohols of the 6,14-endoethenotetrahydrothebaine series[108] of general structure (406) are unstable in acid media, suffering dehydration and rearrangement, the speed, extent, and course of which depends on the nature of the alcoholic group and the conditions of the reaction.[325] K.W.Bentley et.al.[325-327] have extensively investigated the rearrangement of such carbinols. In all cases the first product appears to be an olefin. The transformations depicted in scheme 35 were found to be effected by heating the appropriate alcohols (406) in 98-100% formic acid. The olefins produced by simple dehydration, e.g. (407) are unstable under acid conditions, but ease of rearrangement appears to depend on the degree of substitution of the double bond. Thus, olefins (407; R_1=R_2=H, Me=Ph) and (407; R_1=R_2=H), were completely rearranged to the 14-alkenyl-codeinones (409; R=H, Me=Ph) and (409; R=H) after boiling in formic acid for 10 min. and 3H., respectively, whereas the trisubstituted olefins (407; R_1=H) are stable to boiling formic acid and required heating with mineral acid before rearrangement occurred. Presumably the ease of rearrangement is dependent on the ease of protonation of the double bond to give the carbonium ion (408), which can either revert to the olefin (407) with the loss of a proton, or can suffer ring fission to give the 14-alkenylcodeinone (409). 14-Alkenyl-codeinones of structure (409; R=Me and Ph) have been isolated


MeO
O
NMe
MeO
HO
C
R
Me
(406)
MeO
O
NMe
MeO
R1
C
Me
R2
(407)
-H⊕
H⊕
H+, H2O
MeO
O
NMe
MeO
C⊕
R
Me
(408)
(98% HCO2H)
MeO
O
NMe
O
R
Me
(409)
(6N HCl)
H+, H2O
MeO
O
NMe
HO
HO
C
R
Me
(411)
H2O
MeO
O
NMe
HO
C⊕
R
Me
(410)

Scheme 35

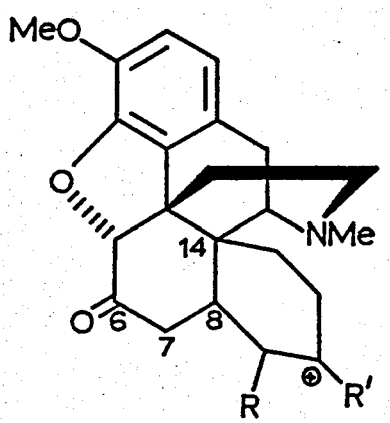


(412)

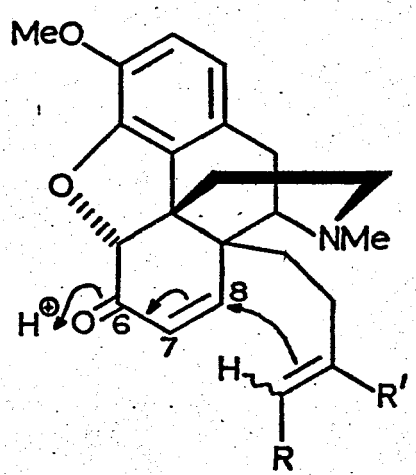


(413)

Prototropic equilibration conc. HCl ⇕ ± H⊕



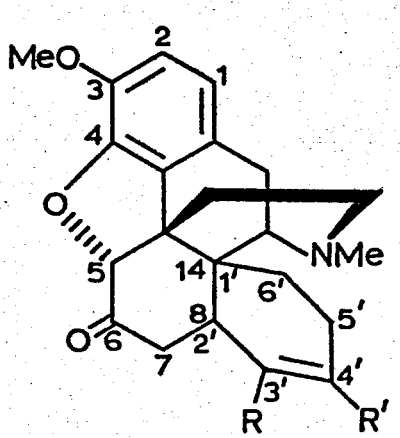
(415)



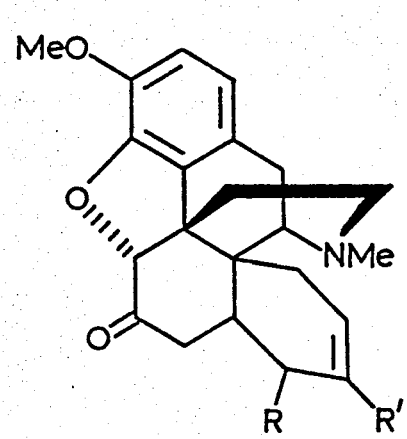
(414)

±H⊕ ⇕

± H⊕ ⇕



(417)



(416)

Scheme 36

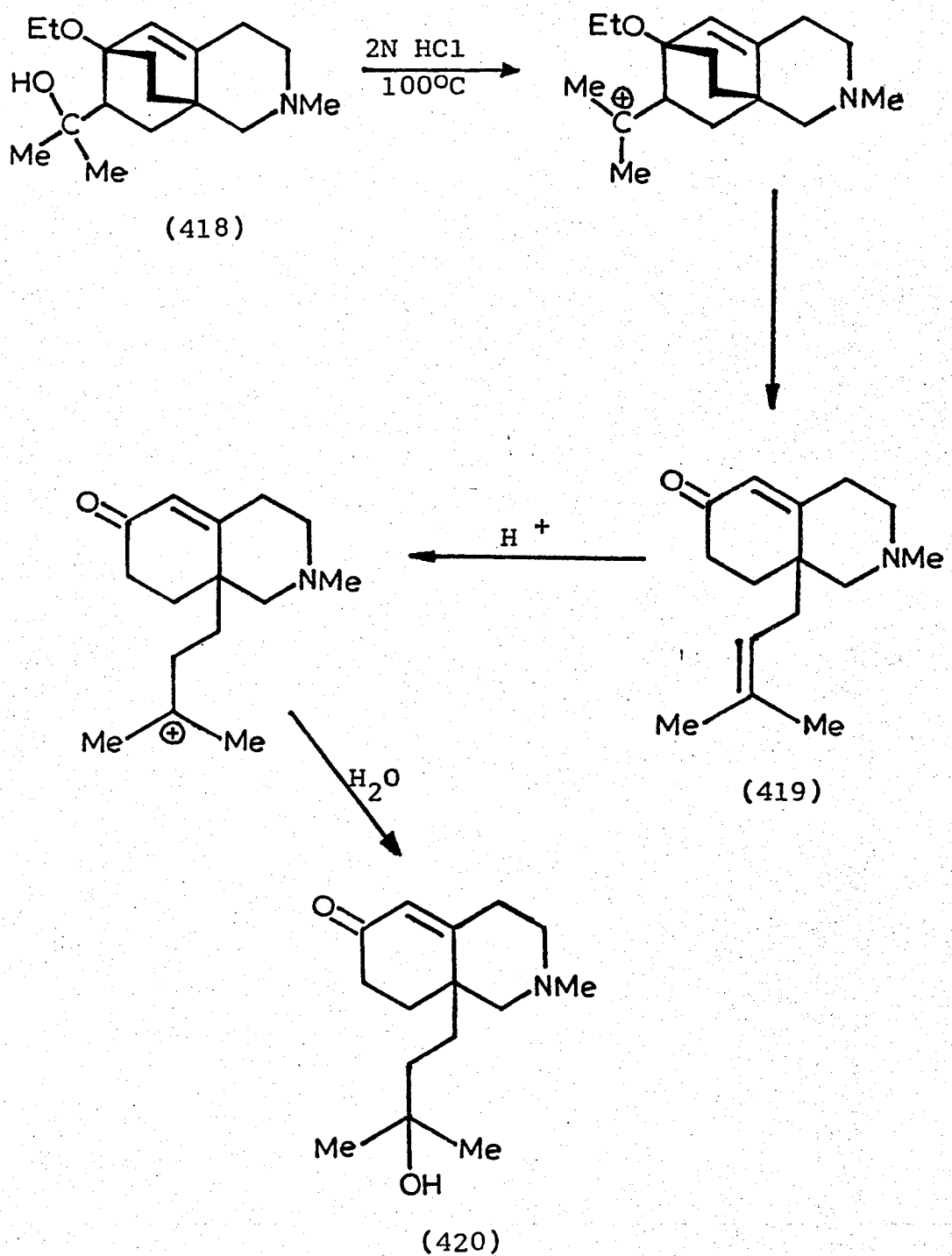
from alcohols (406; R=Me and Ph) in refluxing formic acid.[325]

In the presence of 6N hydrochloric acid, alcohol (406; R=Me) was converted via the 14-alkenylcodeinone (409; R=Me), followed by formation of the carbonium ion (410; R=Me), to the recyclised 6-hydroxy analogue (411; R=Me).[325]

The 14-alkenylcodeinones (413), derived from the carbinols of general structure (412) can undergo further transformation by concentrated hydrochloric acid[326,328], as shown in scheme 36 . Prototropic equilibration of the 14-alkenylcodeinone (413) gives the isomeric enone (414). Then protonation of the enone system and Markownikoff addition of the resultant carbonium ion to the double bond in the side chain gives the carbonium ion (415), which can lose a proton in either of two ways to yield ketone (416) or (417).[326] In the case where R is a hydrogen atom and R' is a methyl group in (412), the rearrangement proceeds only as far as the 14-alkenylcodeinone (413), in which the favoured position of the double bond in the alkenyl side chain is as shown. Where R=R'=Me, however, hyperconjugation effects make the isomeric codeinone (414) the favoured form and cyclisation to the end product, e.g. (417) can be accomplished.[326,328]

In the 6,8a-ethano bridged isoquinoline series an example incorporating the first sequence described above (i.e. to the equivalent of the 14-alkenylcodeinone) has been reported by Crabb and Wilkinson.[324] The dimethylcarbinol (418) (exo or endo at C-7) on treatment with 2N-hydrochloric acid at 100°C underwent the sequence shown below.[324]

The equivalent of the 14-alkenylcodeinone (413) (see scheme 36) is (419). As expected a cyclisation did not ensue, although (419) was not isolated as such but as its hydration product (420).[324]

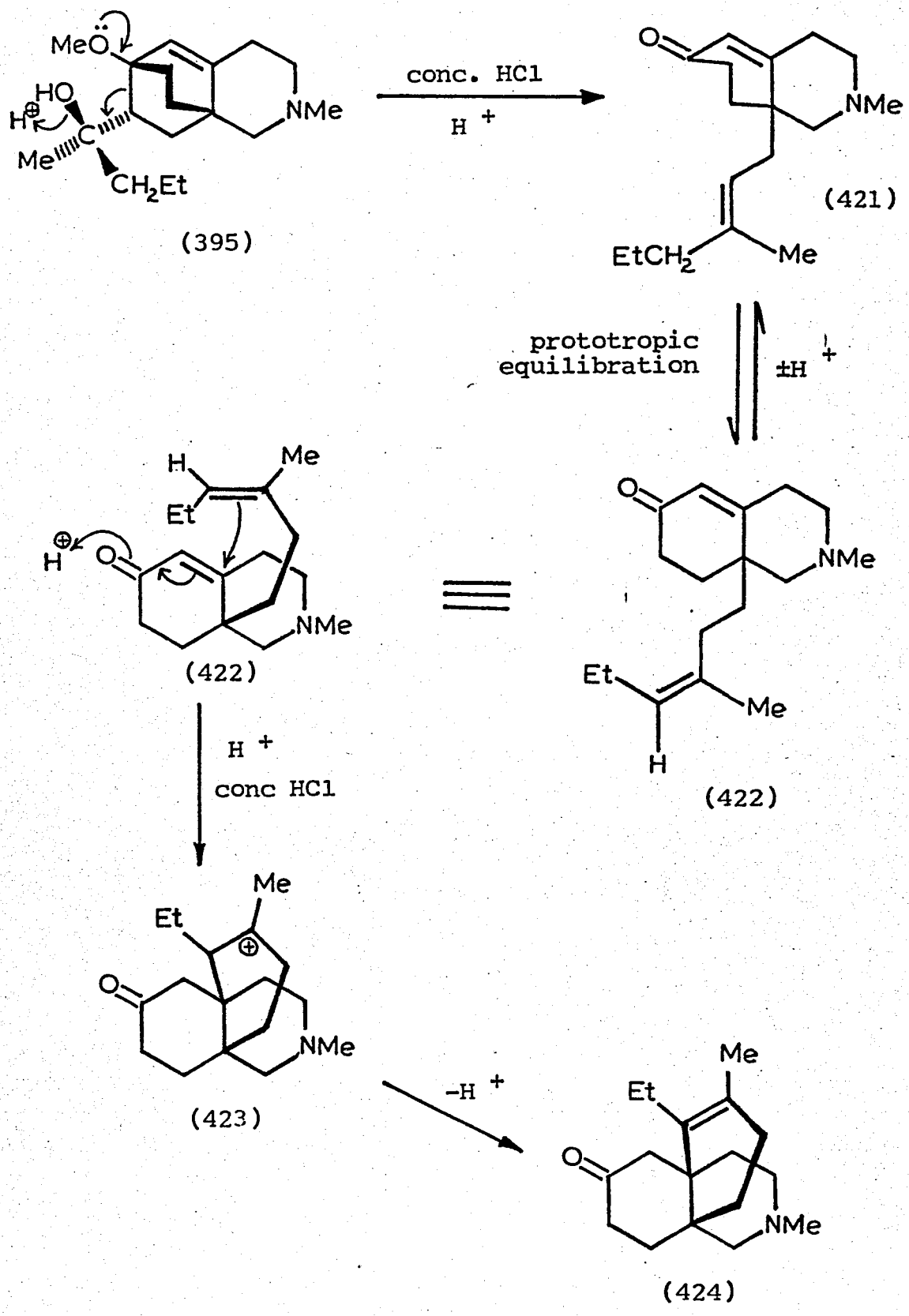


The carbinols we have made, however, are analogous to (412) where R'=Me and R=Et or Ph (i.e. not H). Therefore acid catalysed ring opening to an 8a-alkenyl enone similar to (419) could possibly be followed by cyclisation to the enone after prototropic equilibration, somewhat equivalent to (413) leading to (417).

The four tertiary carbinols prepared in the present work were each unstable to the presence of concentrated hydrochloric acid. Treatment of the endo-methyl n-propyl carbinol (395) with concentrated hydrochloric acid for 2h. at 100°C afforded a viscous oil. The infrared spectrum showed a strong carbonyl absorption at 1705cm^{-1} suggesting a saturated ketone. No major absorption above 220nm. was seen in the ultraviolet spectrum suggesting the absence of a conjugated enone : (420) has λ_{max} 235nm(ε, 11,000).[234] The n.m.r. spectrum of our product (Fig.15) showed no vinyl proton absorption. The well defined triplet (J 7Hz) centred at δ1.0 was assigned to a terminal methyl group adjacent to CH_2 and the 3-proton singlet at δ1.65 to a methyl group probably attached to a carbon-carbon double-bond. The sharp singlet at δ2.20 was assigned to an N-methyl group.

The proposed course of the acid-catalysed reaction of the carbinol (395) is depicted in scheme 37 . Ring opening to the 8a-alkenyl enone (421) occurs first. Prototropic equilibration of the intermediate enone (421) proceeds to give the isomeric 8a-alkenylisoquinoline enone (422)[equally favoured as (421) by hyperconjugation]. Protonation of the enone-system and Markownikoff addition of the resultant carbonium ion at C-4a to the double bond in the side chain will lead to the carbonium ion (423). This can lose a proton in any of three ways, the most likely being to give the tetrasubstituted double bond shown in (424). The above spectroscopic evidence indicates that the product of the rearrangement is indeed the ketone (424). The analytical data for the methiodide (m.p. 261-264°C) and the hydrochloride [m.p.242-243°C(dec.)] was also consistent with the molecular formula of (424). Accurate mass measurement of the free base further confirmed the molecular formula as $C_{17}H_{27}NO$.

The tricyclic ketone (424) belongs to the class of compounds named "propellanes" and the nomenclature of such systems[329] has been adopted by us in naming (424) as 3-aza-7-ethyl-3,8-dimethyl[4,4,4]propell-7-en-13-one.


MeO
HO
H
Me
CH2Et
NMe
(395)
conc. HCl
H +
O
NMe
(421)
EtCH2
Me
prototropic
equilibration
±H +
H
Me
Et
O
NMe
(422)
O
NMe
Et
Me
H
(422)
H +
conc HCl
Me
Et
O
NMe
(423)
-H +
Me
Et
O
NMe
(424)

Scheme 37

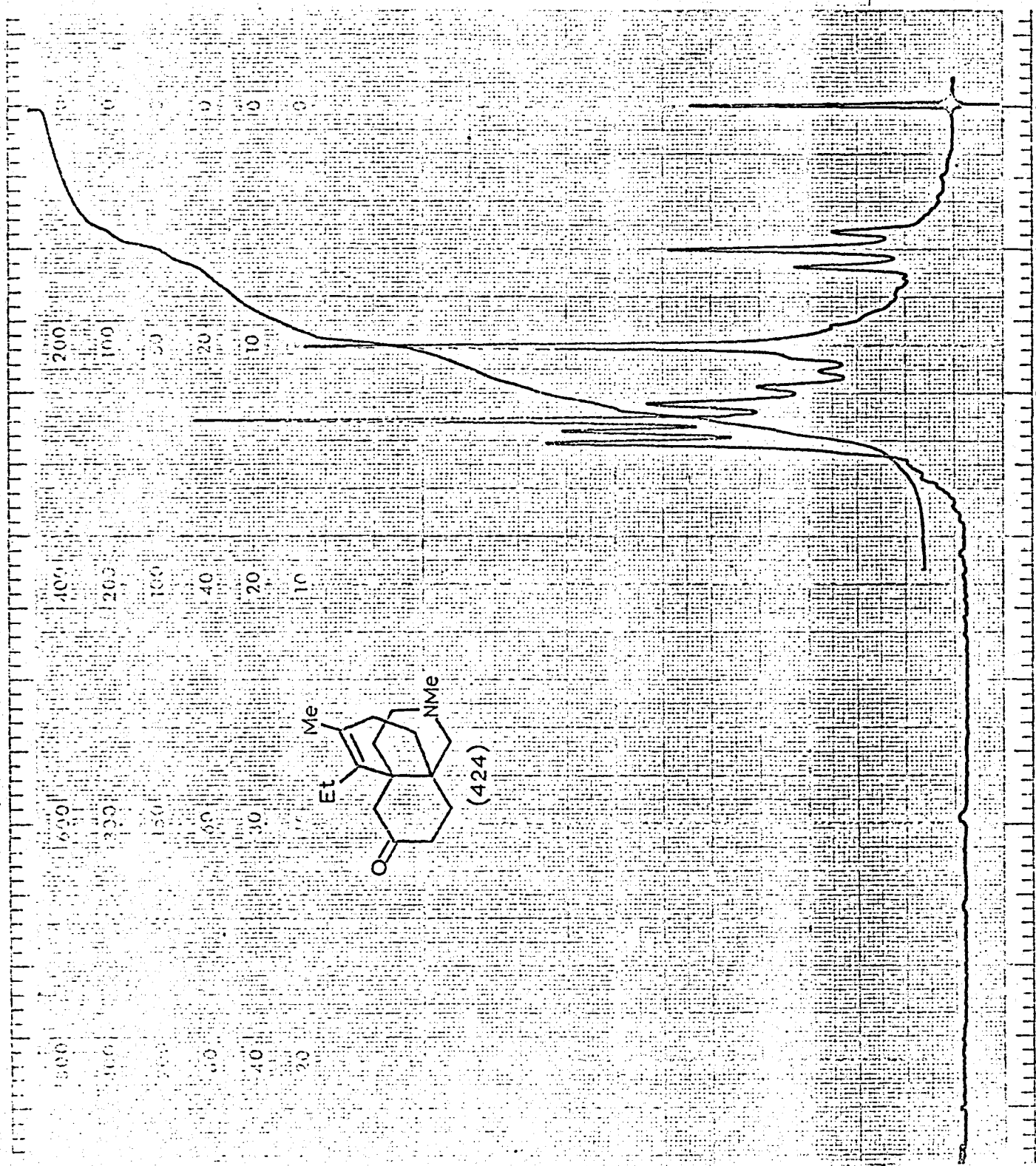
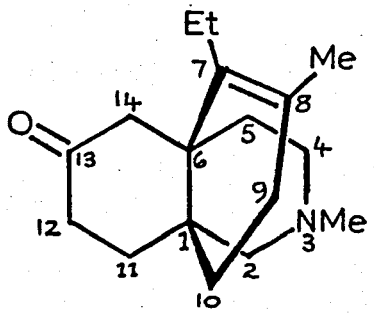


Fig.15.

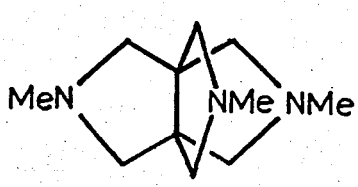


(424)

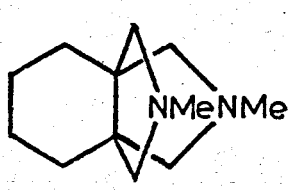
Ginsburg, Altman and co-workers initiated in 1966 an extensive study on [4,4,4], [4,4,3], [4,4,2] and [3,3,3] carbocyclic heterocyclic propellanes.[329-333] A book is also available on the synthesis, structure and reactions of propellanes.[334]

To date no propellanes possessing the aza[4,4,4] ring system have been reported, and the rearrangement of carbinol (395) provides a direct entry into this novel ring system.

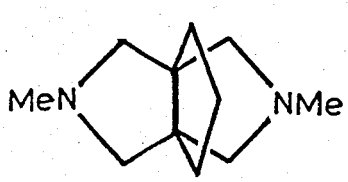
In relation to the synthesis of heterocyclic propellanes, triaza[3,3,3]propellane (425) has been synthesised[331], the diaza[4,3,3]propellane (426)[329] and the diaza[3,3,3]propellane (427) together with the aza[4,4,3] propellane (428)[329] a typical synthesis of (428), is shown.



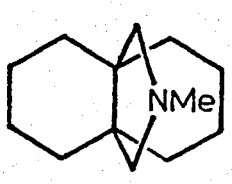
(425)



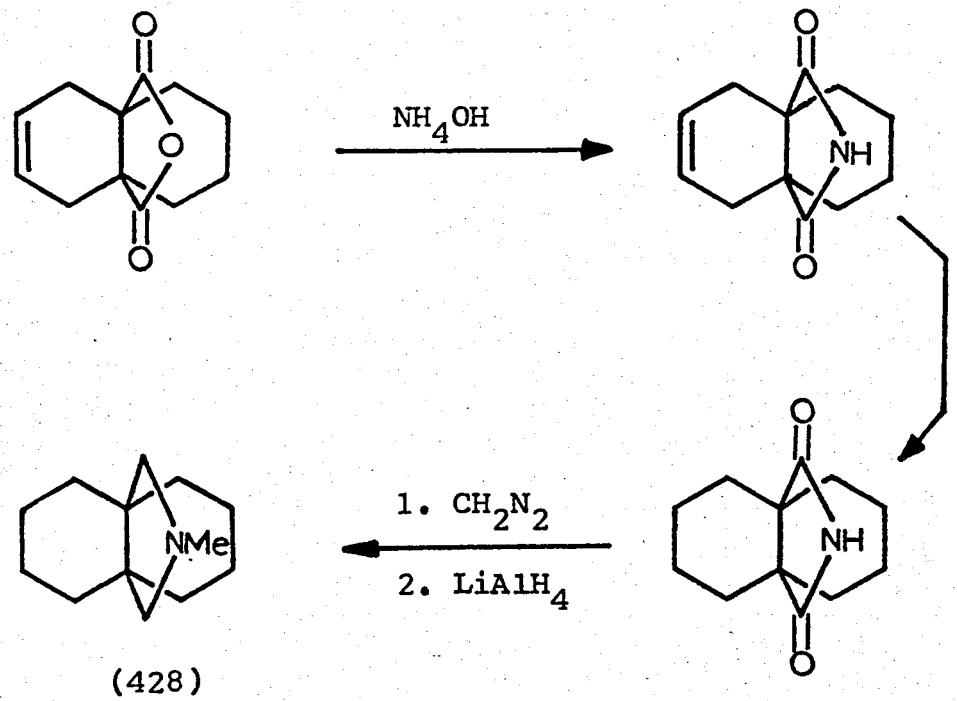
(426)



(427)

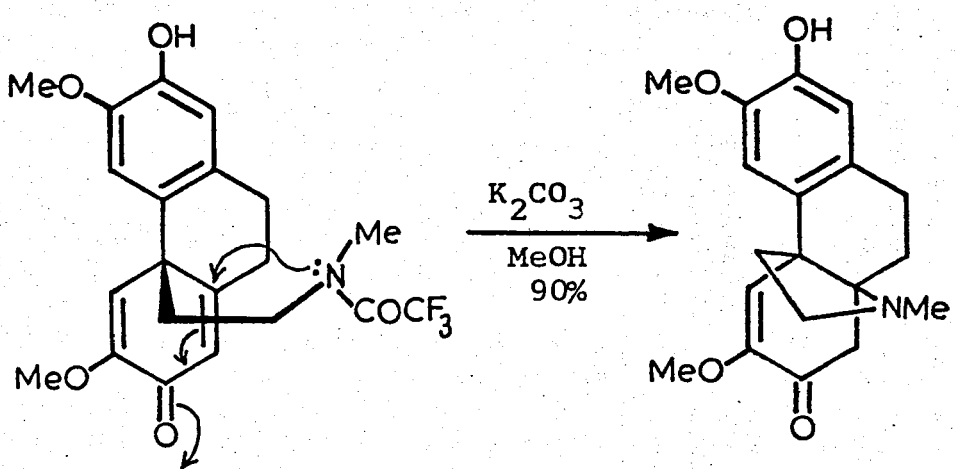


(428)

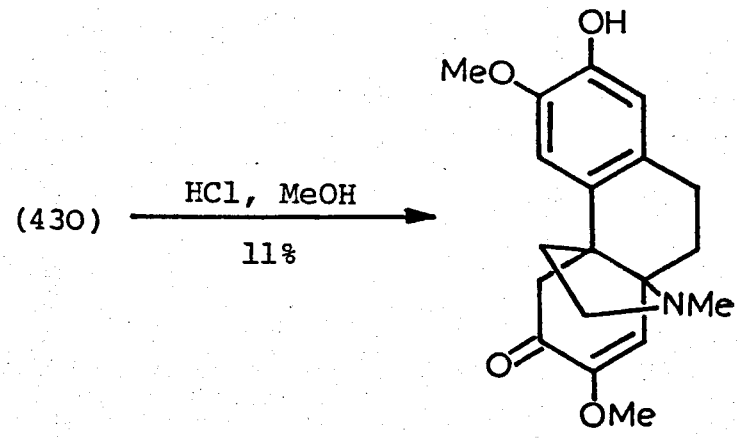


(428)

Ring closure to a propellane involving addition to an enone is provided by the synthesis of the alkaloid (431) by Kametani et.al.[335] Reticuline was employed as starting material for the synthesis by phenolic oxidation of the dienone (429). Treatment with base afforded after further acidic isomerisation of the resulting enone (430) the final product (431) having the hasubanan skeleton.

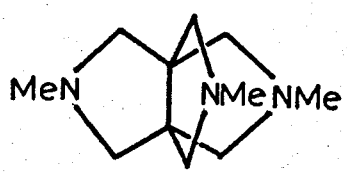


(429) (430)



(431)

The behaviour of propellanes on electron impact has been investigated by D.Ginsburg et.al.[329,331] They report the fragmentation of the triaza[3,3,3]propellane(425).



(425)

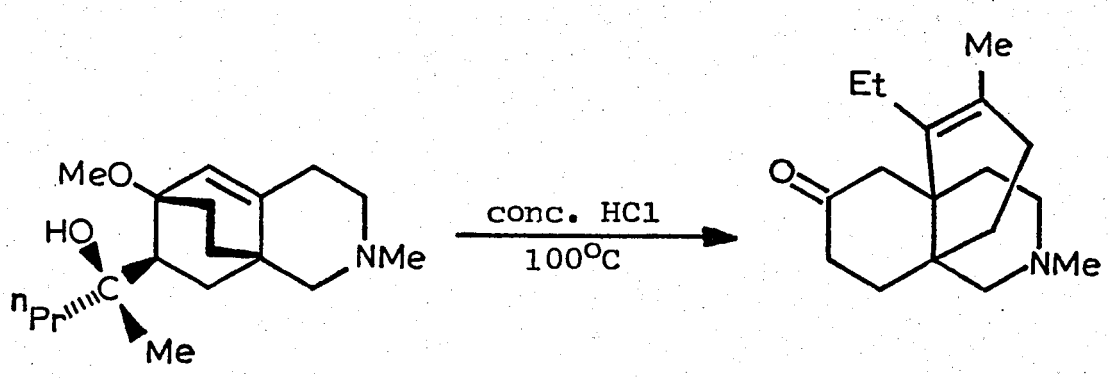
The compound (425) exhibited the molecular ion M^+ at m/e 195 and the following fragmentations :

$$M^+ \xrightarrow{-CH_3} \text{m/e } 180 \; ; \; M^+ \xrightarrow[m^*]{-CH_2NHCH_3} \text{m/e } 151$$

$$\xrightarrow{-CH_3NCH_2} \text{m/e } 108 \text{ (base peak)} \; ;$$

$$M^+ \xrightarrow[m^*]{-NH_2Me} 164 \xrightarrow[m^*]{-H} 163.$$

We found that the exo-methyl n-propyl carbinol (397) also underwent rearrangement upon treatment with concentrated hydrochloric acid at 100°C to afford the propellane ketone (424) in 96% yield, isolated as its hydrochloride salt.



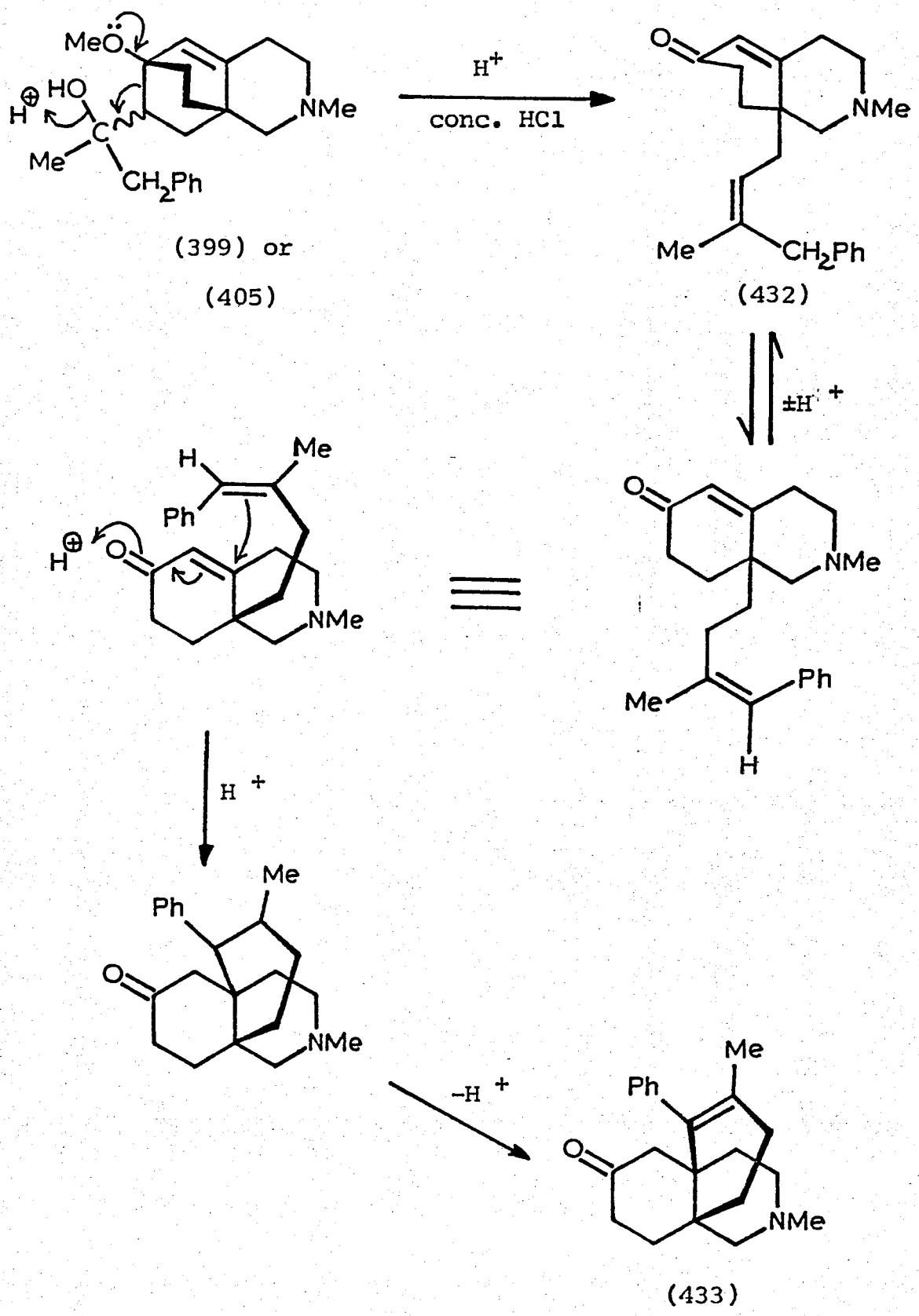
(397) (424)

Acid-catalysed rearrangement of the related methyl benzyl carbinols (399) and (405) was next investigated. The rearrangement could proceed in a similar manner to that already described for the methyl n-propyl carbinols (395) and (397) and depicted in Scheme 38.

Treatment of either the exo-carbinol (405) or a mixture of both the exo and endo carbinol (399) with concentrated hydrochloric acid at 100°C for 2.5-3h afforded a viscous oil. T.l.c. analysis showed the rearrangement product to be a mixture of three components. Column chromatography of the oil over netral alumina afforded the propellane (433) as a viscous oil. The other two products are discussed below.

The infrared spectrum of (433) showed a strong carbonyl absorption at 1705 cm^{-1} and the n.m.r. spectrum showed singlets corresponding to a methyl group at δ1.30, an N-methyl group at 2.24 and phenyl absorption centred at 7.2, no vinyl proton absorption was present. Accurate mass measurement and elemental analysis confirmed the molecular formula as $C_{21}H_{27}NO$. The u.v. spectrum of the propellane (433) showed λ_{max} 217(ε, 1580) and 258nm(420). The lack of appreciable absorption for the styrenoid chromophore is thought to be due to steric factors: styrene itself shows u.v. bands at 244nm(ε, 12000) and 282(450)[336]. Examination of a model of (433) indicates that the phenyl group at C-7 could not freely adopt a configuration planar with the 7,8 double bond due to steric interference with the 7-substituent and the 8-methyl group.

The mass spectra of the propellane (433) and the ethyl analogue (424) showed similar fragmentation characteristics. In particular an important fragmentation



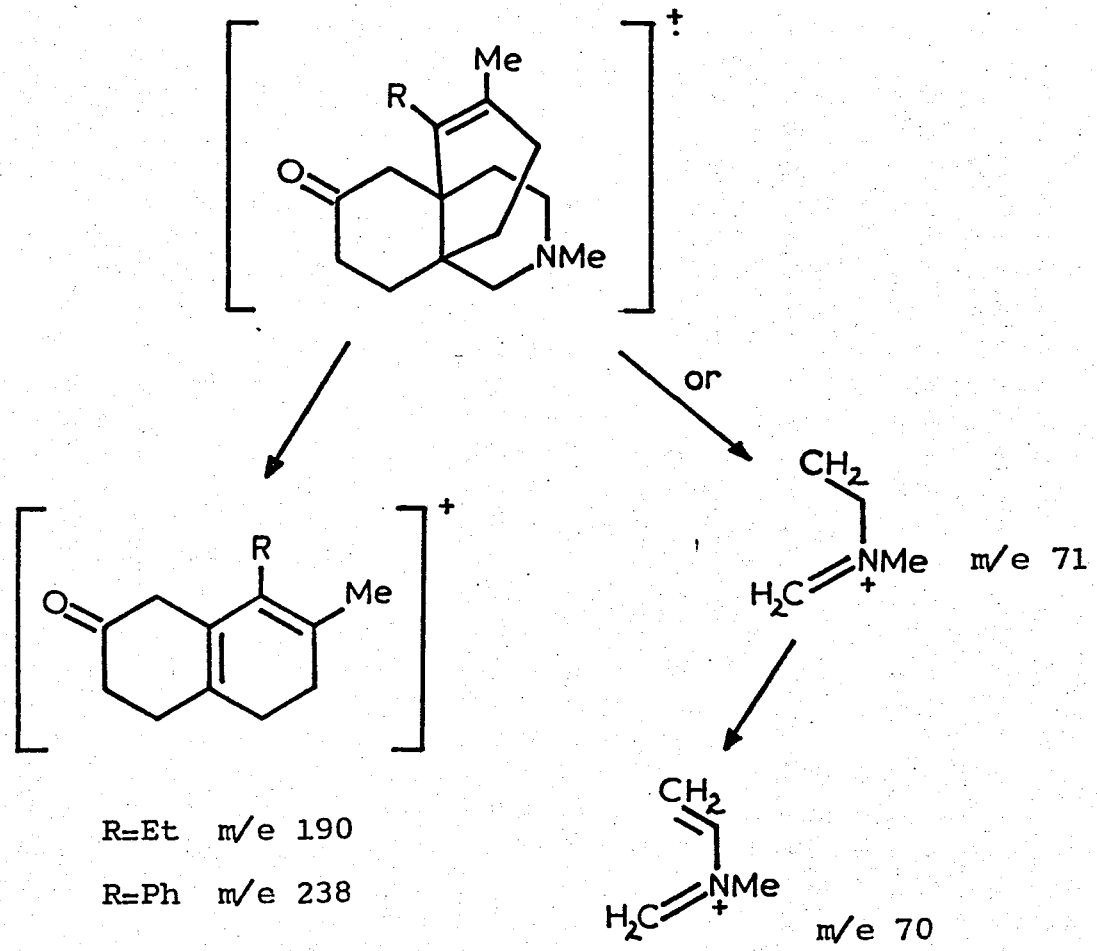
(399) or (405)

(432)

(433)

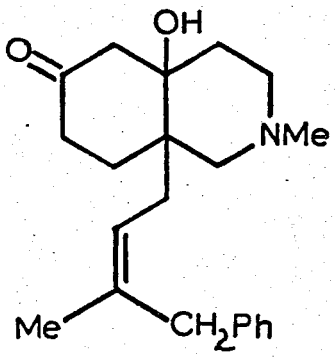
Scheme 38

is envisaged as a retro Diels-Alder-type cleavage[337] of the piperidine ring in the parent molecular ions giving rise to the fragment ions as depicted :

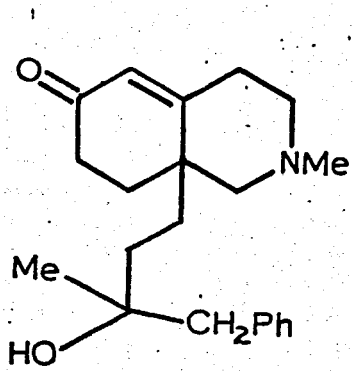


The two other products from the acid-catalysed rearrangement of the benzyl carbinols could not be obtained in a sufficiently pure state for a satisfactory structural assignment to be made. The n.m.r. spectrum of by-product (A) showed vinyl proton absorption at δ5.44 ($w_{\frac{1}{2}}$ 10Hz), and singlets attributable to a benzylic methylene group at 3.24 an N-methyl group at 2.26 and a methyl group at 1.26 together with phenyl absorption at 7.2. The infrared spectrum showed hydroxyl group absorption at 3400 cm^{-1} and

a carbonyl group at 1705 cm^{-1}. By-product (B) also showed vinyl proton absorption at δ5.12 ($w_{\frac{1}{2}}$ 4Hz) in its n.m.r. spectrum together with absorptions attributable to a benzylic methylene group at 3.24 an N-methyl group at 2.18 a methyl group at 1.24 and phenyl absorption at 7.2. The infrared spectrum showed hydroxyl group absorption at 3400 cm^{-1} and carbonyl group absorption at 1665 cm^{-1}. Both by-products showed a molecular ion at m/e 327 in the mass spectrum. On the basis of these data it is postulated that the by-products could be the carbinols (434) and (435) arising from hydroxylation of the intermediate carbnium ions produced during the acid-catalysed rearrangment (see Scheme 38).



(434)



(435)

PHARMACOLOGY

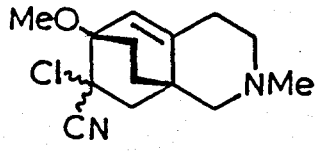
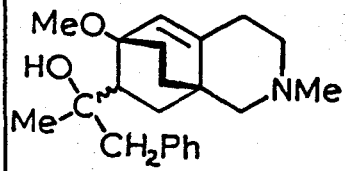
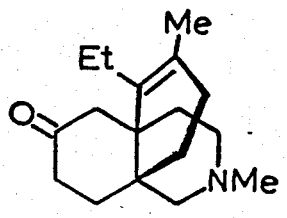
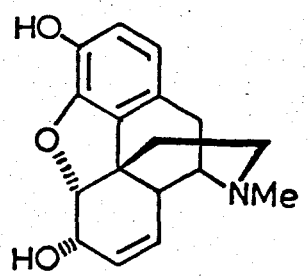
Some of the compounds synthesised as discussed in Part 2 and Part 4 of this work were submitted for pharmacological evaluation as potential analgesics by Reckitt and Colman, Pharmaceutical Division, Hull.

Analgesic activity was assessed by the phenylquinone-writhing test (H & F test)[339] and the Rat Tail Pressure test.[340] The former test relies on the ability of morphine-like drugs to abolish the writhing or stretching response produced in mice by the intraperitoneal injection of phenyl-p-benzoquinone.[341] In the latter, analgesia is indicated by abolition of the squeaking response to tail pressure. The results are summarised in Table 5 compared with the values for morphine.

The potency of an analgesic can be expressed as the ED_{50}, the dose in milligrams per kilogram of body weight that produces a significant effect in 50% of test animals.

It is most interesting that the chloroacrylonitrile adducts (291) and (292) and the MVK-benzyl-carbinol adducts (399) and (405) are so active. The chloroacrylonitrile adducts (291) and (292) are slightly the more active, both the H & F and Rat Tail Pressure values being better than morphine. For the carbinols, the Rat Tail Pressure value is slightly better than for morphine and not so good as morphine in the H & F test.

The azapropellane (424) is more active when administered i.v. in the H & F test, but not much use by the s.c. route.

COMPOUND	NUMBER	TEST	ROUTE	ED_{50}, mg/kg
	(291) and (292)	H & F Rat Tail Pressure	s.c. s.c.	0.35 0.46 (0.30 - 0.72)
	(399) and (405)	H & F Rat Tail Pressure	s.c. s.c.	5.1 1.17 (0.56 - 2.46)
	(424)	H & F	s.c. i.v.	>30 2.8
 morphine	(1)	H & F Rat Tail Pressure	s.c. s.c.	0.65 2 (administered as sulphate)

i.v. = intravenous

s.c. = subcutaneous

Table 5. Pharmacology of prepared compounds compared with morphine.

EXPERIMENTAL

Unless otherwise stated the following conditions apply. All melting points are uncorrected and were measured on a Kofler hot stage apparatus. Proton magnetic resonance spectra were recorded by a Varian EM360A spectrometer (60Mhz spectra) a Perkin-Elmer R32 spectrometer (90MHz spectra) and a Jeol MH100 spectrometer (100MHz spectra) for solutions in deuterochloroform and/or DMSO-d_6 with tetramethylsilane as internal reference. Ultraviolet spectra were obtained, using a Unicam S.P.800 spectrophotometer, for solutions in absolute ethanol. Infrared spectra were recorded as KBr discs, liquid films or carbon tetrachloride solutions by means of a Perkin-Elmer 177 grating spectrophotometer. Mass spectra were obtained on an A.E.I. MS12 machine. Accurate mass measurements were carried out on an A.E.I. MS902 machine. Elemental analyses were carried out at the University of Manchester, the University of Nottingham and by the Butterworth Microanalytical Consultancy Ltd. Column chromatography was carried out on neutral alumina, Brockmann activity 3. Thin-layer chromatography (t.l.c.) used plates coated with alumina GF254 (0.7mm layers). Commercial grade solvents and reagents were used except for the following which were dried by standard procedures before use : diethyl ether, tetrahydrofuran, pyridine, tert-butanol, tert-pentanol, benzene, dimethyl-formamide and dimethylsulphoxide.

The following abbreviations are used in the text : s = singlet, d = doublet, q = quartet, t = triplet, m = multiplet, w = weak, sh = shoulder, br = broad.

I would like to thank Mr.M.Harris (n.m.r. spectra), Mr.A.Greenfield (mass spectra) and Mr.E.Marriott for their technical assistance.

Part 1. Synthetic Approaches to Certain Partially Hydrogenated 8-Ketoisoquinolines.

A Approaches to 8-Keto-5,6,7,8-tetrahydroisoquinolines via 5,6,7,8-tetrahydroisoquinoline.

Ethyl 2-Ethoxycarbonylcyclohexylidinecyanoacetate (127).[113]

A mixture of ethyl cyclohexanone-2-carboxylate (126) (112.5g); ethyl cyanoacetate (85g); ammonium acetate (11.5g) and glacial acetic acid (36g) were heated under reflux in benzene (150ml) at 160°C in an oil bath for 6-7h with simultaneous separation of the water formed (22.5ml). After heating for a further 1h the mixture was cooled and ether (100ml) was added. The ethereal layer was washed successively with $NaHCO_3$ solution and water, dried ($MgSO_4$), filtered and evaporated. The residual liquid was distilled at reduced pressure to afford 132g (75%) of ethyl 2-ethoxycarbonylcyclohexylidenecyanoacetate (127) as a colourless sweet smelling liquid b.p.132-134°C (0.15mm Hg) (Lit.[113] 155°C/0.3mm).
ν_{max} : 2210cm^{-1} (C≡N)

1,3-Dihydroxy-5,6,7,8-tetrahydroisoquinoline (129)[150]

To 85% aqueous sulphuric acid solution (40ml) compound (127) (35g; 0.132M) was slowly added dropwise at 80-90°C with stirring. The reaction mixture was stirred for a further five hours at this temperature. The mixture was cooled to room temperature and poured cautiously into ice-water (300ml). The pH of the solution was carefully adjusted to 5 using ice-cold aqueous ammonia solution. After standing overnight at room temperature, the yellow crystals that had separated were collected by suction filtration and washed thoroughly with water to remove any ammonium sulphate. Recrystallisation from 70% aqueous acetic acid afforded 17.5g (80%) of yellow needles of 1,3-dihydroxy-5,6,7,8-tetrahydroisoquinoline (129) m.p.204-205°C (Lit.[150] 202-205°C).

1,3-Dichloro-5,6,7,8-tetrahydroisoquinoline (130)[150]

A mixture of compound (129) (5g, 0.03M), phosphorus oxychloride (9.2ml, 0.1M) and pyridine (1.6g, 0.02M) was

allowed to react for 2h at 200°C in a sealed glass carius tube. After reaction, the dark coloured liquid was poured into ice-water (50ml). The aqueous solution was neutralised with ammonium hydroxide solution and the dark crystals that separated were collected by filtration, washed with water and dried in vacuo. The dried crystals were purified by distillation b.p.135-137°C(0.2mm Hg)(lit.[150] 145-147°C/0.5mm). The distillate rapidly solidified to afford needles 2.5g(48%) of 1,3-dichloro-5,6,7,8-tetrahydroisoquinoline, m.p.84-85°C (lit.[150] 84-85°C).
δ1.84(4H, m, C-6 and C-7); 2.73(4H, m, C-5 and C-8); 6.95 (1H, s, C-4).

5,6,7,8-tetrahydroisoquinoline (66)[152]

Isoquinoline (6.45g, 0.05M) was placed in a 500ml Parr bottle, and dissolved in ice-cold 12N hydrochloric acid (40ml) and platinum oxide (750mg) was added. The bottle was connected to the hydrogenator and the air removed, hydrogen at 50psi pressure was applied and the mixture was hydrogenated for 12-18h. The catalyst was filtered from the solution through a glass fibre filter, the solution was diluted with water, chilled in ice and made basic with strong aqueous NaOH. The product was extracted with ether, dried over KOH pellets and the solvent evaporated. The residue was distilled at reduced pressure to afford a colourless liquid 6.3g (95%) b.p.79-80°C(1.0mm) (lit.[150] 77-81°C/1mm). A picrate was readily formed by reaction with an equimolar quantity of picric acid in warm ethanol, m.p. 143-144°C (lit.[152] 143-144°C).
δ1.80(4H, m, C-6 and C-7); 2.73(4H, m, C-5 and C-8); 6.95(1H, d, J 7Hz, C-4); 8.26(1H, d, J 7Hz, C-3); 8.30(1H, s, C-1).

B Approaches to 8-Keto-1,2,3,4,5,6,7,8-octahydroisoquinolines via heterocyclic ring closure.

(i) Syntheses starting from Cyclohex-2-enone.

Epoxidation of Cyclohex-2-enone.[157]

In a 2 litre three necked round bottomed flask equipped with a dropping funnel, a mechanical stirrer and a thermometer was placed a solution of cyclohex-2-enone (133)

(76.8g, 0.8M) and 30% aqueous hydrogen peroxide (230ml, 2.4M) in methanol (800ml). The contents of the flask were cooled to 15°C by means of an ice-bath: 6N aqueous sodium hydroxide (66ml, 0.4M) was added dropwise with stirring over a period of 1h. During the addition the temperature of the reaction was maintained at 15-20°C with an ice-bath. After addition was completed the mixture was stirred for 3h at 20-25°C. The mixture was then poured into 1 litre of saturated sodium chloride solution and extracted with 3 x 500ml portions of chloroform. The chloroform extracts were washed with water and dried over anhydrous $MgSO_4$. Excess chloroform was removed in vacuo and the residual liquid distilled through a vigreux column at reduced pressure. The epoxy-ketone (134) was collected as a colourless liquid 45.4g (51%) b.p.105-106°C (35mm); 65-68°C (4mm). (Lit.[157] 75-78°C/10mm).
ν_{max} : 1710cm^{-1} (C=O), m/e 112.
δ3.2(1H, d, $J_{2,3}$ 4Hz); 3.6(1H, m) epoxide protons.

Knoevenagel condensation with the epoxide of cyclohex-2-enone (134).

The epoxide of cyclohex-2-enone (134)(5g, 0.04M), cyanoacetic acid (3,45g, 0.04M) and ammonium acetate (0.5g) were refluxed in benzene (50ml) with simultaneous separation of the water liberated for 6h. Only a small quantity of water was collected. The mixture was cooled and diluted with benzene (50ml) and ether (100ml). The ethereal layer was washed with water (3 x 50ml), dried ($MgSO_4$) and evaporated to afford a red liquid. T.l.c. analysis (silica gel, benzene/ether, 50:50) indicated the presence of starting ketone (Rf 0.6) together with two other spots (Rf 0.3 and 0.17). Column chromatography of a portion of the product (2.5g) on silica gel (100-200 mesh) eluting with petroleum ether and benzene afforded first the starting epoxy-ketone (134)(1.8g); ν_{max} : 1710 cm^{-1} (C=O), m/e 112. Further elution with benzene gave cyclohexanon-2,3-diol (143)(0.5g), as colourless needles; m.p. 87-88°C (lit.[158] 87°C), ν_{max} 1705cm^{-1} (C=O), 3300-3600 (H bonded OH), m/e 130. Further elution with benzene/diethyl ether and diethyl ether gave an oil (0.1g); ν_{max} : 2200 (C≡N);

1785 and 1715 (C=O x 2); 3300-3700(H-bonded OH); 1660(C=C). This compound was assigned the β,γ unsaturated lactone structure (144).

Cyanomethyltriphenylphosphonium chloride (158).[168]

Chloroacetonitrile (8g, 0.108M) and triphenylphosphine (20.8g, 0.08M) were dissolved in nitromethane (120ml) and the resultant solution refluxed for 5h and cooled to give cyanomethyltriphenylphosphonium chloride as colourless crystals 20.5g (75%), m.p. 276-278°C (lit.[168] 278-279°C). ν_{max} 2220cm^{-1} (C≡N).

α-Cyanomethylenetriphenylphosphorane (159).[168]

Cyanomethyltriphenylphosphonium chloride (158)(15g) was dissolved in ice-cold water and any undissolved solid was removed by filtration. Immediately excess ice-cold aqueous 2N sodium hydroxide was added and the resultant flocculent white precipitate filtered at the pump and washed with a small quantity of ice-cold ethanol. After about 1min. the solid was quickly transferred to a vacuum oven previously heated to 120°C. The phosphorane was dried *in vacuo* for 1h and then stored in a vacuum dessicator. Recrystallisation of the phosphorane from ethyl acetate afforded α-cyanomethylene-triphenylphosphorane (159)(13.5g) as a colourless crystalline material m.p. 194-196°C (lit.[168] 195-196°C) ν_{max} : 2140cm^{-1} (C≡N).

Wittig reaction with the epoxide of cyclohex-2-enone (134)

Cyclohex-2-enone epoxide (134)(9.67g, 0.086M) in dry xylene was added dropwise at room temperature with stirring to α-cyanomethylenetriphenylphosphorane (26g, 0.086M) in dry xylene (200ml) in an atmosphere of nitrogen. The resultant solution was heated under reflux for 6h; excess xylene was removed by distillation *in vacuo* and petroleum ether added to the liquid remaining. The white precipitate of triphenylphosphine oxide was removed by filtration and washed with a small quantity of petroleum ether. The combined organic filtrate was concentrated at reduced pressure to afford a greenish-yellow liquid which was distilled at

reduced pressure whereupon it turned a deep orange. The first fractions to be collected consisted of xylene and starting epoxy-ketone (b.p. 80°C/3mm). 2,3-Epoxycyclohexylideneacetonitrile (136) distilled at 106-108°C (3mm) as a colourless liquid which was further purified by fractional distillation at reduced pressure b.p. 94-96°C/1mm 4.5g (39%). ν_{max} : 2220cm^{-1} (C≡N) 3.5(2H, m, epoxide protons), 5.5(1H, br.s, olefinic proton), m/e 135.

1-Cyclohexenylacetonitrile (160)[338]

Cyclohexanone (39.2g), cyanoacetic acid (34g) and ammonium acetate (156g) were refluxed in benzene (100ml) for 5h with continuous removal of the water formed. The benzene solution was distilled with an additional 50ml of hot benzene and allowed to cool. Ether (100ml) was added and the resultant solution washed with water (2 x 50ml). The ether was removed on a rotary evaporator and the benzene solution concentrated *in vacuo*. The resultant solution was cooled to ∿10°C in the refrigerator. The resultant crystals were collected by suction filtration and washed with cold benzene (2 x 50ml) and dried in a vacuum dessicator to afford cyclohexylidenecyanoacetic acid (36.5g, 60%) m.p.110-111°C (lit.[338] 110-110.5°C). This was heated slowly in an oil bath at 165-175°C while the system was evacuated with a water pump to a pressure of 35-45mm. The acid melted, decarboxylation occurred and crude 1-cyclohexenylacetonitrile distilled as a colourless liquid b.p. 100-120°C (35-45mm). The crude nitrile was distilled with ether (50ml) and washed with 5% sodium carbonate solution (10ml) and water (10ml), dried ($MgSO_4$) and the ether removed by distillation. Distillation of the residue at reduced pressure afforded 21.4g (80%) of 1-cyclohexenylacetonitrile b.p. 99-100°C (15mm) (lit.[338] 74-75°/4mm). λ_{max} : 218nm. ν_{max} : 2250cm^{-1} (C≡N). δ1.66(4H, m); 2.05(4H, m); 3.0(2H, br.s) α-CH_2 ; 5.8(1H, m, olefinic). m/e 121

(ii) Syntheses starting from cyclohexan-1,3-dione. Preparation of monoethylene ketal (147) of cyclohexan-1,3-dione.

Cyclohexan-1,3-dione (12.88g, 0.11M), ethylene

glycol (6.2g, 0.1M) and p-toluenesulphonic acid (100mg) in benzene (100ml) was stirred and refluxed for 3h with simultaneous removal of the water formed. The cooled reaction mixture was washed with aqueous sodium bicarbonate (2 x 25ml) and water (25ml), dried ($MgSO_4$) and excess solvent removed. The residual liquid was distilled at reduced pressure to afford the monoketal (147) as a colourless liquid b.p. 84-88°C (1.0mm) (Lit.[164] 103-108°C/4.5mm)

ν_{max} : 1720cm^{-1} (C=O).

δ1.64(2H, br.s, C-5); 1.9(2H, m, C-4); 2.35(2H, m, C-6); 2.6(2H, s, C-2); 4.0(4H, s, ketal protons). m/e 156 (M^+); 99 (base peak).

Cyanomethylphosphoric acid dimethyl ester (162, R=Me)

Chloroacetonitrile (15.2g, 0.204M) was added dropwise to trimethylphosphite (27.2g, 0.22M) under reflux. The resultant mixture was refluxed for 1½h and then fractionally distilled in vacuo. The dimethyl cyanomethylphosphonate (162, R=Me) distilled as a colourless liquid b.p. 121-123°C (3 mm) (Lit.120-1°C/3mm)[342] 11.0g (36%).

ν_{max} :2300 cm^{-1} (C≡N).

δ2.97(2H, d, J_{p-h} 12Hz, 2 x MeO)

Wadsworth-Emmons-Homer modified Wittig reaction with the monoethylene ketal (147) of cyclohexan-1,3-dione.

In an atmosphere of nitrogen sodium hydride (80% dispersion in mineral oil) (1.99g, 0.066M) was washed with sodium dried ether (3 x 10ml), the ether being removed with a pipette. 1,2-Dimethoxyethane (previously dried by distillation from calcium hydride) (100ml) was added followed by the phosphonate (162) (9.9g, 0.066M) dropwise with stirring at 20°C. After completion of the addition the reaction mixture was stirred for 1h under a nitrogen atmosphere until gas evolution ceased. The ketal (147) (10.36g, 0.066M) was added dropwise at such a rate that the temperature of the reaction mixture was maintained below 30°C. After the addition the solution was stirred and a viscous semi-solid material separated; after a further 30 minutes at

room temperature the mixture was taken up in a large excess of water and the resultant aqueous solution extracted with diethyl ether (3 x 100ml), dried ($MgSO_4$) and the ether removed. The residue distilled at 94-96°C(0.1mm) to give the ethylene ketal of 3-ketocyclohexylideneacetonitrile(161) (Z and E isomers), 8.0g (70%). Found : C, 66.65; H, 7.12; N, 7.55. $C_{10}H_{13}NO_2$ requires : C, 67.02; H, 7.31; N, 7.82.
λ_{max} : 222nm(ε 9432)
ν_{max} : 2220cm^{-1}(C≡N conj.); 1640 (C=C conj.).
δ1.5-2.26(6H, m, $-CH_2CH_2CH_2-$); 2.45(2H, s, C-2); 3.95(4H, s, ketal protons; 5.10(1H, br.s, olefinic, Z isomer); 5.20(1H, br.s, olefinic, E isomer). m/e 179(M^+), 99 (base peak).

(iii) Syntheses starting from 3-methoxybenzaldehyde.

3-Methoxy-β-nitrostyrene.(166)[179a]

3-Methoxybenzaldehyde (144g), nitromethane (120g) and ammonium acetate (40g) were heated for 2h at 130°C on an oil bath in glacial acetic acid (400ml). Upon cooling to room temperature and subsequent refrigeration the nitrostyrene crystallised. It was collected by suction filtration washed well with cold water and dried by air suction. Upon recrystallisation from ethanol or methanol 3-methoxy-β-nitrostyrene was obtained as pale yellow needles 132g(78%) m.p. 91-92°C (Lit.[237] 91-92°C).
λ_{max} : 306nm (ε 13,300). ν_{max} : 1640cm^{-1} (C=C) and 1350cm^{-1} (NO_2). δ3.85(3H, s, OMe), 7.55 and 7.95(2H, ABq, olefinic, J 14Hz) and 6.90-7.45(4H, m, aromatic).

β-(3-Methoxyphenyl)ethylamine (167).

(i) By lithium aluminium hydride reduction of 3-methoxy-β-nitrostyrene.(166)

To a well stirred solution of lithium aluminium hydride (25g) and anhydrous ether (1500ml) was added 3-methoxy-β-nitrostyrene (36g) by the Soxhlet extraction technique[179b] under reflux for 36h. After cooling in ice, water (25ml) was cautiously added dropwise with stirring and then 2N NaOH (25ml) followed by water (75ml). After stirring for 30min. the ethereal solution was filtered and

the precipitated lithium salts washed well with ether. The combined ethereal solution was concentrated on the rotary evaporator and the residual oil taken up in ether and dried (K_2CO_3). After removal of the ether the resultant oily amine distilled at 92-94°C/1mm Hg. (Lit.[179a] b.p. 63-65°C/0.01mm Hg), (27.5g, 90.5%).
λ_{max} : 273nm (ε, 1790), ν_{max}^{film} : 3370 and 3270 cm^{-1}(NH_2).
δ1.15(2H, s, NH_2); 2.56-3.10(4H, m, $-CH_2CH_2-$); 3.76(3H, s, OMe), 6.6-7.3(4H, m, aromatic).

(ii) By diborane reduction of 3-methoxyphenylacetamide (170).

a) Preparation of borane-T.H.F. complex.

Boron trifluoride etherate was purified by distillation from calcium hydride under vacuum. The apparatus was thoroughly flushed with nitrogen and the purified BF_3-etherate (180g, 1.27M) was added dropwise to sodium borohydride (38g, 1.0M) dissolved in diglyme (300ml). The diborane evolved was bubbled through a solution of sodium borohydride in diglyme to further ensure removal of boron trifluoride gas and then passed through a dry ice condenser to remove any diethyl ether which might have been carried over in the nitrogen-diborane stream. Finally the stream was passed into a sintered glass bubbler into freshly distilled tetrahydrofuran at -25°C. Following completion of the addition of BF_3-etherate, the diglyme solution was stirred for 1h and then heated at 100°C for 1h as nitrogen was continually passed through. The resulting borane-T.H.F. solution was standardised by removing an aliquot with an analytical syringe and injecting it into a 1:1:1 water-glycerine-T.H.F. solution, with subsequent measurement of the hydrogen evolved in a gas burette. The resulting borane-T.H.F. solution (Approx. 2M in BH_3) was stored under nitrogen at 0°C.

b) Diborane reduction.

3-Methoxyphenylacetamide (170) m.p. 128-129°C was prepared from 3-methoxyphenylacetic acid via the acid chloride in 87% yield. The amide (20g, 0.12M) was dissolved in freshly

distilled tetrahydrofuran (450ml) and added slowly with stirring under nitrogen at 0°C to the previously prepared borane-T.H.F. solution (200ml, 0.3M); the temperature being maintained at approximately 0°C throughout the addition. The colourless solution was then brought to reflux and maintained there for 3h. The flask was permitted to cool to room temperature and 6M hydrochloric acid (75ml) was added slowly through a dropping funnel. The THF was removed by distillation at atmospheric pressure as hydrogen was evolved from the hydrolysis of the amine-borane complex. Sodium hydroxide pellets were added to saturate the aqueous phase and the latter was extracted with diethyl ether. After drying (K_2CO_3) distillation yielded β-(3-methoxyphenyl)-ethylamine as a colourless oil b.p. 80-82°C/0.1mm Hg (18.3g, 100%), identical in all respects with the compound synthesised by method (i) above.

β-(5-Methoxy-1,4-cyclohexadienyl)ethylamine. (171)

Sodium metal (20g) was added in small pieces to a solution of β-(3-methoxyphenyl)ethylamine (167)(25g) in redistilled liquid ammonia (1 litre) and absolute ethanol (125ml) at -55°C in a solid CO_2/acetone bath during 1h. The resultant deep blue solution was stirred at ∿-50°C until decolouration occurred (approx. 1h). The ammonia was evaporated in a slow stream of nitrogen overnight. Water (300ml) was added with stirring to the residue and the resultant solution and oily base extracted thoroughly with diethyl ether; the ether extracts dried (K_2CO_3), and evaporated. The residual oil was distilled at reduced pressure to afford the pure amine (171) as a clear colourless liquid (23g, 91%) b.p. 96-98°C(1mm).

ν_{max}^{film} : 3370 and 3280 (NH_2), 1696 and 1664cm^{-1} (dihydroanisole).

δ1.20(2H, br.s, NH_2); 2.13(2H, t, J 7Hz, β-CH_2); 2.75(2H, m, J 7Hz, α-CH_2-N); 2.65(4H, br.s, CH_2 at C-3 and C-6); 3.50(3H, s, MeO); 4.50(1H, m, C-4); 5.43(1H, m, C-2).

N-[2-(5-Methoxy-1,4-cyclohexadienyl)ethyl]-4-methoxyphenylacetamide.(173)

β-(5-Methoxy-1,4-cyclohexadienyl)ethylamine (171) (2.08g) in benzene (40ml), under a nitrogen atmosphere, and 5% aqueous sodium bicarbonate solution (50ml) was treated dropwise with 4-methoxyphenylacetyl chloride (2.5g) in benzene (10ml), with stirring and ice-cooling. After addition was completed the resultant mixture was stirred for 1.5h. The benzene layer was separated and the aqueous solution extracted with benzene (50ml) : the combined organic extracts were washed with aqueous 2N sodium hydroxide and water and dried over potassium carbonate. Removal of the benzene in vacuo afforded an oil which was heated with diethyl ether and the resultant hot ethereal solution decanted from any insoluble material. Cooling in ice and trituration afforded fine needles which were collected by filtration (3.0g, 73%); concentration of the mother liquors afforded a further 0.5g of slightly less pure material. The analytical sample of N-[2-(5-methoxy-1,4-cyclohexadienyl)-ethyl]-4-methoxyphenylacetamide (173) m.p. 60-61°C was recrystallised from diethyl ether. Found : C, 71.3; H, 7.6; N, 4.9. $C_{18}H_{23}NO_3$ requires C, 71.73; H, 7.69; N, 4.65.

λ_{max} : 230nm (11,320); 277(1773); 284(1509).

ν_{max}^{KBr} : 3280(NH), 3060(C=C-H), 1698 and 1666 (dihydroanisole system), 1640 (Amide C=O).

δ2.10(2H, t, J 7Hz, β-CH_2); 2.60(4H, br.s, C-3 and C-6); 3.30((2H, m, J 7Hz, α-CH_2); 3.46(2H, s, benzyl CH_2); 3.52(3H, s, C-5 MeO); 3.80(3H, s, aromatic MeO); 4.56(1H, m, $w_{\frac{1}{2}}$ 6Hz, C-4); 5.27(1H, m, $w_{\frac{1}{2}}$ 8Hz, C-2); 5.72(1H, br.m, NH); 6.83 and 7.13(4H, A_2B_2 q, J_o 9Hz, J_m 1.5Hz, aromatic).

N-[2-(3-oxocyclohex-1-enyl)ethyl]-4-methoxy phenylacetamide.(175)

The previously prepared amide (173) (25g, 83mM) in tetrahydrofuran (250ml) and 10% aqueous hydrochloric acid (50ml) was stirred at room temperature for 24h. The reaction was followed by t.l.c. (alumina plates, ether/

$CHCl_3$ 50:50 eluent). When no more starting material was evident tetrahydrofuran was removed in vacuo and water and excess 2N sodium hydroxide was added until the mixture was basic. The resultant mixture was extracted with chloroform (3 x 100ml); dried (K_2CO_3) and evaporated to afford a viscous oil which solidified to a pale yellow mass on standing. Recrystallisation from diethyl ether afforded translucent golden leaflets of N-[2-(3-oxocyclohex-1-enyl)-ethyl]-4-methoxyphenylacetamide (175) (18.6g, 78%) m.p. 62-63°C. Found : C, 71.15; H, 7.24; N, 4.77. $C_{17}H_{21}NO_3$ requires : C, 71.05; H, 7.36; N, 4.87.

λ_{max}^{EtOH} : 230nm (ε, 17.930); 277(1950); 284(1600).

ν_{max}^{KBr} : 3250(amide NH); 3050(C=C-H); 1660(enone C=O); 1640(amide C=O); 1240 and 1030cm^{-1} (C-O stretch).

δ1.96(2H, m, J 7Hz); 2.30(6H, m, cyclohexene ring protons); 3.40(2H, m, J 7Hz α-CH_2); 3.47(2H, s, benzyl CH_2); 3.80(3H, s, OMe); 5.76(1H, s, $w_{\frac{1}{2}}$ 4.5Hz, olefinic); 6.16 1H, broadened triplet (J, 5Hz) NH ; 6.85 and 7.15(4H, A_2B_2q, J_o 9Hz, J_m 1.5 Hz, aromatic).

N-[2-(3-oxocyclohex-1-enyl)ethyl]-4-methoxyphenylacetamide ethylene ketal.(205)

(1) Dioxolanation with ethylene glycol.

The amide (175)(1.0g) in benzene (50ml) and ethylene glycol (0.9g) with p-toluenesulphonic acid (50mg) was heated under reflux for 24h with simultaneous separation of the water formed (Dean-Stark trap). After cooling to room temperature; the benzene solution was washed with aqueous sodium bicarbonate solution and water; dried (K_2CO_3) and the benzene removed in vacuo to afford a viscous syrup (1.1g). Column chromatography over neutral alumina (Act 3, 50g) eluting with diethyl ether and chloroform afforded N-[2-(3-oxocyclohex-1-enyl)ethyl]-4-methoxyphenylacetamide ethylene ketal (205) as a viscous syrup (0.95g, 82%) b.p. 216-218°C/0.1mm. Found : C, 68.52; H, 7.30; N, 3.95 $C_{19}H_{25}O_4N$ requires : C, 68.84; H, 7.60; N, 4.23.

λ_{max}^{EtOH} : 229nm (ε, 6200); 277 (1333); 284 (1133).

ν_{max}^{film} : 3300cm^{-1}(NH); 3080(C=CH); 1640(amide C=O).
δ1.60(2H, m, J 7Hz, β-CH_2); 2.10(6H, m, cyclohexene ring protons); 3.28(2H, m, J 7Hz, α-CH_2); 3.50(2H, s, benzyl CH_2); 3.80(3H,s, OMe); 3.95(4H, s, ketal protons); 5.28(1H, m, $w_{\frac{1}{2}}$ = 5Hz, olefinic); 5.48(1H, broad peak, NH); 6.86 and 7.16 (4H, A_2B_2q, J_o 9Hz, J_m 1.5Hz, aromatic).

(2) By exchange dioxolanation.[213]

The amide (175)(0.5g), 2-methyl-2-ethyl-1,3-dioxolane (prepared by ethylene glycol dioxolanation of butanone)(20ml) and p-toluenesulphonic acid (50mg) was heated in an oil bath and the liberated butanone, admixed with reactant dioxolane, distilled slowly through a small claisen-vigreux column at atmospheric pressure for a period of 5h. The cooled reaction mixture was diluted with benzene, washed successively with 5% sodium bicarbonate solution and water, dried ($MgSO_4$) and excess solvent removed at reduced pressure. Purification of the residue as described in (1) above afforded the ethylene ketal (205)(0.4g, 69%) as a viscous syrup identical in all respects with that prepared by method (1).

N-[2-(3-hydroxycyclohex-1-enyl)ethyl]-4-methoxyphenyl-acetamide.(213)

The enone amide (175)(5.8g) in methanol (80ml) and water (0.5ml) was stirred and cooled to 0°C in an ice-bath. Sodium borohydride (2.1g) was added in small portions, and the resultant mixture then stirred for 2h at 0-5°C. Thin layer chromatographic analysis on alumina plates with chloroform as developing solvent indicated loss of enone (175) (R_f 0.5) and the appearance of a new spot (R_f 0.3). After evaporation of methanol *in vacuo* the residue was partitioned between water and chloroform and the aqueous phase extracted with chloroform. The combined chloroform extracts were washed with brine, dried ($MgSO_4$) and evaporated to afford a colourless syrup. This solidified on standing and scratching to a white solid which crystallised from ether/light petroleum (b.p.40-60°C) to afford colourless leaflets of N-[2-(3-hydroxycyclohex-1-enyl)ethyl]-4-methoxy-

phenylacetamide (213), (5.6g, 96%) m.p.65-67°C.
Found : C, 71.0; H, 8.30; N, 4.90. $C_{17}H_{23}NO_3$ requires : C, 70.56; H, 8.01; N, 4.84.
λ_{max} : 229nm (8210); 277 (1474); 284 (1263).
ν_{max}^{KBr} : 3350(OH); 3250(amide NH); 3040(C=CH); 1640(amide C=O); 1240 and 1030cm^{-1} (C-O stretch).
δ1.3-2.0(6H, m, cyclohexene ring protons); 2.1(2H, t, J 7Hz, β-CH_2); 2.23(1H, broad s, OH); 3.27(2H, m, J 7Hz, α-CH_2N); 3.5(2H, s, benzylic CH_2); 3.8(3H, s, OMe); 4.1(1H, m, -OCH-); 5.4(1H, s, $w_{\frac{1}{2}}$ 6Hz, olefinic); 5.7(1H, broad t, -NHCO-); 7.0(4H, A_2B_2q, aromatic).

N-[2-(3-acetoxycyclohex-1-enyl)ethyl]-4-methoxyphenylacetamide. (214)

The hydroxy-amide (213) (0.5g) in dry pyridine (20ml) was treated dropwise with acetic anhydride (5ml) the resulting solution was stirred for 24h at room temperature. Excess solvent and acetic anhydride was removed in vacuo and the residue treated with iced water and extracted with methylene chloride. The combined extracts were washed successively with 2N hydrochloric acid and water; dried ($MgSO_4$) and evaporated to afford N-[2-(3-acetoxycyclohex-1-enyl)ethyl]-4-methoxyphenylacetamide (214) as a pale yellow viscous syrup (0.15g, 90%) b.p.194-196°C (0.1mm). Found : C, 68.6; H, 7.45; N, 4.2. $C_{19}H_{24}NO_4$ requires : C, 68.84; H, 7.6; N, 4.23.
λ_{max} : 229nm (6267); 277 (1467); 284 (1267).
ν_{max} : 3250cm^{-1} (amide NH); 1725 (acetate C=O); 1640 (amide C=O); 1610 (C=C).
δ1.4-2.0(6H, m, cyclohexene ring protons); 2.02(3H, s, CH_3CO); 2.10(2H, t, J 7Hz, β-CH_2); 3.26(2H, m, J 7Hz, α-CH_2N); 3.46 (2H, s, benzylic CH_2); 3.80(3H, s, OMe); 5.17(1H, m, -OCH-); 5.38(1H, m, $w_{\frac{1}{2}}$ 6Hz, olefinic); 5.8(1H, broad t, -NHCO-); 7.0(4H, A_2B_2q, aromatic).

N-{2-[3-(3,5-Dinitrobenzoyloxy)cyclohex-1-enyl]ethyl}-4-methoxyphenylacetamide.(217)

The allylic alcohol (213)(0.25g) in dry pyridine (10ml) was treated with 3,5-dinitrobenzoyl chloride (0.22g) at 0°C with stirring. The resultant mixture was stirred at room temperature for 24h. The red solution thus produced was evaporated at reduced pressure and treated with iced water and extracted with methylene chloride. The combined methylene chloride extracts were washed with 2N hydrochloric acid and water and dried ($MgSO_4$). Evaporation of the methylene chloride afforded a yellow solid which was crystallised from ethanol to afford N-{2-[3-(3,5-Dinitrobenzoyloxy)cyclohex-1-enyl]ethyl}-4-methoxyphenylacetamide (217) as pale yellow plates (0.28g, 67%) m.p.135-136°C. Found : C, 59.9; H, 5.3; N, 8.6. $C_{24}H_{25}N_3O_8$ requires : C, 59.62; H, 5.21; N, 8.69.

λ_{max} : 225nm (38000); 277 (4000); 284 (3334).

ν_{max}^{Br} : 3320cm^{-1} (amide NH); 1730 (ester C=O); 1642 (amide C=O).

δ1.5 - 2.1(6H, m, cyclohexene ring protons); 2.18(2H, t, J 7Hz, β-CH_2); 3.32(2H, t, J 7Hz, α-CH_2N); 3.5(2H, s, benzylic CH_2); 3.8(3H, s, OMe); 5.5(1H, s, $w_{\frac{1}{2}}$ 5Hz, olefinic); 7.0(4H, A_2B_2q, aromatic protons); 9.16(3H, m, 3,5-dinitrobenzoate aromatic protons).

Attempted Bischler-Napieralski cyclodehydration of N-[2-(3-oxocyclohex-1-enyl)ethyl]-4-methoxyphenyl acetamide(175)

A solution of the acetamide (175)(1.0g; 3.5mM), freshly distilled phosphoryl chloride (1.5g; 9.8mM) and dry benzene (20ml) was heated under reflux for 2.5h and allowed to stand overnight at room temperature. The reaction mixture was concentrated under reduced pressure and then treated with iced water. The solution was extracted with chloroform. The combined organic extracts were washed with 5% sodium carbonate solution until the washings were basic, water until the washings were neutral, dried ($MgSO_4$) and evaporated to afford a syrup (0.9g) which was shown by t.l.c. and infrared spectroscopic analysis to be starting material.

Repetition of the reaction utilising toluene as reaction solvent also gave unchanged starting material. With phosphorus pentoxide and phosphoryl chloride in refluxing xylene only black intractable tarry material was obtained.

Attempted Bischler-Napieralski cyclodehydration of N-[2-(3-oxocyclohex-1-enyl)ethyl]-4-methoxyphenylacetamide ethylene ketal (205).

The amide (205)(0.8g) in pure dry pyridine (30ml) was heated under gentle reflux, and to this solution was added an intimate mixture of phosphorus pentoxide (5g) and dry sand (50g) in four portions with stirring. Some time later, stirring became impossible due to caking of the dehydrating agent. After being refluxed for 6h., the dark-coloured pyridine layer was decanted and the residual extracted with 3 x 10ml portions of hot pyridine. From the combined pyridine solution the solvent was removed *in vacuo*, leaving a dark tarry residue from which no pure products could be obtained.

Part 2. The Synthesis of Ring-A Bridged Isoquinolines.

(1) Diels-Alder reactions with dihydrophenylacetamides

β-(1,4-Cyclohexadienyl)ethylamine (240).[232]

Lithium metal (7g) was added in small portions with stirring to a solution of β-phenylethylamine (12g) in liquid ammonia (300ml) and absolute ethanol (45.6g), while cooling in a solid carbon dioxide-acetone bath. The added metal was rapidly consumed and the mixture developed a deep blue colour. After all the metal had been added the solution was stirred until decolourisation occurred (ca. 2h). After evaporation of the ammonia the residue was treated with water (300ml) and extracted with ether. After drying ($MgSO_4$) and removal of excess solvent in vacuo the residual oil was distilled at reduced pressure to afford the primary amine (240) as a colourless oil, b.p. 58-60°C (3mm) (lit.[232] 61-62°C/4.5mm) 9.6g(78%).

ν_{max}^{film} : 3360, 3270(NH_2), 1645(C=C), 3020(=CH), 670cm^{-1}(=CH). δ1.0(2H, br.s, NH_2); 2.10(2H, t, J 7Hz, β-CH_2); 2.60(4H, br.s, CH_2 at C-3 and C-6); 2.75(2H, t, J 7Hz, α-CH_2-N); 5.46(1H, br.s, C-2H olefin); 5.68(2H, br.s, C-4H and C-5H olefins).

N-[2-(1,4-Cyclohexadienyl)ethyl]acetamide (236)[232]

β-(1,4-cyclohexadienyl)ethylamine (240)(3.5g) in benzene (30ml) was acylated with acetyl chloride (2.4g) in the presence of sodium hydroxide solution with stirring and ice-cooling. After stirring 1h at room temperature the benzene layer was separated and the aqueous solution extracted with diethyl ether : the combined organic extracts were washed with aqueous sodium hydroxide and water and dried (K_2CO_3). Removal of solvents on the rotary evaporator afforded a pale yellow solid which was recrystallised from petroleum ether (b.p.60-80°C) to afford colourless needles 3.8g(80%) of N-[2-(1,4-cyclohexadienyl)ethyl]acetamide (236) m.p. 47°C (lit.[232] 46.5-47.5°C).

ν_{max} : 3300(NH); 3080(=CH); 1660cm^{-1}(amide C=O). δ1.96(3H, s, amide CH_3); 2.10(2H, t, J 7Hz, β-CH_2); 2.55 (4H, br.s, C-3 and C-6); 2.80(2H, t, J 7Hz), α-CH_2-N);

5.46(1H, br.s, olefinic); 5.65(2H, br.s, olefinics); 5.80(1H, br, NH). m/e 165(M^+), 43 (base).

N-[2-(1,4-Cyclohexadienyl)ethyl]-4-methoxyphenylacetamide(238)

β-(1,4-Cyclohexadienyl)ethylamine (240) (2.6g) in benzene (50ml) was treated with 4-methoxyphenylacetyl chloride (3.87g) in benzene (30ml) in the presence of sodium bicarbonate solution (5%, 100ml) with cooling and stirring. After 1h a white crystalline solid separated. After stirring for a further 1h at room temperature work-up in the usual manner afforded the amide (238) which was purified from a mixture of n-hexane and benzene to give colourless scales of N-[2-(1,4-cyclohexadienyl)ethyl]-4-methoxyphenylacetamide (238), 5.3g(93%), m.p. 84-85°C (lit.[233] 86-86.5°C).

λ_{max} : 228nm (11,143); 277 (1744); 284 (1356).

ν_{max} : 3250 (NH), 3070 (=CH), 1640 (amide C=O), 1620cm^{-1} (C=C).

δ2.08(2H, t, J 7Hz, β-CH_2); 2.53(4H, br.s, C-3 and C-6 CH_2); 3.28(2H, m, J 7Hz, α-CH_2-N); 3.50(2H, s, benzyl CH_2); 3.80(3H, s, OMe); 5.27(1H, br,s, C-2 olefinic); 5.45(1H, br, NH); 5.65(2H, br.s, C-4 and C-5 olefinics); 7.0(4H, A_2B_2q, aromatics). m/e 271 (M^+), 121 (base).

Diels-Alder reaction with methylacrylate.

N-[2-(1,4-cyclohexadienyl)ethyl]acetamide (236) (5.0g), methyl acrylate (25ml) and hydroquinone (0.5g) was heated in a sealed Carius tube (flushed with nitrogen and sealed at 0.1mm Hg) at 150°C for 72h. After removal of excess dienophile in vacuo the resultant dark coloured viscous oil was chromatographed over neutral alumina (activity II) eluting with petroleum ether/diethyl ether and finally chloroform, column fractions were monitored by t.l.c. (alumina plates; ether/chloroform 50:50 eluent). The first fractions from the column consisted mainly of starting material. Further elution with diethyl ether afforded the mixture of epimeric esters (241) and (242) as a colourless viscous oil which formed a semi-solid mass on standing, 3.8g (50%), but which was not obtained analytically

pure.

ν_{max} : 3300(amide NH); 1735(ester C=O); 1665cm^{-1}(amide C=O). δ2.0(3H, s, amide CH_3); 2.16(2H, t, J 7Hz, β-CH_2); 2.80(2H, t, J 7Hz, α-CH_2-N); 3.70(3H, s, OMe); 5.48(0.47H, s, exo olefinic); 5.70(0.53H, s, endo olefinic) ratio exo:endo = 47 : 53. m/e 251 (M^+).

(2) Diels-Alder syntheses with hexahydroisoquinolines.

(A) Synthesis of hexahydroisoquinolines.

1,2,3,4-Tetrahydro-6-methoxyisoquinoline.(307)

20% Formaldehyde solution (25g) was added to β-(3-methoxyphenyl)ethylamine(167)(24.5g) (cf.pg.250) and the mixture heated for 1h on the water bath. Extraction with benzene gave the azomethine (27g) which was then dissolved in 20% hydrochloric acid (32g) and the solution evaporated to dryness (Pictet-Spengler synthesis). The crystalline product was dissolved in water and the amine was liberated by addition of 10% sodium hydroxide solution. After extraction with ether, drying over magnesium sulphate and evaporation of the ether, the residual oil was vacuum distilled to yield 1,2,3,4-tetrahydro-6-methoxyisoquinoline 21.5g (81%) b.p. 128-130°C(2mm)(lit.[236a] 143-144°/6mm).

λ_{max} : 279nm(1700).

ν_{max} : 3270cm^{-1} (NH).

δ1.32(1H, s, NH); 2.60(2H, t, J 7Hz, C-4 CH_2); 2.95(2H, t, J 7Hz, C-3 CH_2); 3.68(3H, s, OMe); 3.78(2H, s, C-1 CH_2); 6.4 - 6.9(3H, m, aromatic).

1,2,3,4-Tetrahydro-6-methoxy-2-methylisoquinoline (246)

A mixture of 1,2,3,4-tetrahydro-6-methoxyisoquinoline (20.0g), 90% formic acid (31.3g) and 35% formaldehyde solution (23.0g) was refluxed for 1h. after the evolution of carbon dioxide had ceased (2-3h in all), (Eschweiler-Clarke methylation[236b]). After cooling dilute hydrochloric acid was added until the solution was acid to Congo Red and neutral substances were removed by extraction with ether. The tertiary base was liberated with sodium hydroxide and extracted with ether. After

After drying ($MgSO_4$), ether was evaporated and the residue distilled to afford 1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (246), 21.2g (98%) b.p. 108-110°C(1mm) (lit.[236b] 138°C/13mm).

λ_{max} : 279nm (1700).

δ2.42(3H, s, NMe); 2.5 - 3.0(4H, m, $ArCH_2CH_2N$); 3.50(2H, s, $ArCH_2N$); 3.75(3H, s, OMe); 6.4-6.9(3H, m, aromatic).

1,2,3,4,5,8-Hexahydro-6-methoxy-2-methylisoquinoline(248)[234,236]

Sodium (24g) was added during 1h with stirring to 1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (246)(20.0g) in methanol (100ml) and liquid ammonia (500ml). After cautious addition of ether and water, ammonia was allowed to evaporate and the reduction product extracted with ether. The dried ether solution was evaporated and the residue was distilled to give 1,2,3,4,5,8-hexahydro-6-methoxy-2-methylisoquinoline (248) 19.0g (94%) as a colourless oil, b.p. 84-86° (0.1mm)(lit.[234] 114-116°/5mm).

ν_{max} : 1705 and 1670cm^{-1} (dihydroanisole C=C[188a,241]).

δ2.0(2H, br.t, C-4 CH_2); 2.24((3H, s, NMe); 2.43(2H, t, J 6.5Hz, C-3 CH_2); 2.54(4H, br.s, C-5 and C-8 CH_2); 2.65(2H, br.s, C-1 CH_2); 3.50(3H, s, OMe); 4.52[1H, s($w_{\frac{1}{2}}$ ≃ 5Hz), olefinic].

Isomerisation of 1,2,3,4,5,8-hexahydro-6-methoxy-2-methylisoquinoline (248) to 1,2,3,4,7,8-hexahydro-6-methoxy-2-methylisoquinoline (250).[234]

The unconjugated diene (248)(15.0g) was dissolved in a solution of potassium t-pentyl oxide (from 7.5g of potassium) in t-pentyl alcohol and the mixture was heated at 100°C in a nitrogen atmosphere for 4h. t-Pentyl alcohol was removed in vacuo, water was added and the organic product was extracted with ether. The dried ethereal solution was evaporated and the residue distilled at 114-118°(3mm)(14.5g) (lit.[234] 90-94°/2mm). This mixture contained the conjugated diene (250)(ca. 75%) and was used without further purification in subsequent Diels-Alder reactions.

λ_{max} : 272nm (4000).

ν_{max} : 1675 and 1620cm^{-1} (C=C).

δ4.52(0.25H, br.s, unconjugated diene olefin); 4.62(0.75H, br.s, conjugated diene olefin).

(B) Diels-Alder condensations of 1,2,3,4,7,8-hexahydro-6-methoxy-2-methylisoquinoline.

1) With methyl vinyl ketone.

7β-(260) and 7α-Acetyl-1,2,3,4,6,7,8,8a-octahydro-6-methoxy-2-methyl-6,8a-ethanoisoquinoline (261)

The isomerisation mixture (10g) containing 75% of 1,2,3,4,7,8-hexahydro-6-methoxy-2-methylisoquinoline (250) was heated under reflux with methyl vinyl ketone (50ml) in the presence of hydroquinone (0.1g) for 4h at 100°C. Excess dienophile was removed *in vacuo* and the unconjugated diene (248) b.p. 88-92°(0.3mm), 1.5g, was recovered by vacuum distillation. The mixture of ketone adducts distilled over at 120-130°C(0.3mm)(lit.[249] 110-120°C/0.03mm)(8.0g). The mixture of ketone adducts (5.0g) was dissolved in light petroleum (10.0ml) and applied to the surface of an alumina column (Wöelm neutral alumina activity III), (200g). Elution with light petroleum removed aromatic impurities and unconjugated diene (248). Further elution with light petroleum ether containing 5% diethyl ether afforded the *exo*-ketone (260). Further elution with petroleum ether/diethyl ether 90:10 afforded a mixture of (260) and (261); continued elution gave the *endo*-ketone (261) which was eluted completely with 100% ether. The *exo-ketone* (260) (1.6g), b.p. 124-126°C/0.02mm) formed a *methiodide* on treatment with methyl iodide in dry ether, which crystallised as pale yellow rhombs from methanol m.p. 208°C; lit.[249] 206°(decomp.). Found : C, 49.5 ; H, 6.9 ; N, 3.4. $C_{16}H_{26}NO_2I$ requires : C, 49.1 : H, 6.7 ; N, 3.6%. The *endo-ketone* (261)(2.6g), b.p. 128-130°C(0.3mm)(lit.[249] 116-118°C/0.02mm) m.p. 35°C (lit.[249] 35°C) formed a *methiodide*, m.p. 200-202°C which crystallised as yellow platelets from acetone. Found : C, 49.1 ; H, 6.7 ; N, 3.5. $C_{16}H_{26}NO_2I$ requires : C, 49.1 ; H, 6.7 ; N, 3.6. The *exo-ketone* (260) showed ν_{max} : 1710cm^{-1} (C=O).

δ2.23(3H, s, COMe); 2.27(3H, s, NMe); 2.91(C-7 Hα), $J_{7\alpha,8\alpha}$ 11.5, $J_{7\alpha,8\beta}$ 4.5, $J_{7\alpha,10\alpha}$ 1.5Hz; 3.36(3H, s, OMe); 6.02(1H, s, C-5 olefin).

The endo-ketone (261) showed ν_{max} 1710 cm^{-1}(C=O).

δ2.10(3H,s,COMe); 2.30(3H,s,NMe); 3.02(C-7 Hβ),$J_{7\beta,8\beta}$ 9,$J_{7\beta,8\alpha}$ 6Hz,3.32(3H,s,OMe);5.86(1H,s,C-5 olefin). $^{m}/e$ 249($M^{\cdot}$),43(Base peak)

2) With phenyl vinyl ketone

7β-(262) and 7α-Benzoyl-1,2,3,4,6,7,8,8a-octahydro-6-methoxy-2-methyl-6-8a-ethanoisoquinoline (263).

The isomerisation mixture (4g) containing 75% of 1,2,3,4,7,8-hexahydro-6-methoxy-2-methylisoquinoline (250) in benzene (30ml) was treated with freshly distilled phenyl vinyl ketone (3.0g) and the resulting mixture heated under reflux for 8h in the presence of a trace of hydroquinone as stabiliser. After removal of excess benzene the residue was distilled when excess phenyl vinyl ketone and unconjugated diene (248) was recovered. The mixture of phenyl ketone adducts distilled at 184-192°C(0.1mm), (3.0g). The mixture of adducts (10g) was subjected to preparative thin-layer chromatography on alumina plates (0.75mm layers) with light petroleum/diethyl ether (1:1) as eluent solvent. The exo-ketone (262) was eluted as the less polar component, the endo-ketone (263) being the more polar. The exo-keto (0.26g) formed a methiodide on treatment with MeI in dry acetone. The methiodide crystallised as yellow plates from methanol/ether m.p. 250-251°C. Found : C, 55.6 ; H, 6.1 ; N, 3.2. $C_{21}H_{28}NO_2I$ requires : C, 55.6 ; H, 6.2 : N, 3.1%. The endo-ketone (0.52g) formed a picrate when treated with an equimolar amount of picric acid in ethanol and was recrystallised from ethanol m.p. 212°(dec.). Found : C, 57.6; H, 5.3 ; N, 10.15. $C_{26}H_{28}N_4O_9$ requires : C, 57.8 ; H, 5.2 ; N, 10.4%. The exo-ketone (262) showed λ_{max} : 210(ε 13500), 245(13800), 280nm(1400).

ν_{max} : 1680cm^{-1} (C=O).

δ2.20(3H, s, NMe); 3.10(3H, s, OMe); 3.56(C-7 Hα), $J_{7\alpha,8\alpha}$ 12, $J_{7\alpha,8\beta}$ 4, $J_{7\alpha,10\alpha}$ 1.5 Hz; 6.03(1H, s, C-5 olefin); 7.2(3H, m) and 8.08(2H, m)(aromatic). The endo-ketone (263) showed λ_{max} : 210(ε, 14000), 245(15000), 280nm(1800).

ν_{max} : 1680cm^{-1}(C=O).
δ2.20(3H, s, NMe); 3.13(3H, s, OMe); 3.76(C-7 Hβ), $J_{7\beta,8\beta}$ 9.5, $J_{7\beta,8\alpha}$ 6 Hz; 5.83(1H, s, C-5 olefin); 7.33(3H, m) and 7.85(2H, m)(aromatic).

3) With N-phenylmaleimide.

The isomerisation mixture (1.5g) containing 75% of 1,2,3,4,7,8-hexahydro-6-methoxy-2-methylisoquinoline (250) was heated under reflux with N-phenylmaleimide (1.1g) in toluene for 24h. The toluene was removed in vacuo and the oily residue (2.6g) was chromatographed over neutral alumina (Camag activity III)(120g) eluting with petroleum ether, petroleum ether/diethyl ether (95:5) and (90:10) and 100% diethyl ether. Initial eluents from the column proved to be starting unconjugated diene (248) and N-phenylmaleimide. Upon elution with diethyl ether the mixture of epimeric adducts (264) and (265) was obtained as a pale yellow oil (1.85g). The mixture of adducts showed ν_{max} : 1710 and 1775cm^{-1}.
δ2.36(3H, s, NMe); 2.85 and 3.15(1H, AB quartet, J 9Hz, C-7Hα and C-8 Hα in the exo adduct); 3.20 and 3.35(1H, AB quartet, J 9Hz, C-7 Hβ and C-8 Hβ in the endo adduct); 3.51(1.5H, s, OMe); 3.54(1.5H, s, OMe); 5.95(0.5H, s, endo C-5 olefin); 6.12(0.5H, s, exo C-5 olefin); 7.34(5H, m, aromatic).
Upon mixing equimolar amounts of the mixed adducts and picric acid in hot ethanol a picrate was formed m.p. 122-128°C. The n.m.r. showed that a mixed picrate had been formed.
δ3.0(3H, s, $-\overset{+}{N}$Me); 3.52(1.5H, s, OMe); 3.58(1.5H, s, OMe); 6.2(0.5H, s, exo olefin); 6.4(0.5H, s, endo olefin); 8.85 (2H, s, picrate protons).
Repeated recrystallisation of the picrate from ethanol and ethanol/acetone gave the same mixture, which did not prove analytically pure.

(C) Addition of the elements of ketene to the hexahydroisoquinoline system.

Synthesis of 2-Acetoxyacrylonitrile.[251]

(i) 3-Chlorolactonitrile.

Chloroacetaldehyde dimethyl acetal (50g, 0.4M) was heated with water (50ml) and 85% phosphoric acid (3ml) for 3h on the steam bath. After cooling the resultant solution was neutralised to pH 7 with aqueous 2N sodium hydroxide. Glacial acetic acid (24.4g) was added and the solution cooled in an ice-salt bath. Sodium cyanide (19.6g) in water (67ml) was added slowly with stirring while maintaining the temperature between -10^{o} and $+5^{o}C$. Stirring was continued for 1h after addition was complete. The cyanohydrin was extracted with ether. The ether solution was dried ($MgSO_4$), concentrated, and fractionated through a 12-in. Vigreux column to yield 26.4g (62%) of 3-chloro-lactonitrile as a colourless liquid b.p. 80-82^{o}C (1 mm) (lit.[251] 88-90^{o}C/2.5mm).

ν_{max} : 3400(OH) and 2240cm^{-1}(C≡N).

(ii) 2-Chloro-1-cyanomethyl Acetate.

3-Chlorolactonitrile (26g) was treated at 0^{o}C with excess acetic anhydride and 5 drops of pyridine and the resultant solution allowed to stand 1h at 0^{o}C and then stirred for 24h at room temperature. Excess acetic anhydride and pyridine were removed on the rotary evaporator and the residue was fractionally distilled at reduced pressure to give 2-chloro-1-cyanoethyl acetate as a colourless liquid 30.2g, (83%), b.p. 65-67^{o}C (1mm) (lit.[251] 65^{o}C/1mm).

ν_{max} : 2250(w, C≡N), 1755(C=O).

δ2.2(3H, s, acetate Me); 3.80(2H, d, J 7Hz, $-CH_2-$); 5.52(1H, t, J 7Hz, -CH-).

(iii) 2-Acetoxyacrylonitrile.

Triethylamine (28.4g, 0.28M) in ether (50ml) was added slowly to 2-chloro-1-cyanoethyl acetate (41.4g, 0.28M) in ether (300ml) with stirring and cooling below 30^{o}C. After addition, the solution which now contains a

copious precipitate of amine hydrochloride was stirred for 6h. To the solution was added excess dilute aqueous hydrochloric acid to both dissolve the amine hydrochloride and neutralise any unreacted amine. After separation of the ether layer it was washed with dilute hydrochloric acid and water and dried ($MgSO_4$). To the ether solution was added a pinch of t-butylcatechol (or hydroquinone) as a polymerisation inhibitor. The ether solution was concentrated and the residue fractionally distilled to give 22g(71%) of 2-acetoxyacrylonitrile as a clear colourless liquid, b.p.92-94°(30mm), (lit.[251] 65°/12mm).

ν_{max} : 2235(C≡N), 1775(C=O), 1636cm^{-1}(C=C).

δ2.2(3H, s, acetate Me); 5.65(2H, q, $=CH_2$).

7β-Cyano-7α-chloro (291) and 7α-cyano-7β-chloro-1,2,3,4,6,7-8,8a-octahydro-6-methoxy-2-methyl-6,8a-ethanoisoquinoline(292)

The isomerisation mixture (6g) containing 75% of 1,2,3,4,7,8-hexahydro-6-methoxy-2-methylisoquinoline (250) was heated at 100°C with 2-chloroacrylonitrile (20ml) and benzene (20ml) for 12h. Removal of excess solvent and dienophile *in vacuo* afforded a black viscous product. This was dissolved in the minimum amount of chloroform and applied to the top of an alumina column (Wöelm alumina activity III, 150g). Elution with light petroleum ether removed unconjugated diene (248) ; further increase of slovent polarity by addition of ether (5%) and (10%) afforded the chloronitrile adducts (291) and (292) which crystallised as pale yellow rhombs m.p. 98-100°C; 6.0g(89%). (R_f 0.75, alumina plates, ether eluent). Ratio *exo*-nitrile adduct (291) : *endo*-nitrile adduct (292) = 2 : 1. Found : C, 62.9 ; H, 6.9 ; N, 10.4. $C_{14}H_{19}ON_2Cl$ requires : C, 63.0 ; H, 7.2 ; N, 10.5%.

ν_{max}^{KBr} : 2250(C≡N), 1650(C=C), 786cm^{-1}(C-Cl).

δ2.30(3H, s, NMe); 3.50(3H,s, OMe); 5.90(0.67H, s, C-5 olefin of *exo*-nitrile) ; 6.06(0.33H, s, C-5 olefin of *endo*-nitrile).

7β-Cyano-7α-chloro-1,2,3,4,6,7,8,8a-octahydro-6-methoxy-2-methyl-6,8a-ethanoisoquinoline (291)

Obtained after preferential hydrolysis of the exo-chloro compound (292) from the mixture of adducts (6.09g) as discussed below. Pale yellow rhombs m.p. 106-108°C (2.5g). Found : C, 63.0 ; H, 7.2 ; N, 10.2. $C_{14}H_{19}ON_2Cl$ requires C, 63.0 ; H, 7.2 ; N, 10.5%.
ν_{max} : 2250(C≡N), 1650(C=C), 786cm^{-1}(C-Cl).
δ2.3(3H, s, NMe); 3.5(3H, s, OMe); 5.8(1H, s, C-5 olefin).

7-Oxo-1,2,3,4,6,7,8,8a-octahydro-6-methoxy-2-methyl-6,8a-ethanoisoquinoline (276)

The previously prepared chloronitrile adducts (291) and (292)(6.09g) in tetrahydrofuran (100ml) were treated with 14% aqueous potassium hydroxide (50ml) and methanol was added until a clear solution was obtained. The resultant solution was boiled under reflux for 12hrs. with stirring. After removal of excess solvents in vacuo the residue was partitioned between chloroform and water and the aqueous phase extracted with chloroform. The combined organic extracts were dried ($MgSO_4$) and evaporated to afford 5.5g of an oil. This was applied to a column of alumina (Camag neutral alumina, Act.3, 200g)and eluted successively with petroleum ether, and petroleum ether/diethyl ether 95 : 5 and 90 : 10. First to be eluted from the column was the 7β-cyano-7α-chloro adduct (291)(2.5g) m.p. 106-108°C. Further elution with petroleum ether/diethyl ether 90 : 10 and 100% diethyl ether afforded 7-oxo-1,2,3,4,6,7,8,8a-octahydro-6-methoxy-2-methyl-6,8a-ethanoisoquinoline (276) as a pale yellow oil b.p.120-122°C (0.5mm) 1.8g(87% based on recovered exo-nitrile).
Found : C, 70.9 ; H, 9.0 ; N, 6.4. $C_{13}H_{19}O_2N$ requires : C, 70.55 ; H, 8.65 ; N, 6.3%.
λ_{max} : 294nm (ε, 271).
ν_{max} : 1730cm^{-1}(C=O).
δ2.25(3H,s, NMe); 3.45(3H,s, OMe); 5.80(1H, s, C-5 olefinic).
When the exo-nitrile (291) (1.0g) was hydrolysed in a similar

manner with dioxan as solvent under reflux for 24h and worked-up in the same manner as described above, the product obtained 0.53g(64%) showed the same t.l.c. and spectral characteristics as the bicyclo[2.2.2]octenone (276) obtained from the hydrolysis of the mixed adducts.

(D) Synthesis and Diels-Alder reaction of N-formyl-hexahydroisoquinolines.

1,2,3,4,5,8-hexahydro-6-methoxyisoquinoline (308).

Sodium metal (12g) was added with stirring, over 1h to a solution of 1,2,3,4-tetrahydro-6-methoxyisoquinoline (307)(10.0g) (preparation p.261) in liquid ammonia (500ml), dry ether (50ml) and methanol (50ml). When the deep blue colour had disappeared the ammonia was evaporated overnight in a nitrogen atmosphere. Water (ca. 200ml) was then cautiously added and the resulting solution extracted with ether. The ethereal solution was dried ($MgSO_4$) and concentrated in vacuo. The residue was distilled to give 1,2,3,4,5,8-hexahydro-6-methoxyisoquinoline (308) as a colourless oil, 9.2g(91%) b.p. 102-104°(0.5mm), 110-112°C (0.1mm)(lit.[180] 138-140°/14mm).

ν_{max} : 3280 (NH), 3000 (=CH), 1705 and 1670cm^{-1}(dihydroanisole C=C).

δ1.20(1H, s, NH); 1.90(2H, t, C-4 CH_2); 2.50(4H, s, C-5 and C-8 CH_2); 2.87(2H, t, J 7Hz, C-3 CH_2); 3.06(2H, s, C-1 CH_2); 3.50(3H, s, OMe); 4.50(1H, s, C-7 olefin).

1,2,3,4,5,8-Hexahydro-6-methoxy-N-formylisoquinoline (306)

The 1,2,3,4,5,8-hexahydro-6-methoxyisoquinoline (308) (5.5g) in toluene (40ml) and ethyl formate (30ml) was refluxed for 6h in a nitrogen atmosphere. Toluene and excess ethyl formate were recovered by distillation and the residual oil dissolved in warm diethyl ether and refrigerated, the resultant crystalline mass was collected by filtration to afford 1,2,3,4,5,8-hexahydro-6-methoxy-N-formylisoquinoline (306) (5.4g, 92%). The analytical sample was recrystallised from diethyl ether m.p. 57-59°C. Found : C, 68.5 ; H, 7.8 ; N, 7.5. $C_{11}H_{15}O_2N$ requires : C, 68.4; H, 7.8; N, 7.25%.

ν_{max} : 3000(=CH), 1705 and 1670 (sh)(dihydroanisole system), 1660cm^{-1} (C=O).

δ2.12(2H, br.t, C-4 CH_2); 2.65(4H, br.s, C-5 and C-8 CH_2); 3.5(2H, t, J 7Hz, C-3 CH_2); 3.56(3H, s, OMe); 3.86(2H, br.s, C-1 CH_2); 4.63(1H, s, C-7 olefinic); 8.07 and 8.14(1H, 2 singlets, formyl proton, two rotamers. Ratio 5:4).

Isomerisation of 1,2,3,4,5,8-hexahydro-6-methoxy-N-formylisoquinoline (306) to 1,2,3,4,7,8-hexahydro-6-methoxy-N-formylisoquinoline (311)

Potassium-t-pentoxide was prepared from potassium metal (0.1g) in dry t-pentyl alcohol (5ml). t-Pentyl alcohol was removed under vacuum and the resultant white amorphous solid dried at 80-100°C and 0.1mm for 1h. After cooling to room temperature,dry nitrogen was introduced into the system and dry DMSO (20ml) was added. After stirring 30min at room temperature 1,2,3,4,5,8-hexahydro-6-methoxy-N-formylisoquinoline (306)(6g) in dry DMSO (30ml) was added slowly at room temperature. The resultant deep orange solution was stirred overnight under nitrogen at room temperature and then heated for 6h at 60-70°C. After cooling the mixture was poured into excess iced-water and extracted with chloroform. The combined chloroform extracts were thoroughly washed with water and dried ($MgSO_4$). Chloroform was removed on the rotary evaporator and last traces of solvent removed under high vacuum (0.1mm) to afford 1,2,3,4,7,8-hexahydro-6-methoxy-N-formylisoquinoline (311)(ca. 75-80%) together with unchanged starting material (306)(ca. 20-25%)(5.95g).

λ_{max} : 272nm (ε, 4230).

ν_{max} : 1660(C=O); 1620(conj. C=C).

δ3.60(3H, s, OMe); 3.90(2H, s, C-1 CH_2); 4.63(0.25H, br.s, unconjugated diene olefin); 4.73(0.75H, s, comjugated diene olefin); 8.07 and 8.14(1H, 2 singlets, rotamer formyl protons).

7β- (314) and 7α-Acetyl-1,2,3,4,6,7,8,8a-octahydro-6-methoxy-N-formyl-6,8a-ethanoisoquinoline (315)

The isomerisation mixture (3.0g), from the previous experiment, containing 75% of 1,2,3,4,7,8-hexahydro-6-methoxy-N-formylisoquinoline (311) was heated under reflux with methyl vinyl ketone (25ml) in the presence of hydroquinone (0.1g) for 6h on the steam bath. Excess dienophile was removed *in vacuo* and the residue (4.3g) was chromatographed on alumina (Camag neutral alumina, Act.3, 200g). Elution with petroleum ether with successively increasing amounts of ether (5%, 10% and 100%) afforded the unconjugated diene (306) and aromatic material. Further elution with diethyl ether containing increasing amounts of chloroform (5%, 10% and 100%) afforded first the *exo*-ketone (314) then a mixture of adducts and finally the *endo*-ketone (315). The *exo*-ketone (314)(0.7g) crystallised on prolonged refrigeration and was recrystallised from diethyl ether as colourless rhombs m.p. 116-118°C. Found : C, 68.6 ; H, 8.2 ; N, 5.3. $C_{15}H_{21}O_3N$ requires : C, 68.4 ; H, 8.0 ; N, 5.3.

ν_{max}^{KBr} : 1710(acetyl C=O) and 1660cm^{-1} (amide C=O).
δ2.28(3H, s, acetyl Me); 2.50(2H, t, J 7Hz, C-4 CH_2); 2.92 (1H, C-7 Hα, $J_{7\alpha,8\alpha}$ 11, $J_{7\alpha,8\beta}$ 5, $J_{7\alpha,10\alpha}$ 1.5Hz); 3,34(2H,s, C-1 CH_2); 3.40(3H, s, OMe); 3.48(2H, t, J 7Hz, C-3 CH_2); 6.12(1H, s, C-5 olefin); 8.04 and 8.14(1H, 2 singlets, rotamer formyl protons).

The *endo*-ketone (315)(1.6g) crystallised on standing and was recrystallised from diethyl ether as pale fawn rhombs m.p. 125-127°C. Found : C, 68.8 ; H, 8.3 ; n, 5.2. $C_{15}H_{21}O_3N$ requires : C, 68.4 ; H, 8.0 ; N, 5.3.

ν_{max}^{KBr} : 1710(acetyl C=O) and 1660cm^{-1}(amide C=O).
δ2.16(3H, s, COMe); 2.54(2H, br.t, C-4 CH_2); 3.07(1H, t, C-7 Hβ, $J_{7\beta,8\beta} = J_{7\beta,8\alpha}$ 7.5Hz); 3.36(3H, s, OMe); 3.36(2H, s, C-1 CH_2) 3.52(2H, t, J 7Hz, C-3 CH_2); 5.88(1H, s, C-5 olefin); 8.02 and 8.12(1H, 2 singlets, rotamer formyl protons).

PART 3 Synthesis of and Diels-Alder studies with 6-methoxy-2-substituted-1-benzyl-1,2,3,4,7,8-hexahydroisoquinolines.

A Attempts to synthesise 6-methoxy-2-methyl-1-(4'-methoxybenzyl)-1,2,3,4,5,8-hexahydroisoquinoline via a Stevens rearrangement of an isoquinolinium salt.

6-Methoxy-2-(4'-methoxybenzyl)-2-methyl-1,2,3,4,5,8-hexahydroisoquinolinium chloride (346).

A solution of 6-methoxy-2-methyl-1,2,3,4,5,8-hexahydroisoquinoline (246) (5g, 0.028M) in dry benzene (50ml) and 4-methoxybenzyl chloride (4.5g, 0.028M) was kept standing under nitrogen at 35-40°C for 15h. The crude product obtained by evaporation of the solvent was triturated with dry ether to give 8.45g (90%) of 6-methoxy-2-(4'-methoxybenzyl)-2-methyl-1,2,3,4,5,8-hexahydroisoquinolinium chloride (346) as a pale yellow hygroscopic solid. The quaternary salt (346) was dried for two days over phosphorus pentoxide under reduced pressure. The crude (346) was used for the following rearrangement without further purification.[286]

$\nu_{max}^{cm^{-1}}$: 1705(w), 1670(dihydroanisole C=C).

δ3.35(3H,s, $\overset{+}{N}$-CH_3); 3.80(6H, s, C-5 OMe and C-4' OMe); 5.04 br (2H, s, $>\overset{+}{N}$-$\underline{CH_2}$-Ar).

Stevens rearrangement of 6-methoxy-2-(4'-methoxybenzyl)-2-methyl-1,2,3,4,5,8-hexahydroisoquinolinium chloride (346).

A slurry of dry powdered potassium bicarbonate (4.5g) in dry dimethylformamide (100ml) was stirred and heated in a nitrogen atmosphere at 140°C. The isoquinolinium salt (346) (7.6g) in dry DMF (50ml) was added and the resulting deep red-brown mixture refluxed for 5h. After cooling to room temperature the solution was quenched with water and extracted with diethyl ether. The ether extracts were washed with water, dried ($MgSO_4$) and evaporated to afford an orange viscous syrup (6.5g). T.l.c. (alumina plates,ether/chloroform 50:50) indicated four components. Distillation of the oil at reduced pressure afforded a pale

yellow viscous syrup, b.p. 120-122°C (0.5mm) (5.0g). G.l.c. analysis of the distillate (3% SE 30 on 80-100 Gas Chrom Q at 175°C) indicated a mixture of at least four components. Column chromatography of a portion of the product on neutral alumina with diethyl ether and chloroform as eluants yielded no pure material. The infrared spectrum of the mixture showed strong bands at 1675, 1610 and 1510cm^{-1} and the mass spectrum showed $^{m}/e$ (% base) : 297(2.5), 271(25), 241(1), 190(5), 176(25), 150(75), 121(Base 100), 91(32), 77(62), 51(32).

B Synthesis of 1-benzyl-1,2,3,4,5,8-hexahydro-6-methoxy-isoquinolines via the partial Birch reduction of 1-benzyl-isoquinoline derivatives.

(1) Synthesis of 1-benzyl-3,4-dihydroisoquinolines.

N-(3-Methoxyphenethyl)-4-benzyloxyphenylacetamide (356).

(a) By direct condensation of 4-benzyloxyphenylacetic acid with the amine inxylene.

4-Benzyloxyphenylacetic acid (355)(8g, 0.03M) and 3-methoxyphenylethylamine (167)(5g, 0.03M) were heated under reflux in an atmosphere of nitrogen in xylene (50ml) with azeotropic removal of the water produced (Dean Stark trap) for 8h. Upon cooling the amide crystallised and was collected by suction filtration and recrystallised from benzene/cyclohexane to afford N-(3-methoxyphenethyl)-4-benzyloxyphenylacetamide (356) as translucent wispy needles 11.25g(90%) m.p. 96-96.5°C. Found : C, 76.6; H, 6.8; N, 4.0%. $C_{24}H_{25}O_3N$ requires : C, 76.8; H, 6.7; N, 3.7%.
λ_{max}^{nm} : 226(ε, 15770), 273(2878), 279(2628).
ν_{max}^{KBr} : 3270(NH), 1640cm^{-1}(C=O).
δ2.7(2H, t, J 7Hz, Ar$\underline{CH_2}CH_2N$); 3.50(2H, m, $\underline{CH_2}N$); 3.47 (2H, s, Ar$\underline{CH_2}CO$); 3.78(3H, s, OMe); 5.07(2H, s, -O$\underline{CH_2}$Ar); 5.45 br(1H, NH); 6.5 - 7.6(13H, m, aromatics).

(b) By condensation of the acid chloride with the amine.

3-Methoxyphenylethylamine hydrochloride, m.p. (prepared from the amine in anhydrous ether and dry HCl gas) (4.35g) in dry chloroform (50ml) was stirred and treated dropwise with ice-cooling with triethylamine (3.9ml) in chloroform (10ml). After 30min a further similar quantity of triethylamine in chloroform and 4-benzyloxyphenyacetyl chloride (6.05g), m.p. 77-78°C, (lit.[297] 77-78°C) (prepared from the acid and thionyl chloride and purified by recrystallisation from petroleum ether b.p. 60-80°C) in chloroform was added alternatively in portions with stirring and ice-cooling. The mixture was stirred for a further 1h at room temperature then water was added. The chloroform layer was separated and washed with water, dried ($MgSO_4$) and evaporated. The crude amide obtained was purified by recrystallisation from benzene/cyclohexane to afford 6.0g (69%) of N-(3-methoxyphenethyl)-4-benzyloxyphenylacetamide (356) m.p. 95-96°C identical in all respects with the compound prepared by method (a) above.

(c) By condensation of the acid and the amine in the absence of solvent.

3-Methoxyphenylethylamine (167)(1.51g) and 4-benzyloxyphenylacetic acid (355)(2.42g) was heated at 180-190°C for 2h in a stream of nitrogen. After cooling, the residue was dissolved in hot benzene and washed successively with 2N hydrochloric acid, 2N sodium hydroxide and water. The benzene solution was dried ($MgSO_4$) concentrated and diluted with light petroleum, the crystals obtained were collected by filtration and recrystallised from benzene/cyclohexane yielding 3.2g(85%) of amide (356) identical in all respects with the material described in procedure (a) above.

N-(3-Methoxyphenethyl)-4-hydroxyphenylacetamide (364).

3-Methoxyphenylethylamine (167)(5.0g, 0.03M) and 4-hydroxyphenylacetic acid (5.0g. 0.03M) was heated at 190°C for 2h in a stream of nitrogen. After cooling,

the solid residue was dissolved in hot ethyl acetate and washed successively with 1N hydrochloric acid and 5% aqueous sodium bicarbonate solution and water. After drying ($MgSO_4$) and evaporation of the solvent *in vacuo* a tan coloured gum was obtained which crystallised on prolonged standing and was recrystallised from ethanol to afford N-(3-methoxyphenethyl)-4-hydroxyphenylacetamide (364) 8.0g, (94%) as colourless rhombs m.p.125-126°C. Found : C, 71.3; H, 6.5 ; N, 4.6% . $C_{17}H_{19}O_3N$ requires : C, 71.6 ; H, 6.7 ; N, 4.9% .

λ_{max} : 224nm(14,860), 274(3286), 280(3570).

ν_{max} : 3420(OH), 3300(NH), 1645cm^{-1} (amide C=O).

δ2.70(2H, t, J 7Hz, Ar$\underline{CH_2}CH_2N$); 3.45(2H, s, Ar$\underline{CH_2}CO$); 3.42(2H, m, $\underline{CH_2}N$); 3.77(3H, s, OMe); 5.65 br(2H, NH and OH); 6.6 - 7.3(8H, m, aromatic).

1-(4-Hydroxybenzyl)-3,4-dihydro-6-methoxyisoquinoline (368)

To stirred and refluxing solution of N-(3-methoxyphenethyl)-4-hydroxyphenylacetamide (364)(10.75g, 0.038M) in dry acetonitrile (100ml) was added freshly distilled phosphorus oxychloride (38g, 0.247M) over 15min. The reaction mixture was refluxed for 1h and then evaporated under reduced pressure. The residual gum was treated with ice-cold absolute methanol, to decompose any excess phosphorus oxychloride. The methanol was removed *in vacuo* and the residue dissolved in ethanol and treated with a small quantity of 2N hydrochloric acid and allowed to refrigerate overnight. (If no crystals formed at this stage the solution was concentrated under reduced pressure and again refrigerated). The crystalline material obtained was collected by suction filtration and recrystallised from ethanol to give 1-(4-hydroxybenzyl)-3,4-dihydro-6-methoxyisoquinoline hydrochloride (368) as colourless platelets m.p.156-158°C, 2.5g (22%). Found : C, 67.5; H, 6.1 ; N, 4.8%. $C_{17}H_{17}NO_2.HCl$ requires: C, 67.2; H, 6.0 ; N, 4.6%.

λ_{max} : 225nm(13,295), 243(6353), 324(14,588).

$\nu_{max}^{cm^{-1}}$: 3480(OH), 1640($\overset{+}{C}$=NH).

δ2.56(1H, s, =$\overset{+}{N}$H); 3.08(2H, t, J 7Hz, Ar$\underline{CH_2}CH_2N$); 3.88(2H,

t, J 7Hz, $\underline{CH_2}N$); 3.95(3H, s, OMe); 4.48(2H, s, $Ar\underline{CH_2}C=\overset{+}{N}$); 6.76 and 7.25(4H, A_2B_2 quartet, ring C aromatics); 7.0 (2H, m, C-5H and C-7H); 8.10(1H, d, J 10Hz, C-8H).

1-Benzyl-3,4-dihydroisoquinoline formation using $PCl_5/CHCl_3$.

1-(4-Benzyloxybenzyl)-3,4-dihydro-6-methoxyisoquinoline hydrochloride (357).

(a) N-(3-Methoxyphenethyl)-4-benzyloxyphenylacetamide (356) (4.7g, 12.5 mmol) was added portionwise with stirring and ice-cooling to a suspension of phosphorus pentachloride (4g, 19 mmol) in dry chloroform (30ml). The resulting solution was then allowed to stir for 24h at room temperature protected from atmospheric moisture. After cooling in a dry ice/acetone bath, absolute methanol (10ml) was added dropwise. Removal of solvents in vacuo below 50°C afforded a dark viscous oil; this was dissolved in ethanol (10ml) and treated with 2N hydrochloric acid (2ml) and the resultant solution refrigerated. After three days the crystalline material was collected by filtration and recrystallised from ethanol containing a trace of concentrated hydrochloric acid to give 3.97g (80%) of 1-(4-benzyloxybenzyl)-3,4-dihydro-6-methoxyisoquinoline hydrochloride (357) m.p. 181-183°C. Found : C, 73.5; H, 6.25; N, 3.35%. $C_{24}H_{23}O_2N.HCl$ requires: C, 73.2; H, 6.1; N, 3.6%.

λ_{max} : 226nm(22090), 245(6312), 280(8284), 325(7890).

ν_{max} : 1640cm^{-1} ($C=\overset{+}{N}$).

δ2.2 br(1H, s, exchangeable with D_2O, $\overset{+}{N}H$); 3.02(2H, t, J 7Hz, C-4 CH_2); 3.90(3H, s, OMe); 3.92(2H, t, J 7Hz, C-3 CH_2); 4.56(2H,s, $\underline{CH_2}Ar$); 5.0(2H, s, $-OCH_2-$); 6.7 - 7.5(11H, m, aromatic protons); 7.9(1H, d, C-8H, $J_{8,7}$ 8.5Hz).

1-(4-Benzyloxybenzoyl)-3,4-dihydro-6-methoxyisoquinoline (369).

N-(3-methoxyphenethyl)-4-benzyloxyphenylacetamide (356) (28g) in dry chloroform (200ml) was cooled in a dry ice-acetone bath and phosphorus pentachloride (24g) was added portionwise with stirring. After 24h at room temperature absolute methanol (50ml) was added cautiously while cooling in a dry ice-acetone bath. After the addition

was complete the mixture was allowed to reach ambient temperature and the solvents were removed in vacuo below 50°C, last traces of solvent being removed with a vacuum pump. The residual oil was dissolved in absolute ethanol (75ml) and treated with 2N hydrochloric acid (100ml). After 24h at room temperature ethanol was removed on the rotary evaporator and the resulting milky-white emulsion basified with excess concentrated potassium hydroxide solution with ice-cooling and extracted with chloroform (3 x 100ml) ; the combined chloroform extracts were dried (K_2CO_3) and the chloroform removed in vacuo to afford 26g of a pale yellow solid . This was dissolved in the minimum quantity of hot ethanol and diethyl ether was added until the solution just became cloudy. The resultant solution was stored in the fridge at 0°C for 24h and the resultant crystalline solid collected and recrystallised from diethyl ether to give 1-(4-benzyloxybenzoyl)-3,4-dihydro-6-methoxyisoquinoline (16.0g, 58%) m.p. 109°C. Found : C, 77.5; H, 5.7; N, 3.9%. $C_{24}H_{21}NO_3$ requires : C, 77.6; H, 5.7; N, 3.8%.

The base readily formed a methiodide upon treatment with methyl iodide in anhydrous ether, which crystallised as yellow needles from acetone, m.p. 199-200°C. Found : C, 58.4; H, 4.6; N, 2.6%. $C_{25}H_{24}NO_3I$ requires : C, 58.5; H, 4.7; N, 2.7%. Concentration of the mother liquors afforded a further 6.4g of less pure material;recrystallisation from diethyl ether afforded 3.0g of the free base (369). Total yield = 19.0g (68%).

The free base showed :

λ_{max} : 231nm(ε, 30,851), 292(28,510).

ν_{max} : 1660cm^{-1} (C=O).

δ2.84(2H, t, J 7Hz, C-4 $\underline{CH_2}$); 3.84(3H, s, OMe); 3.93(2H, t, J 7Hz, C-3 $\underline{CH_2}$); 5.15(2H, s, -O$\underline{CH_2}$-); 6.77(2H, s, aromatic protons); 7.02(2H, dd, J_m = 2Hz, J_o = 9Hz, C-3' and C-5'); 8.02(2H, dd, J_m = 2Hz, J_o = 9Hz, C-2' and C-6'); 7.20 - 7.60(6H, m, aromatic protons).

(b) Other procedures.

(i) N-(3-methoxyphenethyl)-4-benzyloxyphenylacetamide (356)(10g, 26.6 mmol) was dissolved in dry chloroform (75ml) and cooled in an ice-salt bath. Finely pulverised phosphorus pentachloride (13.9g, 66.2 mmol) was added slowly with stirring and the flask closed with a calcium chloride drying tube and stirred at room temperature for 24h. The resultant solution was then poured into anhydrous ether (500ml) and refrigerated for 24h. The resultant yellow solid phosphorus complex was collected by suction filtration and the complex decomposed by addition of ice-cold absolute methanol (50ml). After refrigerating overnight the resultant crystalline material was collected by filtration and recrystallised from ethanol containing a trace of concentrated hydrochloric acid to afford 8.3g (81%) of 1-(4-benzyloxybenzyl-3,4-dihydro-6-methoxyisoquinoline hydrochloride (357) identical in all respects with the compound previously described in procedure (a) above.

(ii) N-(3-methoxyphenethyl)-4-benzyloxyphenylacetamide (356)(10g, 26.6 mmol) was added at 0°C in small portions to a suspension of phosphorus pentachloride (8.4g, 40 mmol) in dry chloroform (27ml). After 24h at room temperature, absolute methanol (20ml) was added at 0°C slowly with stirring. The solvent was removed in vacuo below 50°C. The residual oil was freed of last traces of solvent on a vacuum pump. The viscous residue was dissolved in absolute ethanol (10.6 ml) and concentrated hydrochloric acid (1.3ml) was added with stirring to ensure thorough dissolution. After standing for 5 - 7 days at room temperature the crystalline product was collected by filtration and recrystallised from absolute ethanol containing a trace of concentrated hydrochloric acid to yield the 3,4-dihydroisoquinoline hydrochloride (357); 10g (95%) identical in all respects with the compound prepared by method (a) above.

(2) Synthesis of 1-Benzyl-1,2,3,4-tetrahydroisoquinolines.

1-(4-Benzyloxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (361).

(a) By sodium borohydride reduction of the 3,4-dihydroisoquinolinium salt (357).

1-(4-benzyloxybenzyl)-3,4-dihydro-6-methoxyisoquinoline hydrochloride (357) (13.6g, 34.5 mmol) in ethanol (500ml) was treated portionwise with sodium borohydride (3g, 78.7 mmol) at 20°C. After addition was completed the resultant solution was stirred for a further 2h : 2N hydrochloric acid (44 ml) was then added to give pH 3, followed after 15min. by 4N ammonia to give pH 7. The solvent was evaporated in vacuo and the residue dissolved in a mixture of chloroform (300ml) and 1N ammonia (400ml). After stirring 15min. the mixture was poured into a separating funnel and the chloroform layer separated. The aqueous phase was extracted with chloroform (2 x 50ml). The combined chloroform extracts were washed with 1N ammonia, dried ($MgSO_4$), and the solvent removed in vacuo. The residual syrup solidified to a crystalline mass and was recrystallised from ethanol. From the mother liquor a further quantity of crystals were collected to give a total of 11.7g (94%) of 1-(4-benzyloxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (361) as colourless needles m.p. 131-132°C. Found : C, 80.5; H, 7.1; N, 4.0%. $C_{24}H_{25}O_2N$ requires : C, 80.2; H, 7.0; N, 3.9%.
λ_{max} : 231nm(25000), 278(3833), 286(3333).
δ1.64 br(1H,s, NH); 2.60 - 3.30(6H, m, C-3, C-4 and benzyl CH_2); 3.76(3H, s, OMe); 4.04(1H, m, C-1 H); 5.0(2H, s, $-O\underline{CH_2}Ar$); 6.56(1H, m, C-5H); 6.75(1H, dd, $J_{7,8}$ 10Hz, $J_{7,5}$ 3Hz, C-7H); 6.80 - 7.50(10H, m, aromatic).

(b) By zinc in acetic acid reduction of 1-(4-benzyloxybenzoyl)3,4-dihydro-6-methoxyisoquinoline (369).

The imino-ketone (369)(0.6g) in 50% acetic acid (20ml) was treated with zinc dust (3g) and the resultant mixture heated under reflux for 3h. After cooling the mixture was filtered and the filtrate basified with 10%

ammonia solution and extracted with ether. The ethereal extracts were dried ($MgSO_4$) and evaporated *in vacuo* to afford an oil which was dissolved in hot ethanol and cooled in an ice-bath with scratching. The tetrahydroisoquinoline (361) crystallised and was collected by filtration to afford 0.3g (52%) of material m.p. 130-132°C identical in spectral and t.l.c. characteristics to the compound (361) synthesised by method (a) above.

1-(4-Benzyloxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (362).

1-(4-Benzyloxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (361) (10g, 27.8 mmol) in methanol (450ml) was treated with 37% formaldehyde solution (30ml) and the resulting solution stirred for 2h at room temperature. Sodium borohydride (8.5g, 236 mmol) was added in portions with stirring and the resultant solution stirred for a further 2h at room temperature. Solvents were removed *in vacuo* and the residue treated with 2N ammonia until basic and extracted with chloroform, the combined chloroform extracts were washed with water, dried over magnesium sulphate and evaporated to afford a yellow oil. The oil was dissolved in hot diethyl ether and cooled to 0°C when colourless crystals of 1-(4-benzyloxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (362) were obtained, 10.2g (98%) m.p. 69-71°C. Found : C, 79.95; H, 7.3; N, 3.85%. $C_{25}H_{27}O_2N$ requires: C, 80.4; H, 7.3; N, 3.75%.

λ_{max} : 229nm (ε, 18648), 278 (3243), 286 (2703).

δ 2.48 (3H, s, NMe); 2.50 - 3.25 (6H, m, C-3, C-4 and benzyl CH_2); 3.68 (1H, m, C-1H); 3.76 (3H, s, OMe); 5.0 (2H, s, $-OCH_2Ar$); 6.56 (3H, m, C-5H, C-7H and C-8H); 6.88 (4H, A_2B_2 q, aromatic); 7.30 (5H, m, aromatic).

(3) Birch reduction of 3,4-dihydro and 1,2,3,4-tetrahydro-1-benzylisoquinolines.

The liquid ammonia employed in the following preparations was dried by distillation from sodium prior to use.

(a) By use of Li/liq. NH_3 with ether and ethanol.

Liquid ammonia (150ml) was added at -65°C to 20ml of ether, then 2.2g(0.3M) of small pieces of lithium followed by finely powdered 1-(4-benzyloxybenzyl)-3,4-dihydro-6-methoxyisoquinoline hydrochloride (357)(4.34g, 0.011M) were added with stirring. Stirring was maintained for 3½h at ∿-60°C. A metallic copper bronze layer formed on the surface of the deep-blue ammonia solution and vigorous stirring was necessary to ensure that the mixture remained homogeneous. The temperature was raised to ∿-50° and during 30 minutes 50ml of absolute ethanol was added until the deep-blue colour was discharged. The ammonia was evaporated and the remaining solvents removed under reduced pressure. Water (150ml) was added to the residue followed by 30g of ammonium chloride with stirring. After 15 min. the product was filtered off and washed well with water and dried by air suction. Recrystallisation from ethanol afforded 2.2g (73.5%) of a crystalline material; t.l.c. and n.m.r. data suggested that this was a mixture of the required hexahydro-compound (358) and the 1,2,3,4-tetrahydro-compound (378). Two further recrystallisations from ethanol afforded 1.8g (60%) of 1,2,3,4,5,8-hexahydro-1-(4-hydroxybenzyl)-6-methoxyisoquinoline (358) as colourless hexagons (ethanol) m.p.199-201°C. Found : C, 75.2; H, 8.0; N, 5.2%. $C_{17}H_{21}NO_2$ requires : C, 75.2; H, 7.8; N, 5.2%.

λ_{max} : 230nm(6237), 280(1491).

This showed a bathochromic shift in the presence of alkali to 247(11,695), 298(2373) indicating that the compound was phenolic.[318]

ν_{max}^{KBr} : 3290(NH), 1695 and 1665cm^{-1} (dihydroanisole C=C).

δ (DMSOd_6/$CDCl_3$, 90:10) : 1.93 br (2H, t, C-4 CH_2); 2.60 br (4H, s, C-5 and C-8 CH_2); 2.40 - 3.10(4H, m, C-2 CH_2 and benzyl CH_2); 3.25 br(1H, q, C-1H); 3.50(3H, s, OMe);

4.65(1H, m, C-7 olefin); 6.70 and 7.0(A_2B_2 q, J_{AB} 8.5Hz, aromatic); 9.0 br(1H, OH).

Concentration of the mother liquors from the recrystallisation afforded the by-product 1,2,3,4-tetrahydro-1-(4-hydroxybenzyl)-6-methoxyisoquinoline (378) m.p. 195-197°C characterised by its n.m.r. ($DMSOd_6$). δ2.0(2H, m, C-4 CH_2); 3.80(3H, s, OMe); 4.05(1H, q, C-1H); 6.70(4H, m) and 7.03(3H, m) aromatic protons; 9.0 br(1H, OH).

(b) By use of Li/liq.NH_3 with THF/t-BuOH and Methanol.

(i) From the 3,4-dihydroisoquinoline hydrochloride (357).

1-(4-Benzyloxybenzyl)-3,4-dihydro-6-methoxyisoquinoline hydrochloride (357) (10.4g, 26.4 mmol) was added to a solution of liquid ammonia (200ml) containing dry tetrahydrofuran (100ml) and dry t-butyl alcohol (100ml) in a dry ice and acetone bath at -60°C. The mixture was stirred for 4h at ∿-60°C. After warming to approximately -50°C absolute methanol (40ml) was added slowly until decolourisation indicated that excess lithium had been destroyed. The ammonia was allowed to evaporate and excess solvents removed in vacuo. Water (250ml) was added to the residue with stirring followed by ammonium chloride (45g). After 15min. stirring the product was filtered by suction filtration, washed well with water and dried by air suction to give 7g of crude pale yellow product : recrystallisation form ethanol gave 6.23g (87%) of 1,2,3,4,5,8-hexahydro-1-(4-hydroxybenzyl)-6-methoxyisoquinoline (358) identical in all respects with the compound prepared by method (a) above. A further 0.58g of slightly less pure material was obtained by concentration of the mother liquors.

(ii) From the 1,2,3,4-tetrahydroisoquinoline (free base) (361).

Birch reduction of 1-(4-benzyloxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (361) was carried out by adding a solution of (361) (7.2g, 20 mmol) in tetrahydrofuran (100ml) containing t-butyl alcohol (100ml) to liquid ammonia (250ml) in a dry ice/acetone bath at -60°C over 30 minutes. Lithium wire (2g, 0.285M) was added over 10min

and the mixture stirred at ∿-60°C for 3h. Absolute methanol (30ml) was added slowly at ∿-50°C until decolourisation occurred. The ammonia was evaporated and solvents removed in vacuo and water (150ml) followed by ammonium chloride (30g) was added to the residue with stirring. After 15min the product was collected by filtration and recrystallised from ethanol to give 4.2g(78%) of 1,2,3,4,5,8-hexahydro-1-(4-hydroxybenzyl)-6-methoxyisoquinoline (358).

2-Methyl-1,2,3,4,5,8-hexahydro-1-(4-hydroxybenzyl)-6-methoxyisoquinoline (363).

1-(4-Benzyloxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (362)(6.5g, 17.4 mmol) in t-butanol (25ml) and anhydrous tetrahydrofuran (25ml) was added slowly with stirring to liquid ammonia (250ml) containing t-butanol (100ml) and THF (100ml) at -65°C. Lithium wire (freshly pressed) (2.5g, 0.36M) was added and the resultant deep blue solution and copper-bronze surface layer was stirred under nitrogen at ∿-60°C for 4h. The temperature was raised to ∿-50°C and absolute methanol (50ml) was added slowly while decolourisation occurred. The ammonia was evaporated and remaining solvents removed in vacuo. Water (200ml) was added to the residue followed by ammonium chloride (40g) while stirring constantly. The resultant suspension was extracted with chloroform and the combined chloroform extracts washed with saturated brine, dried ($MgSO_4$) and evaporated in vacuo. The resultant solid was recrystallised from methanol to afford 2-methyl-1,2,3,4,5,8-hexahydro-1-(4-hydroxybenzyl)-6-methoxyisoquinoline (363) as colourless platelets; 4.0g (81%), m.p. 159-160°C.

Found : C, 75.5; H, 8.2; N, 4.9%.

$C_{18}H_{23}O_2N$ requires : C, 75.75; H, 8.1; N, 4.9%.

λ_{max}^{nm} : 228(8210), 281(1526)

$\delta(CDCl_3/DMSOd_6)$: 1.85 br(2H, t, C-4 CH_2); 2.32(3H, s, NMe); 2.60 br(4H, s, C-5 and C-8 CH_2); 2.5 - 3.2(5H, m, C-3 CH_2, C-1 H and benzyl CH_2); 3.50(3H, s, OMe); 4.52(1H, m, C-7 olefin); 6.60 and 7.0(A_2B_2 q, J_o 8.5Hz, J_m 1.5Hz, aromatic);

8.75 br(1H, OH).

2-Formyl-1,2,3,4,5,8-hexahydro-1-(4-hydroxybenzyl)-6-methoxyisoquinoline (359).

1,2,3,4,5,8-Hexahydro-1-(4-hydroxybenzyl)-6-methylisoquinoline (358)(5.4g, 19.9 mmol) was suspended under nitrogen in toluene (155ml) and freshly distilled ethyl formate (70ml). After boiling for 72h t.l.c. (R_f 0.65 ; silica gel, methylene chloride/methanol/2N ammonia 85:15:2) showed that reaction was complete. The solvents were evaporated *in vacuo* and the residue recrystallised from 95% aqueous ethanol (120ml) to afford 4.65g of crystals. A second crop of crystals was obtained from the mother liquor, total yield 5.45g (92%) of 2-formyl-1,2,3,4,5,8-hexahydro-1-(4-hydroxybenzyl)-6-methoxyisoquinoline (359) m.p.204-205°C.
Found : C, 71.9; H, 7.05; N, 4.2%.
$C_{18}H_{21}O_3N$ requires : C, 72.2; H, 7.1; N, 4.7%.
λ_{max} : 227nm(9400), 279(1400)
ν_{max} : 3240(OH), 1695, 1660sh(dihydroanisole C=C str.), 1640cm^{-1} (Amide C=O).
$\delta(CDCl_3/DMSOd_6)$: 2.0 br(2H, C-4 CH_2); 2.50 - 3.20(8H, m, C-3, C-5, C-8 and benzyl CH_2); 3.56(3H, s, OMe); 4.35(1H, q, C-1 H); 4.70(1H, m, C-7 olefin); 6.8(4H, m, aromatic protons); 7.4 and 7.9(1H, 2 singlets, ratio 2:1 rotamers of NCHO); 8.8 br(1H, OH).

2-Formyl-1,2,3,4,5,8-hexahydro-1-(4-methoxybenzyl)-6-methoxyisoquinoline (360)

2-Formyl-1,2,3,4,5,8-hexahydro-1-(4-hydroxybenzyl)-6-methoxyisoquinoline (359)(2.5g, 8.36mmol) was dissolved in absolute methanol (250ml) and treated with excess ethereal diazomethane [generated from p-tolylsulphonylmethylnitrosamide ("Diazald") 30g, by the literature procedure[343]] at 0°C. The resulting deep yellow solution was allowed to stand at room temperature in the dark and protected from atmospheric moisture. After 48h t.l.c. (silica gel, methylene chloride: methanol:2N ammonia 85:15:2) showed that reaction was completed. The solution was concentrated to small volume on the rotary evaporator and cooled in an ice-bath with

scratching to yield crystals, which were collected by filtration and recrystallised from methanol to afford 2.35g (90%) of 2-formyl-1,2,3,4,5,8-hexahydro-1-(4-methoxybenzyl)-6-methoxyisoquinoline (360) m.p.121-122°C. Found : C, 73.1; H, 7.4; N, 4.9%. $C_{19}H_{23}NO_3$ requires : C, 72.8; H, 7.4; N, 4.5%.

λ_{max} : 229nm(10,285), 278(1714), 284(1486).

ν_{max}^{KBr} : 1698, 1665 sh (dihydroanisole C=C str.), 1660cm^{-1} (Amide C=O).

δ2.0br(2H, m, C-4 $\underline{CH_2}$); 2.5-3.2(8H, m, C-3, C-5, C-8 and benzyl $\underline{CH_2}$); 3.58(3H, s, $\underline{MeO}$-C=CH); 3.78(3H,s, MeO-Ar); 4.42(1H, q, C-1H, J_{AX}13.5 Hz, J_{BX} 6.5 Hz); 4.70¾1H, m, C-7 olefinic); 6.90(4H, A_2B_2 q, aromatics); 7.4 and 7.9 (1H, 2 signals, ratio 2:1, rotamers of NCHO).

2-Methyl-1,2,3,4,5,8-hexahydro-1-(4-methoxybenzyl)-6-methoxyisoquinoline (347)

(1) By methylation of the phenolic base (347) with diazomethane.

2-Methyl-1,2,3,4,5,8-hexahydro-1-(4-hydroxybenzyl)-6-methoxyisoquinoline (363)(2.5g, 8.77 mmol) in absolute methanol (250ml) was treated at 0°C with excess ethereal diazomethane [generated from "Diazald" (25g)] and allowed to stand at room temperature for 48h in the dark and protected from atmospheric moisture. The resulting solution was concentrated to small volume in vacuo. Cooling in ice and scratching induced crystallisation of the product which was recrystallised from methanol to afford 2.09g (80%) of 2-methyl-1,2,3,4,5,8-hexahydro-1-(4-methoxybenzyl)-6-methoxyisoquinoline (347) m.p. 84-85°C. Found : C, 76.1; H, 8.4; N, 4.6%. $C_{19}H_{25}NO_2$ requires : C, 76.2; H, 8.4; N, 4.7%.

λ_{max} : 227nm(12,909), 279(2000), 285(1454).

ν_{max}^{KBr} : 1695, 1665cm^{-1} (dihydroanisole C=C str.).

δ1.85(2H, t, J 7Hz, C-4 $\underline{CH_2}$); 2.32(3H, s, NMe); 2.5 - 3.2 (9H, m, C-1H, C-3, C-5 and C-8 CH_2's and benzyl CH_2); 3.50 (3H, s, $\underline{MeO}$-C=CH); 3.73(3H, s, $\underline{MeO}$-Ar); 4.5(1H, m, C-7

olefinic); 6.85(4H, A_2B_2 q, aromatics).

(2) By lithium aluminium hydride reduction of 2-formyl-1,2,3,4,5,8-hexahydro-(4-methoxybenzyl)-6-methoxyisoquinoline (360).

To a suspension of lithium aluminium hydride (2.2g, mmol) in anhydrous tetrahydrofuran (100ml) was added 2-formyl-1,2,3,4,5,8-hexahydro-(4-methoxybenzyl)-6-methoxyisoquinoline (360)(1g, 3.2 mmol) in anhydrous THF slowly with stirring at room temperature. After addition was complete the solution was heated under reflux for 6h in an atmosphere of nitrogen. After cooling in an ice-bath, water (2.2ml) was cautiously added with stirring followed by 2N sodium hydroxide solution (2.2ml) and finally water (6.6ml). After stirring for a further 30min. the solution was filtered and the precipitated lithium salts washed well with THF. The filtrate was dried (K_2CO_3) and evaporated in vacuo. The residue crystallised on standing and was recrystallised from methanol to afford 2-methyl-1,2,3,4,5,8-hexahydro-1-(4-methoxybenzyl)-6-methoxyisoquinoline (347), 0.9g (95%) m.p. 84-85°C identical in all respects to the compound prepared by method (1) above.

C Base-catalysed isomerisation and Diels-Alder studies of 1-benzyl-1,2,3,4,5,8-hexahydroisoquinolines.

Isomerisation of 2-formyl-1,2,3,4,5,8-hexahydro-1-(4-methoxybenzyl)-6-methoxyisoquinoline (360) to 2-formyl-1,2,3,4,7,8-hexahydro-1-(4-methoxybenzyl)-6-methoxyisoquinoline (390).

Potassium-t-pentoxide was prepared from potassium metal (20mg) in dry t-pentyl alcohol (1ml). t-Pentyl alcohol was removed in vacuo and the resultant solid dried at 80-100°C and 0.1mm for 1h. After cooling to room temperature, dry nitrogen was introduced into the system and dry DMSO (10ml) was added. The 2-formyl-1,2,3,4,5,8-hexahydro-1-benzylisoquinoline (360)(1.5g) in dry DMSO was added and the solution stirred overnight at room temperature

and at 60-70°C for 6h. After cooling the pale-red solution was poured into excess ice-water and the resultant solution was saturated with ammonium chloride and extracted with chloroform. The combined chloroform extracts were washed with water, dried (K_2CO_3) and solvents removed under high vacuum. The residual oil (1.48g) contained 2-formyl-1,2,3,4,7,8-hexahydro-1-(4-methoxybenzyl)-6-methoxyisoquinoline (390) (ca. 64%) together with unconjugated diene (360) (ca. 36%).

ν_{max} : 1675sh (C=C), 1660 (amide C=O), 1620cm^{-1} (conj. C=C).
δ3.58 (1.08H, s, MeO unconjugated diene); 3.62 (1.92H, s, MeO conjugated diene); 4.42 (1H, q, C-1H); 4.7 (0.36H, m, unconjugated diene olefin); 4.75 (0.64H, s, conjugated diene olefin); 6.90 (4H, m, aromatic protons); 7.45 and 7.95 (1H, 2 signals, ratio 2:1, rotamers of NCHO).

Dichloromaleic anhydride catalysed isomerisation Diels-Alder cycloaddition of N-formyl-1,2,3,4,5,8-hexahydro-6-methoxyisoquinoline (306) with acrylonitrile.

N-Formyl-1,2,3,4,5,8-hexahydro-6-methoxyisoquinoline (306) (0.5g), acrylonitrile (10ml) and dichloromaleic anhydride (5mg) were heated under reflux for 15h in an atmosphere of nitrogen. Excess acrylonitrile was removed *in vacuo* and the residue chromatographed on alumina (wöelm neutral alumina, Act 3, 20g) eluting with petroleum ether, diethyl ether and chloroform. The mixed adducts (389) were obtained as a pale yellow viscous oil 0.6g (94%). The mixture showed

ν_{max} : 2240 (C≡N), 1660cm^{-1} (amide C=O).
δ3.43 (3H, s, MeO); 5.93 (0.62H, s, *exo*-nitrile C-5 olefin); 6.14 (0.38H, s, *endo*-nitrile C-5 olefin); 8.10br (1H, s, formyl proton).

Isomerisation of 2-methyl-1,2,3,4,5,8-hexahydro-1-(4-methoxybenzyl)-6-methoxyisoquinoline (347) to 2-methyl-1,2,3,4,7,8-hexahydro-1-(4-methoxybenzyl)-6-methoxyisoquinoline (391)

2-Methyl-1,2,3,4,5,8-hexahydro-1-(4-methoxybenzyl)-6-methoxyisoquinoline (347) (1g) in dry DMSO (10ml) was added dropwise to potassium *t*-pentoxide [freshly prepared from

potassium metal (0.5g) and t-pentyl alcohol and dried under high vacuum at 80-100°C before use] in dry DMSO (20ml) at ~60-65°C with stirring under nitrogen. After 1h the solution was poured into excess iced-water and extracted with diethyl ether. The combined ether extract was washed well with water, dried ($MgSO_4$) and solvents removed *in vacuo*. The residual oily isomerisation mixture (1g) contained the conjugated diene (391) *ca.* 90% together with the unconjugated diene (347) *ca.* 10%.

ν_{max} : 1675 and 1620cm^{-1} (C=C).

δ2.32(3H, s, NMe); 3.50(3H, s, MeO-C=CH); 3.70(3H, s, MeO-Ar); 4.5br(~0.1H, s, unconjugated diene olefinic); 4.58(0.9H, s, conjugated diene olefin); 6.85(4H, A_2B_2 q, aromatics).

Diels-Alder reaction of 2-methyl-1,2,3,4,7,8-hexahydro-1-(4-methoxybenzyl)-6-methoxyisoquinoline (391) with acrylonitrile.

The isomerisation mixture (1.0g) containing *ca.* 90% of 2-methyl-1,2,3,4,7,8-hexahydro-1-(4-methoxybenzyl)-6-methoxyisoquinoline (391) was boiled under reflux with acrylonitrile (25ml) together with a trace of hydroquinone for 36h. Excess acrylonitrile was removed *in vacuo* and the resultant dark viscous oil (1.5g) was chromatographed on neutral alumina (Wöelm, Act.3, 60g), eluting with petroleum ether and diethyl ether to afford a green viscous oil (1.2g). T.l.c. alumina plates, ether eluent, spots developed with Dragendorff's reagent) indicated 3 components with similar R_f values : 0.43, 0.47, 0.53. A separation of the mixture into pure components could not be achieved by preparative thick-layer chromatography (alumina plates, ether/petroleum ether; 50:50 eluent) or by further careful column chromatography, the same mixture being obtained in each case.

The mixture showed:

λ_{max} : 226nm, 278, 285.

ν_{max} : 2250 (C≡N), 1640 and 1610cm^{-1} (C=C).

δ2.28 and 2.32 (2 singlets NMe); 3.56 and 3.58 (2 singlets MeO); 3.80 (s, Ar-OMe); 4.7 (0.4H, s, $w_{\frac{1}{2}}$ 4Hz, olefinic); 5.2 (0.2H, s, $w_{\frac{1}{2}}$ 4Hz, olefinic); 5.45 (0.4H, br.t, J 7Hz, olefinic); 6.5-7.2 (4H,m, aromatic).

Accurate mass observed 405.2407 and 351.2077 correspond to $C_{25}H_{31}N_3O_2$ (requires 405.2416) and $C_{22}H_{27}N_2O_2$ (requires 351.2072).

Mass spectrum, m/e (relative intensity) : 405(18), 390(10), 365(8), 352(20), 351(28), 321(2), 298(5), 284(6), 254(4), 231(14), 178(6), 176(6), 147(13), 121(96), 98(92), 97(base, 100), 91(24), 78(16), 77(18), 57(41), 54(96), 44(98).

Part 4 Reactions of Ring-A Bridged Isoquinolines.

A Modification of Substituents.

1. Reaction of ketones (260) and (261) with n-propylmagnesium halides.

Endo ketone (261)

(i) Grignard reaction in benzene/diethyl ether.

Magnesium turnings (1.95g) were placed in a nitrogen flushed, dry 3-necked round-bottomed flask. Dry diethyl ether (60ml) was introduced and 1-iodopropane (13.5g) was slowly added dropwise to maintain a constant reflux. After the addition was completed the mixture was stirred for 1h. at room temperature. The endo-ketone (261) (4.5g) in dry benzene (30ml) was added slowly with stirring to the ethereal solution of the Grignard reagent. After heating under reflux for 6h the mixture was cooled in an ice-bath and excess ammonium chloride solution (saturated aqueous) was added. After stirring for 20min. the organic layer was separated and the aqueous layer separated with ether. The combined organic extracts were dried ($MgSO_4$) and evaporated to afford a pale yellow oil (5.3g). T.l.c. and infrared analysis showed the presence of starting ketone (ν_{max} 1710 cm^{-1}) together with a less polar alcoholic component (ν_{max} 3500 cm^{-1}). Column chromatography of the oil (5.0g) over neutral alumina (Merck. Act. III) with light petroleum as eluent solvent afforded 6-methoxy-1,2,3,4,6,7,8,8a-octahydro-7α-(1-hydroxy-1-methylbutyl)-2-methyl-6,8a-ethanoisoquinoline (395) as colourless needles from light petroleum ether (b.p.40-60°C), 1.3g (25%), m.p.87-88°C. Found : C, 73.5; H, 10.45; N, 4.9%. $C_{18}H_{31}NO_2$ requires : C, 73.7; H, 10.65; N, 4.8%. Further elution with light petroleum and diethyl ether afforded the unchanged endo-ketone (261) (3.2g) [yield of carbinol (395) based on recovered ketone = 85%]. The tertiary carbinol (395) readily formed a methiodide on treatment with methyl iodide in anhydrous ether which recrystallised as very pale yellow rhombs from methanol, m.p.228-231°C. Found : C, 52.0; H, 7.8; N, 3.2%. $C_{19}H_{34}NO_2I$ requires : C, 52.4; H, 7.9; N, 3.2%.

The free base shows :

$\nu_{max}^{CCl_4}$: 3480cm^{-1} (OH, concentration independent).
δ0.85(3H, t, J 7.5Hz, $-CH_2CH_2\underline{CH_3}$); 0.90(3H, s, C-11 Me); 2.12(1H, t, J 8.5Hz, C-7Hβ); 2.30(3H, s, NMe); 4.75(1H, s, OH); 5.85(1H, s, C-5 olefinic).

(ii) Grignard reaction in tetrahydrofuran.

A solution of n-propylmagnesium bromide in dry ether (25ml) was prepared from 1-bromopropane (1.3g) and magnesium turnings (0.27g). Most of the ether was removed by distillation and dry tetrahydrofuran (25ml) was added. [freshly distilled from CaH_2]. The methoxy ketone (261) (1.0g) in dry tetrahydrofuran (10.0ml) was added dropwise with stirring at room temperature. The resultant solution was refluxed for 6h on a water bath. The mixture was cooled in ice and treated with stirring with ammonium chloride solution (10.0g in 25ml water). After stirring for 15 minutes at room temperature the solution was extracted thoroughly with ether; the ethereal extracts dried ($MgSO_4$) and evaporated to afford an oil (1.2g) which was chromatographed over neutral alumina (Camag Act III) and eluted with light petroleum ether and diethyl ether as before to afford the tertiary carbinol (395) as colourless needles from petroleum ether (b.p.40-60°C)(1.0g, 86%), m.p.87-88°C. The product was identical in all respects with the carbinol previously synthesised as described above.

Exo-ketone (260)

A solution of n-propylmagnesium bromide in dry ether (25ml) was prepared from 1-bromopropane (3.25g) and magnesium turnings (0.68g). The ether was removed by distillation under nitrogen and anhydrous THF (50ml) added. The exo-ketone (260) (2.5g) in dry THF (10ml) was added and the mixture refluxed for 6h on the water bath. After cooling in ice, ammonium chloride (10.0g) in 25ml of water was added with stirring, after stirring for an additional 15 minutes at room temperature the solution was extracted with diethyl ether, the ethereal extracts

were dried ($MgSO_4$) and evaporated to afford a pale yellow oil (3g). This was chromatographed over neutral alumina (Camag Act III, 150g) eluting with petroleum ether and diethyl ether. The first component to be eluted was shown by t.l.c. and spectral analysis to be starting exo-ketone (260)(1.1g). Further elution afforded 6-methoxy-1,2,3,4,-6,7,8,8a-octahydro-7β-(1-hydroxy-1-methylbutyl)-2-methyl-6,8a-ethanoisoquinoline (397) as a colourless viscous oil, 1.4g(85%, based on recovered starting material), b.p.132-134°C(0.03mm). Found : C, 73.3; H, 10.35; N, 4.6%. $C_{18}H_{31}NO_2$ requires : C, 73.7; H, 10.65; N, 4.8%. $\nu_{max}^{CCl_4}$: 3480 cm^{-1} (OH, concentration independent). δ0.86(3H, t, $-CH_2CH_2\underline{CH_3}$); 1.30(3H, s, C-11 Me); 2.35(3H, s, NMe); 4.70(1H, s, OH); 6.10(1H, s, C-5 olefinic).

Reaction of ketone adducts (260) and (261) with benzylmagnesium bromide.

Endo-ketone (261)

A solution of benzylmagnesium bromide in dry ether (20ml) was prepared from benzyl bromide (1.8g) and magnesium turnings (0.26g). Ether was removed by distillation under nitrogen and anhydrous tetrahydrofuran (25ml) added. The endo-ketone (261) [1.1g] in anhydrous THF (20ml) was added slowly with stirring. After refluxing for 6h on a water bath and cooling, ammonium chloride (10g) in 50ml of water was added and the mixture extracted with diethyl ether, dried ($MgSO_4$) and evaporated to afford a pale yellow oil (2.8g). This was chromatographed over neutral alumina (Wöelm Act III). Elution with petroleum ether afforded an oil (1.2g) which formed needle crystals on standing m.p. 52-53°C. Spectral analysis showed this to be bibenzyl, lit.[344] m.p. 53°C (produced by coupling of the Grignard reagent with itself). Further elution with petroleum ether containing 5% diethyl ether afforded 6-methoxy-1,2,3,4,6,7,8,8a-octahydro-7α-(1-hydroxy-1-benzylether)-2-methyl-6,8a-ethanoisoquinoline

(399) as a viscous oil, 1.25g(83%) which formed a methiodide on treatment with methyl iodide in dry ether as yellow-orange platelets from methanol m.p. 212-213°C.
Found : C, 57.1; H, 7.0; N, 2.8%. $C_{23}H_{34}NO_2I$ requires : C, 57.1; H, 7.1; N, 2.9%. The free base shows:
λ_{max} : 219nm (ε, 3760); 258(380).
$\nu_{max}^{CCl_4}$: 3490 cm^{-1} (OH, concentration independent).
δ0.95(3H, s, C-11 Me); 2.02(1H, t, J 9.0Hz, C-7 Hβ); 2.25(3H, s, NMe); 2.50(2H, s, benzyl CH_2); 3.32(3H, s, OMe); 4.93(1H, s, OH); 5.84(1H, s, C-5 olefinic); 7.16(5H, m, aromatic protons).

Exo-ketone (260)

A solution of benzylmagnesium bromide was prepared in dry ether from benzyl bromide (3.7g) and magnesium turnings (0.53g). Ether was removed by distillation under nitrogen and anhydrous THF (50ml) added. The exo-ketone (260)(1.8g) in anhydrous THF (10ml) was added slowly with stirring. After refluxing for 6h work up in the same manner as previously described for the endo-ketone (261) afforded an oil (3.5g) which was purified by column chromatography over neutral alumina (Wöelm Act III) to yield 6-methoxy-1,2,3,4,6,7,8,8a-octahydro-7β-(1-hydroxy-1-benzylethyl)-2-methyl-6,8a-ethanoisoquinoline (397) as a viscous oil, 2.0g(81%) which readily formed a methiodide as pale yellow plates m.p.233-234°C (methanol-ether).
Found : C, 56.9; H, 7.05; N, 2.8%. $C_{23}H_{34}NO_2I$ requires : C, 57.1; H, 7.1; N, 2.9%.
The free base shows:
λ_{max} : 219nm (ε, 3776); 258(387).
$\nu_{max}^{CCl_4}$: 3490cm^{-1} (OH, concentration independent).
δ1.30(3H, s, C-11 Me); 2.32(3H, s, NMe); 2.62(2H, s, benzyl CH_2); 3.28(3H, s, OMe); 4.90(1H, s, OH); 5.96(1H, s, C-5 olefinic); 7.20(5H, m, aromatic protons).

B Modification of the Ring System : formation of Azapropellanes.

Acid-catalysed rearrangment of n-propyl carbinols (395) and (397).

The endo n-propyl carbinol (395) (1.5g) and concentrated hydrochloric acid (20ml) was heated on the steam bath at 100°C for 2h. After cooling the solution was basified with aqueous ammonia and extracted with ether, the combined ethereal extracts were dried (K_2CO_3) and evaporated to afford 3-aza-7-ethyl-3,8-dimethyl[4.4.4]propell-7-en-13-one (424) as a viscous oil, 1.3g (97%). The base (424) formed a hydrochloride on treatment with ethereal HCl in methanol; as colourless rhombs from methanol, m.p.242-243°C (dec.). Found : C, 68.3; H, 9.4; N, 5.0; Cl, 12.3%. $C_{17}H_{27}NO.HCl$ requires : C, 68.5; H, 9.5; N, 4.7; Cl, 11.9%.

The methiodide was prepared by treatment with methyl iodide in anhydrous ether and was obtained as pale yellow plates from methanol, m.p.261-264°C. Found : C, 53.1; H, 7.4; N, 3.7%. $C_{18}H_{30}NOI$ requires : C, 53.6; H, 7.5; N, 3.5%.

The free base shows :

ν_{max} : 1705 cm^{-1} (C=O).

δ1.0(3H, t, J 7Hz, $MeCH_2$-); 1.65(3H, s, C-8 Me); 2.2(3H, s, NMe); 1.3 - 2.7(18H, m, unassigned).

Accurate mass observed : 261.2095, $C_{17}H_{27}NO$ requires 261.2093.

Mass spectrum, m/e (relative intensity) : 261(4), 246(0.9), 232(0.65), 218(0.9), 190(2), 162(4), 71(11), 70(26), 58(4), 57(3), 44(Base peak, 100), 43(15).

Acid-catalysed rearrangement of the exo n-propyl carbinol (397)(1.0g) with concentrated hydrochloricacid (20ml) for 3h at 100°C afforded the propellane (424) 0.85g (96%) which formed a hydrochloride m.p.242-243°C(dec) identical in all respects with the compound obtained from the endo-carbinol (395).

Acid-catalysed rearrangement of benzyl carbinols (399) and (405).

The exo-benzylmethyl carbinol (405) (2.2g) and concentrated hydrochloric acid (40ml) was heated on the steam bath at 100°C for 2.5-3h. After cooling and subsequent basification with ice-cold queous ammonia the solution was extracted with chloroform. The combined chloroform extracts were dried (K_2CO_3) and evaporated to afford a viscous oil (1.8g) b.p.188-194°C(3.5mm). T.l.c. (alumina plates ; petroleum ether/diethyl ether 50:50) indicated three components R_f's 0.5, 0.44 and 0.375. Column chromatography of the rearrangement product (1.0g) over neutral alumina (Wöelm activity 3, 50g) eluting with petroleum ether and diethyl ether afforded 3-aza-7-phenyl-3,8-dimethyl 4.4.4 propell-7-en-13-one (433) as a viscous oil (0.5g) R_f 0.44. The analytical sample was purified by short path distillation at 0.1mm. Found : C, 81.4; H, 8.65; N, 4.5%. $C_{21}H_{27}NO$ requires : C, 81.5; H, 8.8; N, 4.5%.

λ_{max} : 217nm(ε, 1580), 258(420).

ν_{max} : 1705cm^{-1}(C=O).

δ1.3(3H, s, C-8 Me); 2.24(3H, s, NMe); 1.4-2.6(16H, m, unassigned); 7.2(5H, m, aromatic).

Mass spectrum, m/e (relative intensity): 309(34), 294(2), 252(1), 238(13), 218(40), 203(5), 162(24), 71(64), 70(Base peak, 100), 58(12), 57(15), 44(41), 43(91).

By-product (A) was obtained as a viscous oil (ca∿0.1g) R_f 0.5, before elution of the propellane (433) from the column and could not be obtained analytically pure, however, it showed the following spectral characteristics:

ν_{max} : 3,400 cm^{-1} (OH), 1705 (C=O).

δ1.26(3H, s, Me); 2.26(3H, s, NMe); 3.24(2H, s, $C\underline{H}_2Ph$); 5.44(1H, s, $w_{\frac{1}{2}}$ 10Hz, olefinic); 7.2(5H, m, aromatic).

Mass spectral analysis gave a molecular ion at m/e 327 and a base peak at m/e 218.

By-product (B) was obtained as a viscous oil (ca∿0.15g) R_f 0.375, after the propellane (433) had been eluted from the column. It could not be obtained analytically pure but

showed the following spectral characteristics:

ν_{max} : 3400 cm^{-1} (OH), 1665 (conjugated C=O).

δ1.24(3H, s, Me); 2.18(3H, s, NMe); 3.24(2H, s, $C\underline{H}_2Ph$); 5.21(1H, s, $w_{\frac{1}{2}}$ 4Hz, olefinic); 7.2(m, aromatic).

Mass spectrum : M^+ at m/e 327, 218(Base).

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