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The extraction and chemistry of the metabolites of Mimosa tenuiflora and Papaver somniferum

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THE EXTRACTION AND CHEMISTRY OF THE METABOLITES OF *MIMOSA TENUIFLORA* AND *PAPAVER SOMNIFERUM*.

submitted by

ALEYAMMA NINAN

for the degree of

Doctor of Philosophy

of the

University of Bath

1990

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To my mother Annamma Chacko

"The chemists are a strange class of mortals impelled by an utmost impulse to seek their pleasure among smoke and vapour, soot and flame, poison and poverty. Yet among all these evils I seem to live so sweetly that may I die, I would not change places with the Persian king."

J.J. Beecher, 1669.

ACKNOWLEDGEMENTS

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My thanks go to Dr. John Davies of MacFarlan Smith Ltd. for his helpful suggestions and to MacFarlan Smith Ltd. for the financial support, in part, for my research work.

Finally, I would like to thank my husband for his love and support and Dr. Ravi Acharya and my children Golda, Silva and Shola for typing and proof-reading this thesis.

SUMMARY

In the first section of this thesis a phytochemical analysis of *Mimosa tenuiflora* P. was undertaken. This plant is claimed to have healing properties and the aim of this work was to identify the extractives of the bark.

The second and major part of this volume is concerned with improvements in the industrial extraction and in *O*- and *N*-demethylation procedures for some important opiate precursors, such as 14-hydroxydihydrocodeinone (oxycodone).

A new synthesis was also developed for noroxymorphone. In this the key step is a double oxidation of a derivative of morphine. High yielding routes to normorphine and hydromorphone were also developed.

CONTENTS

SECTION 1

CHAPTER 1

PHYTOCHEMICAL ANALYSIS OF *MIMOSA TENUIFLORA*

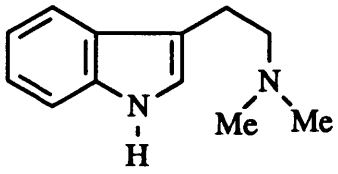
1.1 Introduction

Mimosa tenuiflora Poir[1] (Leguminasae) is a plant that grows in S.E. Mexico. The people of Mexico have known for years the medicinal properties of this plant which is claimed to have pain-relieving, antibacterial and blood clotting properties. Mexican Indians have used this bark in powder form for treating burns and other wounds. For intestinal ulcers, the bark is taken as a tea and for skin problems (acne, herpes, pimples etc.) the powdered bark is applied as a neutral salve. Face packs are made from the powdered bark mixed with egg white, yogurt and rose water and are used to clean the face. The mixture is left on the face for 15-30 minutes and then washed off with lukewarm water.

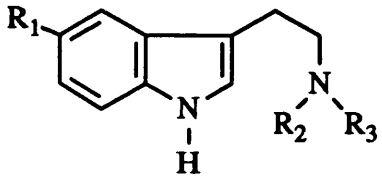
Nowadays the plant is protected by decree of the Mexican government. No previous analytical work on this plant has been reported, so that a phytochemical investigation of the dried, powdered bark of *Mimosa tenuiflora* was undertaken in the expectation that new biologically active compounds would be discovered. Such compounds might then be synthesised and studied individually.

Leguminous plants[2] contain a great variety of physiologically active compounds. However, the plant family is very large and the diversity of extractives is such that we concentrated our initial literature survey on closely related plants within the *Mimosa* genus and its allies, particularly those with plants indigenous to Central and South America. The most common physiological effect reported for extracts of these plants is hallucinogenic activity, thus Fish, Johnson and Horning[3] analysed the seeds and pods of *Piptadenia perigrina* Benth and *P. macrocarpa*

Benth and found that the pods contained *N,N*-dimethyltryptamine (**1**), whereas the seeds contained bufotenine (**2**), bufotenine oxide (**3**), *N,N*-dimethyltryptamine (**1**) and *N,N*-dimethyltryptamine oxide (**4**). The seeds were used by the Indian tribes of South America and the Caribbean to make a snuff to use in their ceremonies to induce a kind of intoxication in order to contact the souls of the dead. *N,N*-Dimethyltryptamine has subsequently been shown to be a potent hallucinogen which is used by western psychiatrists to induce temporary hallucination.



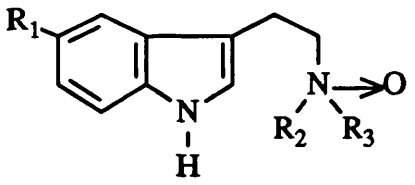
(1)



(2), R_1 = OH, R_2 = R_3 = Me, bufotenine

(5), R_1 = R_2 = H, R_3 = Me

(6), R_1 = OMe, R_2 = R_3 = Me

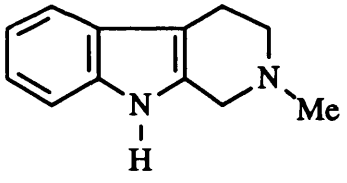


(3), R_1 = OH, R_2 = R_3 = Me

(4), R_1 = H, R_2 = R_3 = Me

N,N-Dimethyltryptamine seems to be a common component of many other Leguminasae species, and it has been identified in *Mimosa hostilis* Benth,[4] a plant which is used by Panaru Indians of Brazil to prepare a beverage called 'wine of Jurema' which is used in their religious ceremonies.

N,N-Dimethyltryptamine (**1**), *N*-methyltryptamine (**5**) and 5-methoxy-*N,N*-dimethyltryptamine (**6**) also occur in *Banisteriopsis rusbyana*.[5] The addition of a single carbon atom is all that is necessary to transform the tryptamine skeleton into that of β-carboline (**8**), and it comes as no surprise that in many Leguminous plants β-carbolines are observed as natural products. Indeed, *N*-methyl-1,2,3,4-tetrahydrocarboline (**7**) co-occurs with the tryptamines in *B. rusbyana*.



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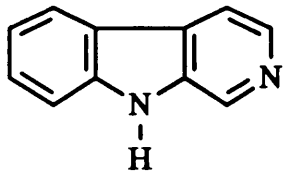
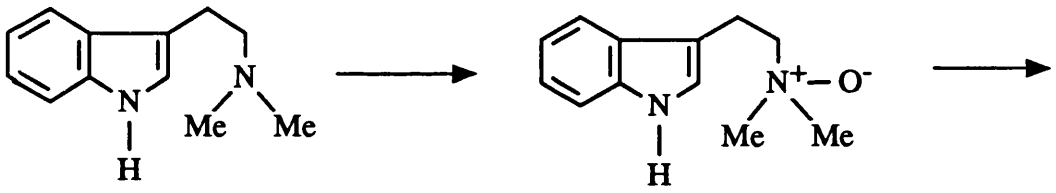
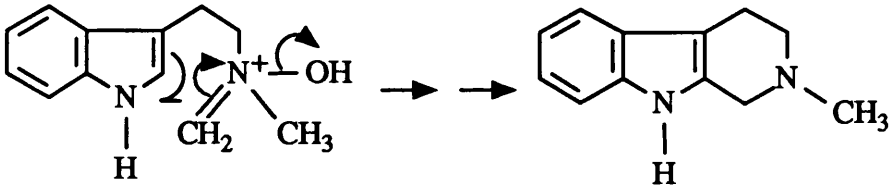


(8), β-carboline

Ghosal and Mukherjee have isolated seven indole alkaloids from *Desmodium pulchellum* Benth[6] and noted the presence of *N,N*-dimethyltryptamine oxide (**4**) and its 5-methoxy analogue (**6**) in this plant. Significantly, amine oxides of this type are considered to facilitate the cyclisation of tryptamines to carbolines and since they are known to undergo rearrangement to carbinolamines *in vitro* this is also thought to be the mechanism which operates *in vivo*.[7]



(1)



(7)

Scheme 1

Rearrangement of tryptamine-N-oxides to 1,2,3,4-tetrahydrocarbolines.

Tetrahydrocarbolines do not give rise to hallucinogenic effects, but they are physiologically active and the extracts of the plant *Hannoa klaineana* from tropical Africa, which only contains β-carbolines is used to treat intestinal disorders.[8]

Armed with these facts we anticipated that biologically active alkaloids would occur in *Mimosa tenuiflora*, but since claims for antibiotic properties are unusual in this plant family, we felt that a search for non-basic components was also justified.

1.2 Discussion and Results

The dry powdered bark of *Mimosa tenuiflora* was defatted with petroleum ether (60 - 80°C) and extracted exhaustively with methanol. This on evaporation under reduced pressure gave a brown solid (Solid 1). Simple qualitative tests on Solid 1 showed the presence of alkaloids (Dragendorff's reagent[9] and iodoplatinate reagent[10]) and also carbohydrates (Molische's test). It was decided to isolate and identify the alkaloids first.

Solid 1 was partitioned between 2M hydrochloric acid and chloroform and the chloroform layer was further extracted with 2M hydrochloric acid. The combined aqueous phases were then basified with ammonia and the chloroform extracts were washed with water, dried and evaporated under reduced pressure (Solid 2). The basified aqueous phase deposited a solid. This basified mixture without separating the solid was extracted with chloroform and the residual solid (Solid 3) was collected.

Alkaloid

Evaporation of the chloroform layer gave a residue which was chromatographed on silica, eluting with chloroform - ethyl acetate - methanol mixtures to afford *N,N*-dimethyltryptamine as the only alkaloid component of the dry bark. Yield 0.4%.

The mass spectrum of this compound exhibits the expected molecular ion at *m/z* 188 and a base peak at *m/z* 58, resulting from fragmentation of the side chain as shown.

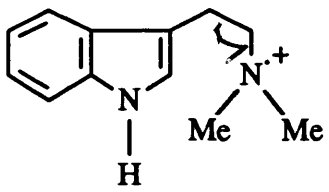


Fig. 1

The ^1H n.m.r. spectrum is easily assigned: thus a broad one-proton resonance at δ 8.2, removable by deuterium exchange, is that of the proton bonded to the indolic nitrogen and a five-proton multiplet between δ 6.99 - 7.63 is associated with the four benzenoid protons and the 2-H atom. Two two-proton triplets centered at δ 2.6 and 3.0 (J = 7.7 Hz) indicate the presence of a $-CH_2\ CH_2-$ group, and the chemical shifts of these signals accord well with those anticipated for the resonances of the side chain methylene protons of *N,N*-dimethyltryptamine. Finally, there is a six-proton singlet at δ 2.35 which relates to the resonance of the *N*-dimethyl unit. We were disappointed not to obtain any other alkaloids and the whole extraction procedure was repeated on a large scale. The result, however, was the same.

Aminoacids

The chloroform insoluble "basic" material (Solid 3) was found to be a mixture of α-aminoacids and peptides. This constituted about 14% by weight of the dry plant material.A solution of Solid 3 in water was analysed for free and bound aminoacids using a Hilger Chromaspek Mark II Chromatograph. The free α-aminoacids present in the material were found to be aspartic acid, threonine, glutamic acid, proline, glycine, alanine, valine, isoleucine, leucine, histidine and arginine. In order to determine the bound amino acids a solution of solid 3 was treated with 6M hydrochloric acid and heated at 105°C for 24 hours. The pH was then adjusted to 7 with a sodium citrate buffer prior to chromatography. Three new

amino acids were found namely serine, trytophan, and lysine. The estimated percentages are given in Table 1.

Aminoacid	% by weight of free aminoacid	% by weight of amino-acid after hydrolysis
Aspartic acid	2.75×10^{-4}	1.46×10^{-3}
Serine	-	3.97×10^{-4}
Glutamic acid	1.84×10^{-3}	4.38×10^{-3}
Glycine	1.02×10^{-4}	1.10×10^{-3}
Alanine	1.71×10^{-3}	2.07×10^{-3}
Valine	2.72×10^{-4}	5.21×10^{-4}
Histidine	1.30×10^{-2}	4.10×10^{-2}
Lysine	-	3.60×10^{-4}
Arginine	1.60×10^{-2}	2.10×10^{-2}

Table 1.1

Free and Bound amino acids present in *M.tenuiflora* bark

Carbohydrates

A sample of Solid 1 was analysed for carbohydrates by TLC on silica using three solvent systems :

(i) *n*-butanol-acetic acid-diethyl ether-water (9:6:3:1),

(ii) ethyl acetate-acetic acid-water (6:3:2) and

(iii) *n*-butanol-acetone-water (4:5:1).

p-Aminobenzoic acid reagent[11] was used for detection and methanolic

solutions of known carbohydrates (glucose, fructose, galactose, xylose, maltose, glucuronic acid, ribose, mannose, raffinose and sucrose) were employed as reference markers. The R_f values of the carbohydrates in the plant material were compared with those of the above carbohydrates, enabling the identification of glucose and a smaller quantity of fructose.

Polyols and Tannins

'Solid 2' was found to consist of polyols and tannins, it was not investigated further.

Antibiotic Tests

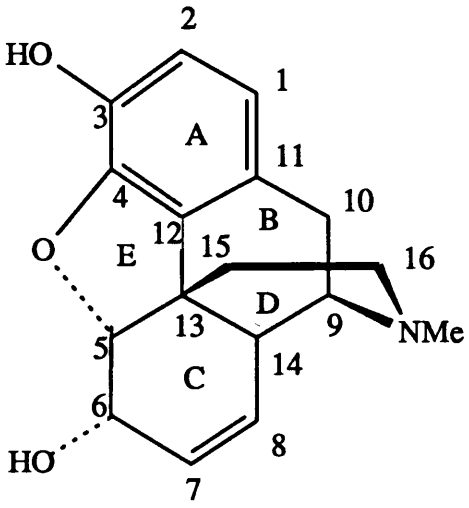
The residue obtained from methanol extraction of the plant material was reextracted with boiling water and aqueous extract was evaporated to give solid 4. The methanol extract (Solid 1) and the aqueous extract (Solid 4) were sent for antibiotic screening. The methanol extract displayed very slight toxicity and weak activity with respect to DNA gyrase from *E.Coli*, HIV Type 1 reverse transcriptase, HIV Type 1 proteinase cloned in *E.Coli*, influenza A, and cell free protein elongation in *Candida albicans* 2005E was noted. Though the aqueous extract was active in all the standard antibiotic screens and displayed slight toxicity, it was decided that the activity displayed in all of these tests was not high enough to continue the investigation.

Conclusion

We are left with the conclusion that the claims made for *M.tenuiflora* are not substantiated by phytochemical evaluation. There is a high sugar and aminoacid content in the bark and some antibiotic activity, which is still unaccounted for, but at a very low level is noted. We did not recognise any new natural products, but the potent hallucinogen *N,N*-dimethyltryptamine is present at a high concentration. Perhaps, after all, it is the action of this compound which has encouraged all the speculative sensation regarding the 'healing properties' of the plant in the press and television recently.

SECTION 2

MORPHINE

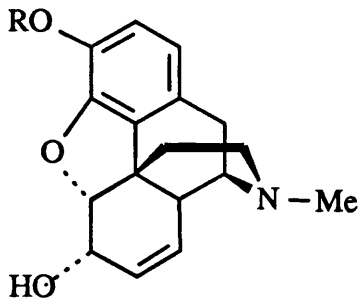


CHAPTER 2

INTRODUCTION

2.1 The Alkaloids of Opium

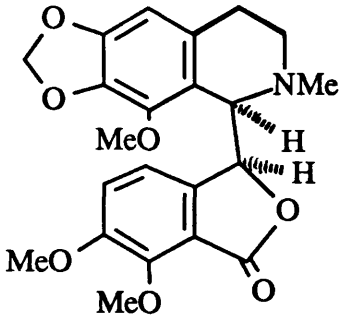
Opium has been used by man for at least 3500 years [1,2] as an analgesic and as an agent which induces euphoria. Opium (the Greek: *opion*) is the sun-dried exudate of the unripe seed capsule of opium poppy, *Papaver somniferum* Linnaeus. The alkaloid morphine (**1**), (named after Morpheus, the Greek god of sleep and dreams) was isolated from opium as a white crystalline solid by a German pharmacist, Friedrich Sertürner as long ago as 1803; opium is still the main source of morphine.[3] Since Sertürner's discovery of morphine many other major and minor alkaloids have been isolated from opium and now the number exceeds fifty. Today morphine is also derived from 'poppy straw' (the dried, milled capsule, after removing the seed) since it is economically more viable to work with the straw than to laboriously scar each seed capsule to obtain the exudate. Poppy seed is also commercially valuable in the food industry.



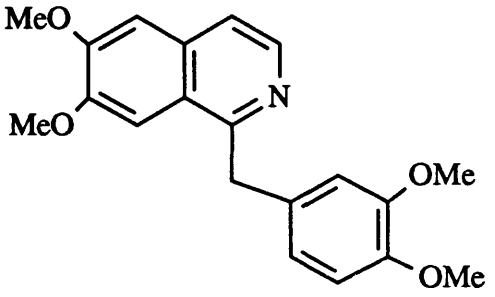
(1) R = H, morphine

(4) R = Me, codeine

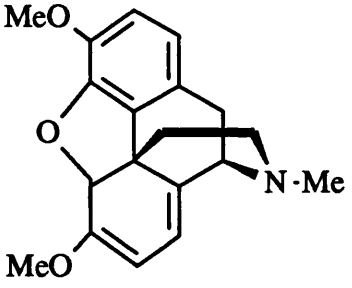
Opium contains about one quarter of its weight of alkaloids of which morphine forms 42%. The other major alkaloids are noscapine (narcotine, **2**, 21%), papaverine (**3**, 18%), codeine (**4**, 12%) and thebaine (**5**, 6.5%). The remaining alkaloids form 0.5% of the total alkaloid content of opium.



(2), noscapine



(3), papaverine

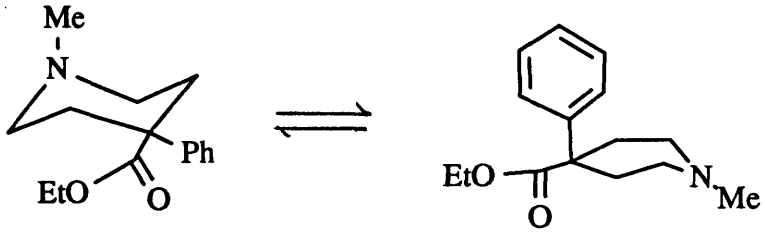


(5), thebaine

2.2 Opiate activity of morphine and the search for selective drugs.

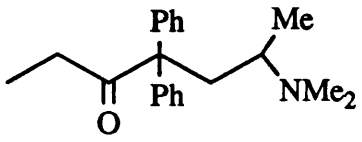
Morphine is a powerful analgesic (Relative Potency, R.P. = 1) whereas its methyl ether codeine is widely used as a mild analgesic (R.P. = 0.1). Morphine is also used as an antidiarrhoeal and as a sedative. Because of the unfortunate side effects of morphine and its allies, which include respiratory depression, nausea, low blood pressure and addictive properties, scientists have been looking for pure analgesic agents for many years. Numerous analogues and derivatives of morphine have been examined.

An alternative method has been to synthesize molecules having some of the structural features of morphine (**1**) which are believed to represent the active sections of the molecule. One such compound prepared in the late 1930s is pethidine (**6**) which is used even today for the management of mild to moderate pain.[4] Though it is less potent than morphine its relatively low toxicity level and low dependence liability make it more attractive.



(6) (6)

Methadone (7) is almost identical in pharmacological properties to morphine.[5] In 1955, further simplified morphines, exemplified by the benzomorphans such as (8) and (9) were discovered. They have lower analgesic activities than morphine, but are essentially non-addictive.



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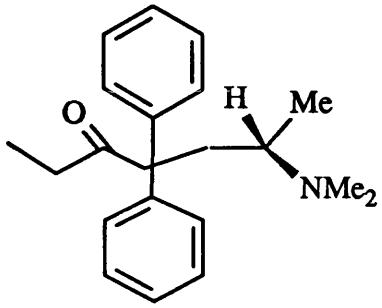

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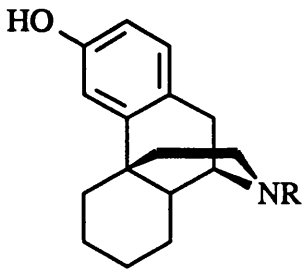

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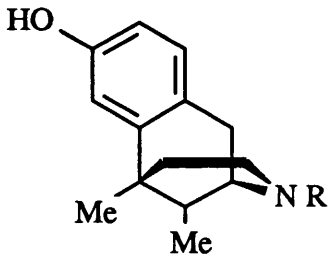
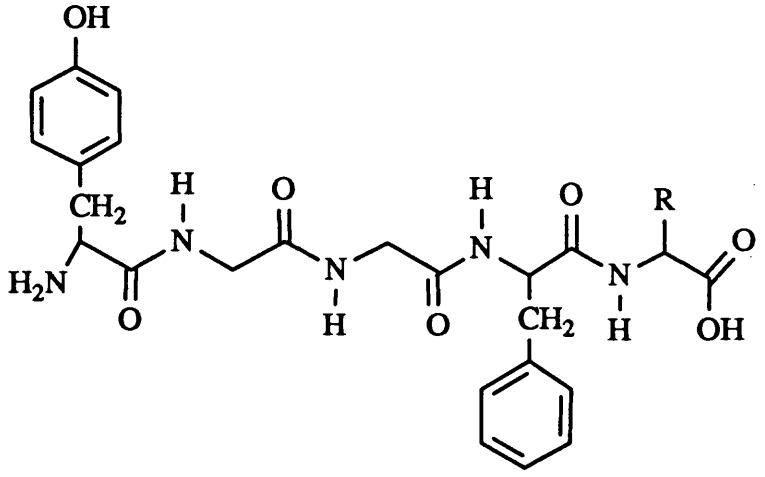


(9)

Thus for a few years the trend was to snip away at the morphine structure in an attempt to achieve more selective action. The more the simplification process goes, the greater flexibility is introduced and in the 1960's and 1970's, Bentley considered that more rigidity and complexity might be important. Since then considerable research has been directed towards the making of rigid molecules.

Recently a group of peptides has been isolated from brain tissue which act as agonists at opioid receptor sites. They are collectively known as 'enkephalins'.[6] One of these peptides, methionine-enkephalin (met-enkephalin), **(10)** has the sequence H-tyr-gly-gly-phe-met-OH; another leucine-enkephalin **(11)** has the same first four aminoacids, but is terminated with leucine in place of methionine. It has been shown that enkephalins have analgesic potency similar to that of morphine.[7]



(10), R = $CH_2CH_2SCH_3$

(11), R = $CH_2CH(CH_3)_2$

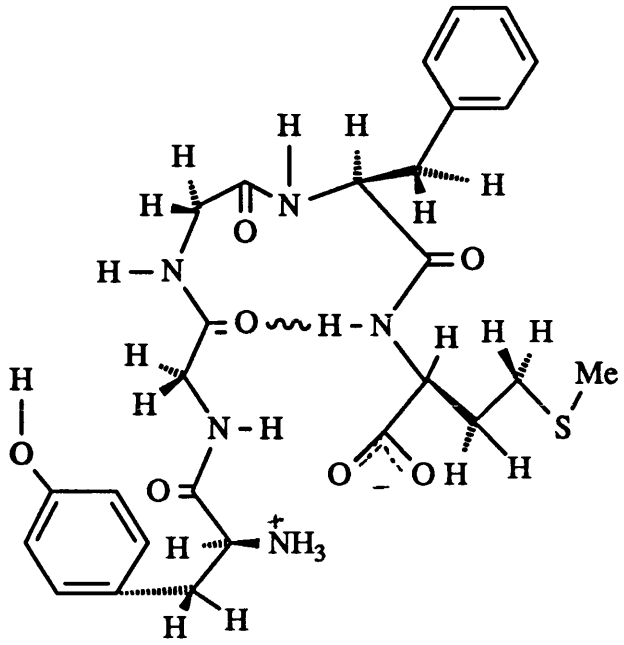


Fig. 1

Diagrammatic representation of one conformation of met.-enkephalin.[8]

The enkephalins and their allies are the natural opiates, it is a coincidence that the morphine molecule has a similar shape as the bio-active conformation of these pentapeptides. This recognition has allowed much computer modelling experiments to be performed, especially within the pharmaceutical companies, in the hope of synthesising stable mimics of the enkephalins which are locked into the appropriate geometry.

Not surprisingly, other analgesically active molecules contain rigid molecular assemblies incorporating some common structural features to morphine. Thus all contain a quaternary carbon atom attached to a benzene ring and a tertiary nitrogen atom situated two carbons away from the quaternary carbon atom (Fig. 2). The other groups may be aromatic or alicyclic rings. The various substituents of the quaternary carbon atom should be bulky to prevent free rotation of the rings.[9]

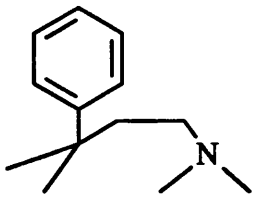


Fig. 2

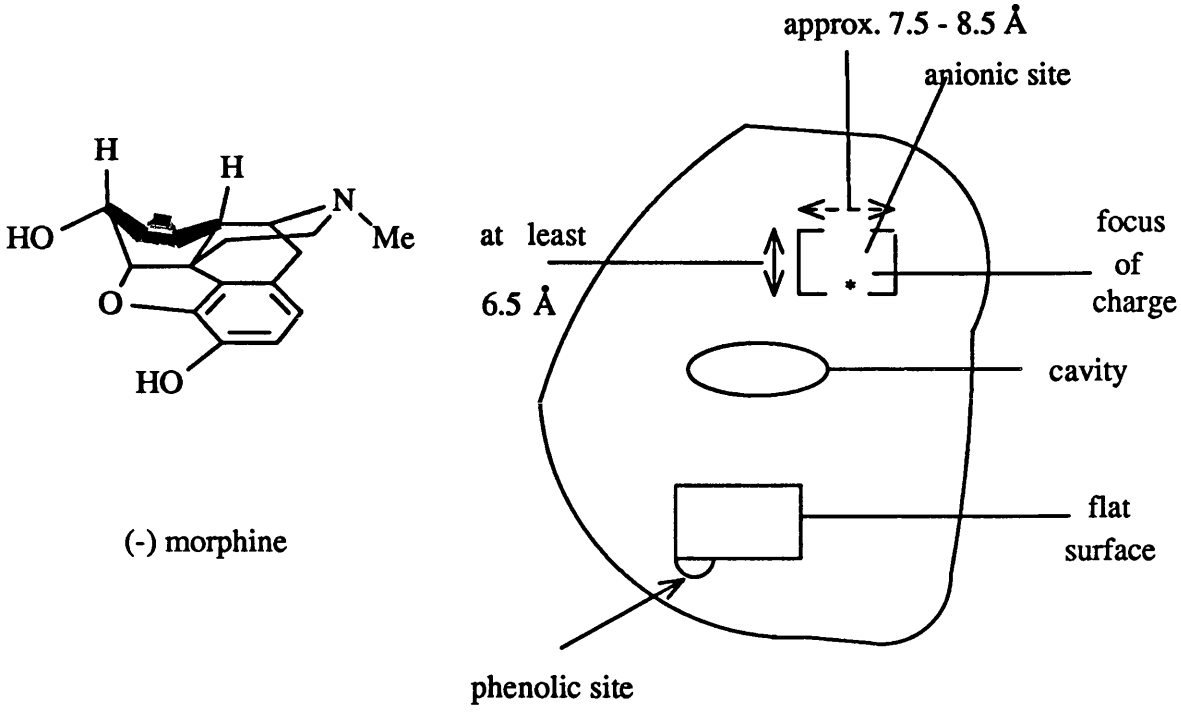
These requirements for analgesic activity[10] of various morphines were recognised some years ago and by a consideration of various morphines and methadone derivatives, Beckett and Casy[11] proposed that the principal features of the analgesic receptor sites are:

(1) a flat surface which allows binding of benzene ring of the analgesic drug through Van der Waals forces.

(2) a cavity to accommodate the projecting portion of the piperidine ring (C-15 and C-16) of morphine.

(3) an anionic site that can form an ionic bond with the cationic nitrogen atom (Fig.3).

Though this model adequately accommodates morphine and the morphinan-benzomorphan groups of analgesics, modification of the above model of receptor site and introduction of new types of receptor sites or subsites are necessary to explain the analgesic action of a large number of compounds, especially those in which the *N*-substituent can be varied, 14-substituted molecules, peptide analgesics etc. Today evidence from behavioural, pharmacological and biochemical studies indicates the existence of at least four receptor classes designated by μ, δ, κ, and σ. The pharmacological actions of opiates, as well as those of the three major classes of opioid peptides (β-endorphin, the enkephalins and dynorphin related peptides),



Receptor site

Fig. 3

are now thought to occur by an interaction with a combination of these sites.

Portoghese[12] suggested that regardless of the binding mode all analgesics are involved in ionic bonding with an identical anionic site that may be envisaged as a pivotal point around which various modes of binding may occur. A model in which sub-sites designated to recognise aromatic portion of the drug molecule was given later.[13]

2.3 Extraction

For many years opium was processed mainly for morphine by the 'Gregory process'[14,15] in which a concentrated aqueous opium extract is treated with concentrated calcium chloride solution. This treatment causes the precipitation of a 'marc' consisting of non-alkaloidal material, together with calcium meconate, sulphate and lactate. The filtrate on concentration and crystallisation gives 'Gregory salt' which is a mixture of morphine and codeine hydrochlorides. From a solution of the salt in water addition of ammonia precipitates morphine.

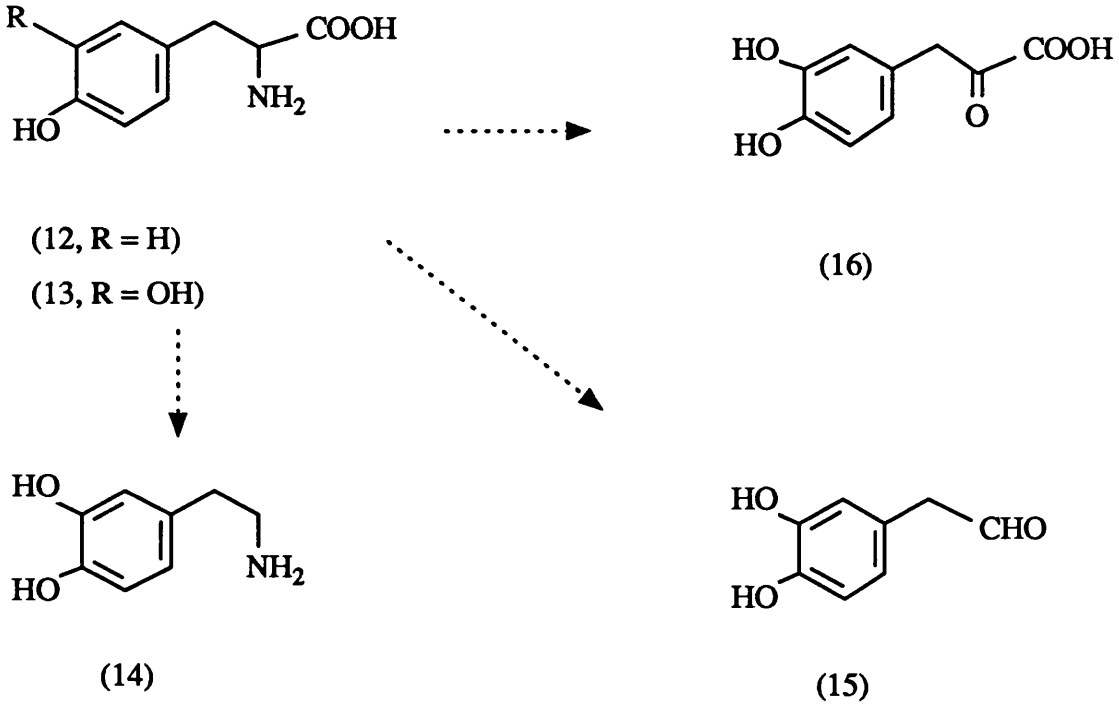
More modern methods isolate not only morphine, but the lesser alkaloids such as codeine, thebaine, noscapine and papaverine. The principles of extraction are based on the relative solubilities of these alkaloids in solutions of different pH values. Morphine which has both acidic and basic properties, remains in solution, at pH values below 6 and above 12. So opium dissolved in organic solvent, after treatment to remove most of the non-opiate materials, is brought to pH 12 with caustic soda and partitioned between aqueous phase and organic phases. Morphine dissolves in the aqueous phase as a phenate salt while the other alkaloids remain in the organic phase as bases. Morphine is recovered from the aqueous phase. The organic phase is extracted with a solution of sulphuric acid at pH 2 and then the pH of this solution is raised to 6 with caustic soda. Noscapine and papaverine, being weak bases are precipitated almost completely between pH 2-6. The filtrate, after basifying to pH 10, is re-extracted with a suitable solvent to yield a mixture of thebaine and codeine, from which thebaine can be separated as insoluble thebaine tartrate, leaving soluble codeine acid tartrate in solution.

MacFarlan Smith Ltd of Edinburgh is the major company in the U.K. which produces opiates from opium. The company isolates morphine, codeine, thebaine, noscapine and papaverine from opium, while the minor alkaloids, as well as the

unrecovered major alkaloids, remain in the side streams during the extraction process. One of the aims of the company is to identify the minor alkaloids in the effluent streams and to find ways of recovering these alkaloids economically. Concentrated or evaporated samples of some of these effluents were given to us for isolation and identification.

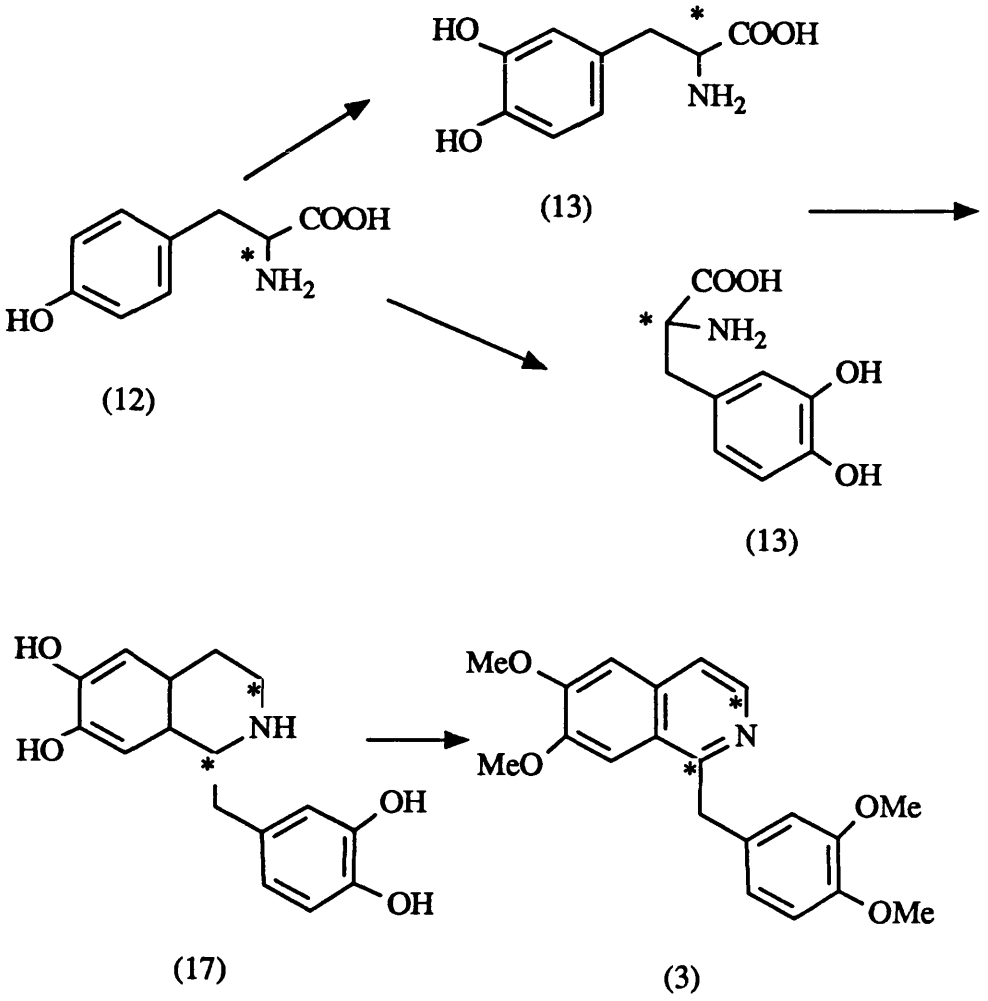
2.4 Biosynthesis

Morphine (**1**), codeine (**4**) and thebaine (**5**) are derived biogenetically from a suitable 1-benzylisoquinoline derivative.[16,17] Tracer experiments have confirmed the general hypothesis of Winterstein and Trier[18] that these alkaloids are formed by a Mannich reaction between 3,4-dihydroxyphenylethylamine (dopamine, **14**) and 3,4-dihydroxyphenylacetaldehyde (**15**) both of which are metabolites of tyrosine (**12**). Since there was doubt about the involvement of 3,4-dihydroxyphenyl-acetaldehyde, Leete suggested that the second compound involved in the initial Mannich reaction was 3,4-dihydroxyphenylpyruvic acid (**16**) which is readily formed in plants from dihydroxyphenylalanine (**13**).[19,20]



Scheme 1

It was shown by Battersby[21,22] that administration of labelled tyrosine-2-^{14}C (**12**) to *P.somniferum* yielded papaverine (**3**) labelled at the C-1 and C-3 positions.

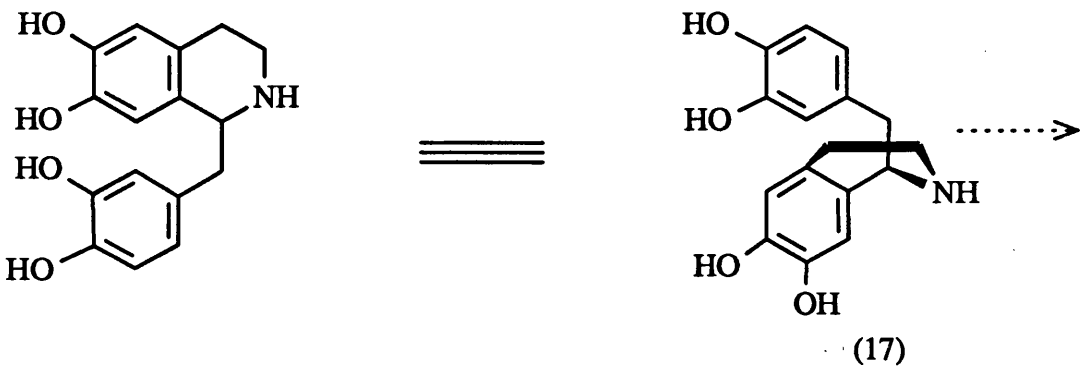


Scheme 2

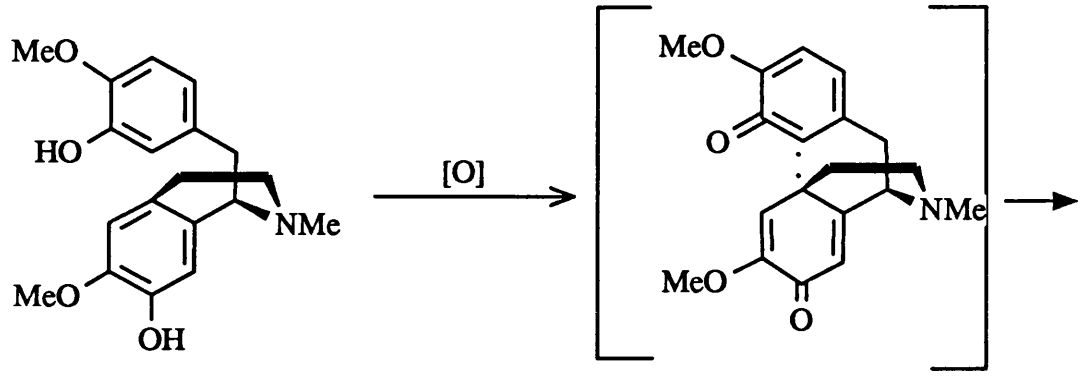
This is in agreement with other experiments[29] which prove that the C_{16} carbon skeleton of papaverine (and morphine) is synthesized in nature from two C_6-C_2 units. It was the recognition that morphine (**1**) might be related biogenetically

to the 1-benzylisoquinoline alkaloids which led Gulland and Robinson,[23,24] many years ago, to propose the correct structure for morphine. The stereochemistry of the alkaloid was confirmed by X-ray analysis techniques by Mackay and Hodgkin.[25] Robinson[26,27] also proposed that the hydrophenanthrene ring (between C-12 and C-13 atoms) in the morphines was formed in the plant by the phenolic oxidative coupling of a 1-benzylisoquinoline precursor (as in **17**). This suggestion was amplified by Barton and Cohen[17,28] who argued that the 1-benzylisoquinoline base (**18**) undergoes electron abstraction to form a radical which on intramolecular coupling yields the dienone (**19**).

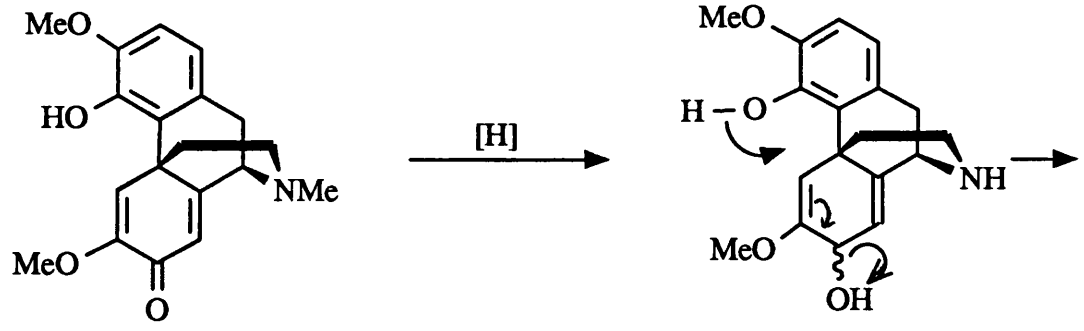
This hypothesis has been confirmed by radio isotopic labelling experiments[29,30] which show that norlaudanosoline (**17**) and its methyl analogue, reticuline (**18**) are precursors of thebaine in poppy plants. Furthermore, reticuline (**18**) undergoes *o*-, *p*- coupling to produce salutaridine (**19**) and salutaridinol (**20**)[31-33] indicating possible steps *en route* to morphine itself.[34,35] (Scheme 3)



(17)

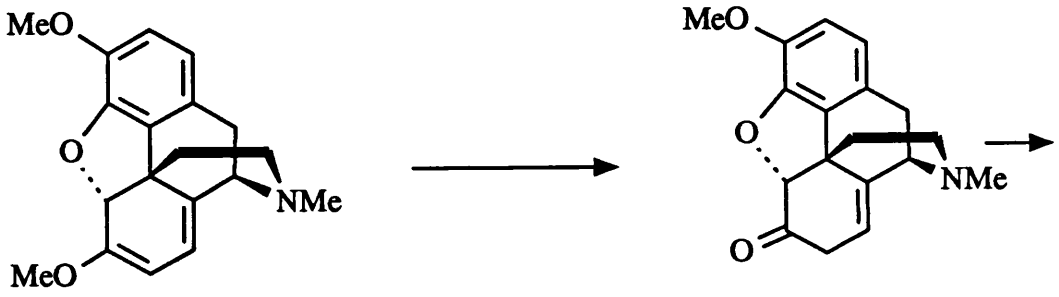


(R) - Reticuline (18)

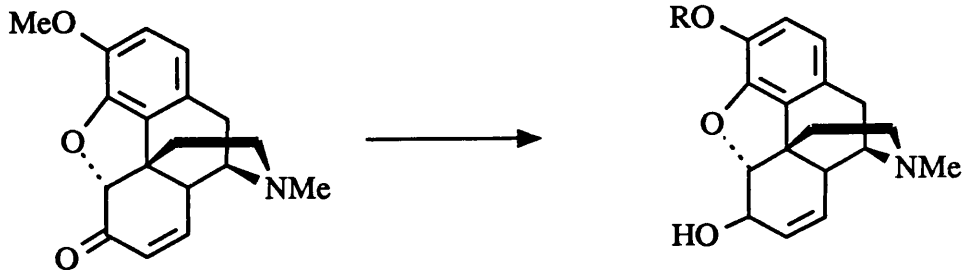


Salutaridine (19)

(20)



(5)



(4), R = Me, codeine

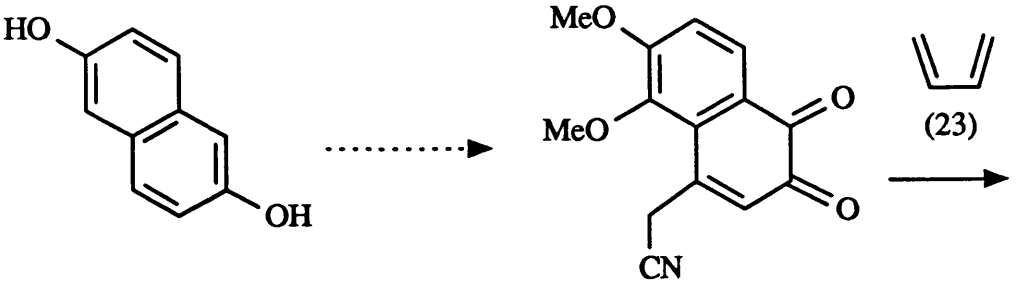
(1), R = H, morphine

Scheme - 3

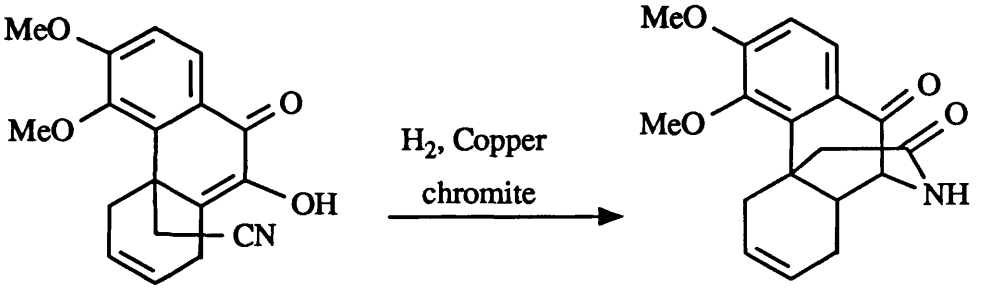
2.5 Synthesis of Morphine

The first complete synthesis of (-) morphine was achieved by Gates and Tschudi[36,37] in 1952 and modified by Elad and Ginsburg[38,39] in 1954.

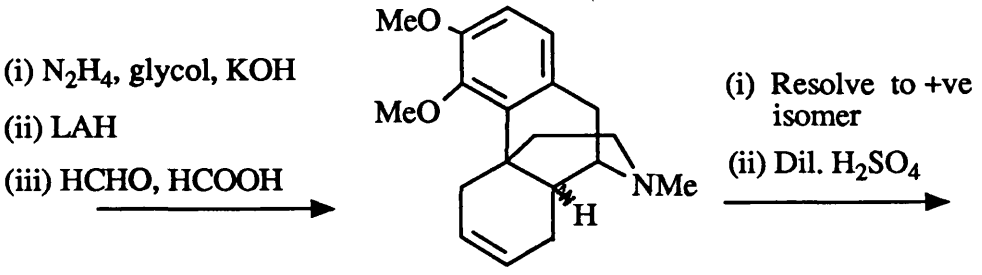
By the selective introduction of various groups into 2,6-dihydroxy-naphthalene (**21**). Gates prepared a suitably substituted 4-cyanomethyl--1,2-naphthoquinone (**22**). This dienophile undergoes Dields-Alder addition with butadiene (**23**) to form the partially saturated phenanthrene (**24**). On catalytic hydrogenation in the presence of copper chromite catalyst, this compound undergoes ring closure to the lactam (**25**). The carbonyl group of (**25**) is removed by Wolff-Kishner reduction and the amide carbonyl group by lithium aluminium hydride reduction. These steps are followed by *N*-methylation with formaldehyde - formic acid to give the racemic compound (**26**). This compound after resolving into the positive enantiomer is hydrated with dilute sulphuric acid to give the 6-hydroxy compound (**27**) which is converted to the compound (**28**) by selective O-demethylation and then by oxidation with the potassium *tert*-butoxide-benzophenone system. Tribromination of the compound (**28**) followed by treatment with 2,4-dinitrophenylhydrazine (DNPH) produces 1-bromocodeinone-2,4-phenyl-hydrazone from which 1-bromocodeinone (**29**) is obtained by treatment with acetone and hydrochloric acid. During dehydrobromination and the formation of α,β-unsaturated ketone, inversion occurs at C-14 giving the natural stereochemistry. 1-Bromocodeinone (**29**) is then reduced directly to codeine (**4**) by lithium aluminium hydride and demethylation of codeine with pyridine hydrochloride gives morphine (**1**). (Scheme 4)



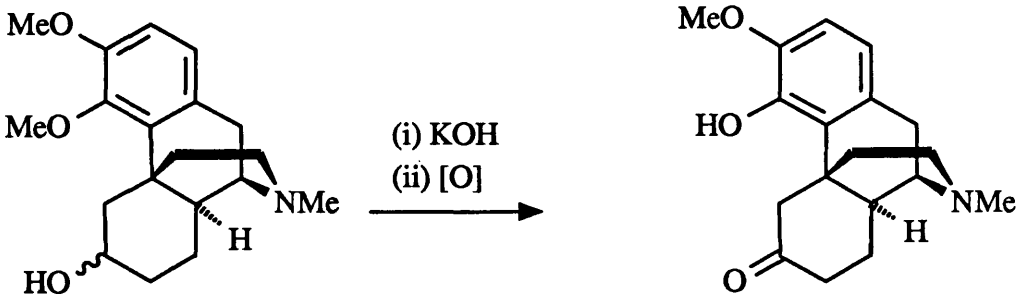
(21) (22)



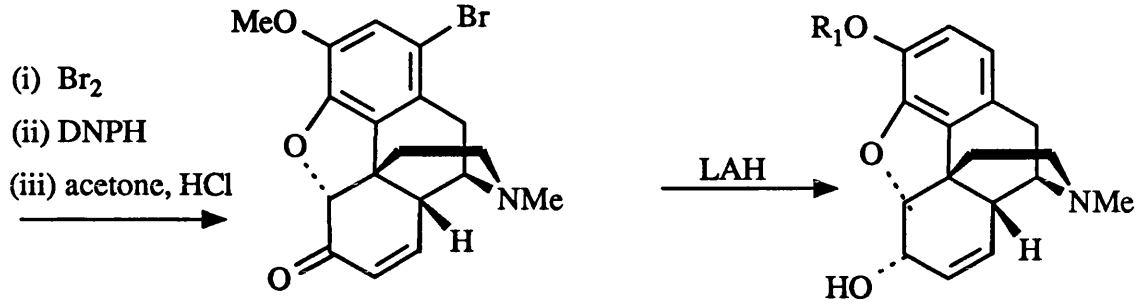
(24) (25)



(26)



(27) (28)



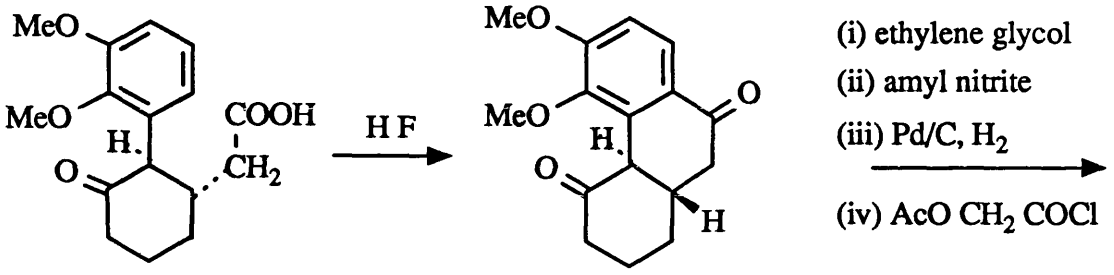
(29)

(4), R = Me

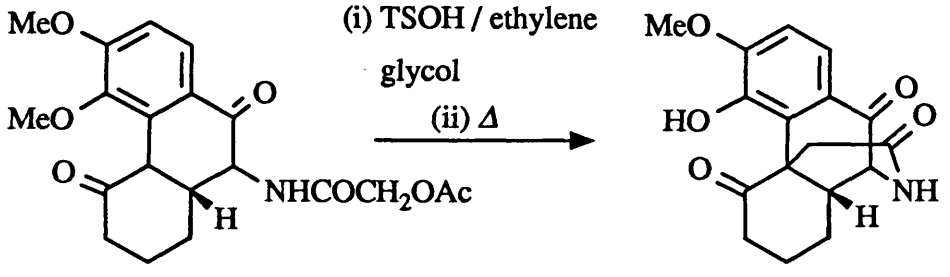
(1), R = H

Scheme - 4

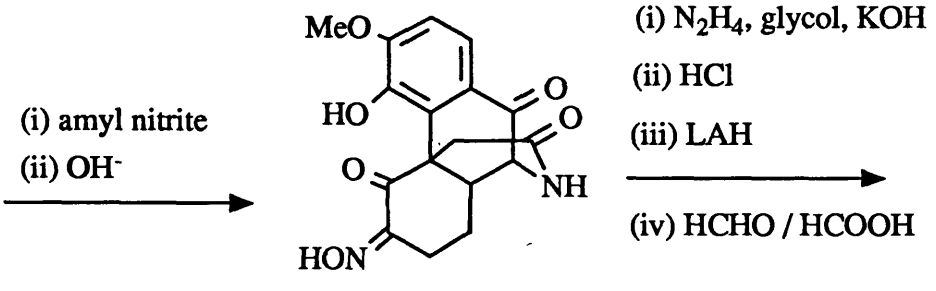
The Elad and Ginsburg approach began with the arylcyclohexanone (**31**) which with anhydrous hydrogen fluoride cyclicised to the diketone (**32**) (Scheme 5). The ketonic group in the C-ring of (**32**) was protected with ethylene glycol in the presence of *p*-toluenesulphonic acid and treatment of the monoketal with amyl nitrite in the presence of sodium ethoxide introduces oxime group at C-9 position. This on reduction and treatment with acetylglycolyl chloride (CH_3COOCH_2COCl) formed the amide (**33**). Ketalization of (**33**) with ethylene glycol and *p*-toluene sulphonic acid effected cyclization as well as 4-O-demethylation to form the compound (**34**) which was then converted to codeine (**4**) following the final stages of scheme 4.


MeO
MeO
H.
O
COOH
CH2
HF
MeO
MeO
H.
O
O
H
(i) ethylene glycol
(ii) amyl nitrite
(iii) Pd/C, H2
(iv) AcO CH2 COCl

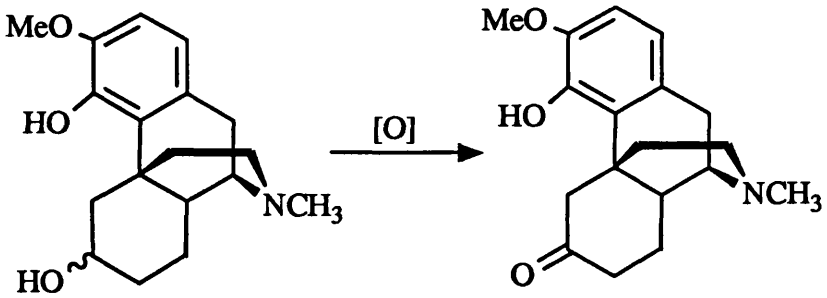
(31) (32)


MeO
MeO
O
O
NHCOCH2OAc
H
(i) TSOH / ethylene glycol
(ii) Δ
MeO
HO
O
O
O
NH
H

(33) (34)

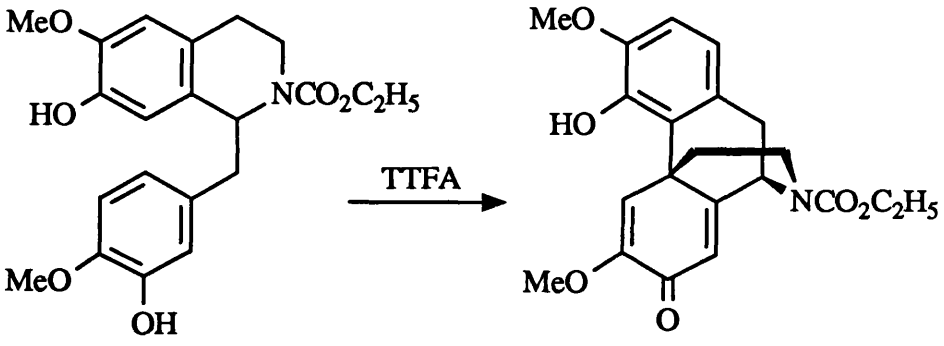

(i) amyl nitrite
(ii) OH-
MeO
HO
O
O
O
NH
HON
(i) N2H4, glycol, KOH
(ii) HCl
(iii) LAH
(iv) HCHO / HCOOH

(35)

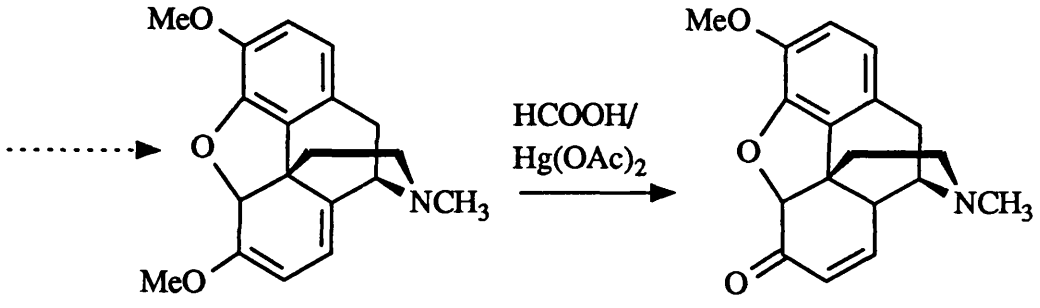


(36) (37)

Scheme - 5



(38) (39)

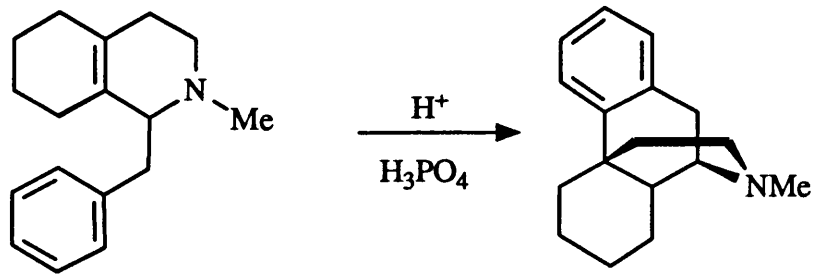


(5) (40)

Scheme 6

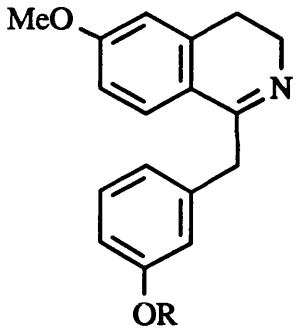
Efforts to obtain morphine by direct biomimetic routes are not successful although the supposed intermediate, salutaridine (**19**) has been prepared from reticuline (**18**) in 0.03% yield by a manganese dioxide oxidation reaction.[40] However, Schwartz and Mamy[41] have succeeded recently in oxidising the urethane (**38**) with thallium tristrifluoroacetate to afford a salutaridine derivative (**39**) in 23% yield, and this compound has been converted to thebaine (**5**).[42] (Scheme 6) Thebaine can be converted to codeinone[43] (**40**), which in turn can be converted to codeine[44] (**4**) and then to morphine[92] (**1**).

The morphine - morphinan skeleton can be formed from properly substituted benzyloctahydroisoquinoline by Grewe cyclization.[45] (Scheme 7a)



Scheme 7a

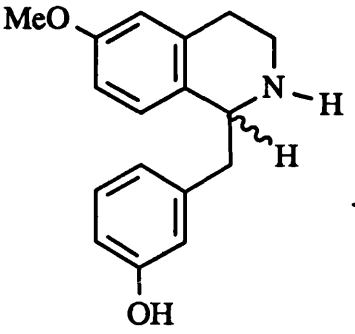
Schmidhammer and Brossi[46] prepared 6-oxo-N-methylmorphinan (**51**) from an appropriately substituted 1-benzylhexahydroisoquinoline using a Grewe cyclization as the key step. They first prepared the 3,4-dihydroisoquinoline (**41**),which was O-demethylated with 48% hydrogen bromide to give the corresponding hydroxy derivative (**42**). Reduction of (**42**) with sodium borohydride afforded the tetrahydroisoquinoline (**43**) and, after resolution of the enantiomers with tartaric acid, the compound (**43**) was converted to (**44**) by Birch reduction. This



(41), R = CH_3

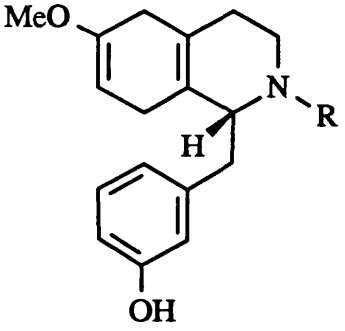
(42), R = H

$NaBH_4$



(43)

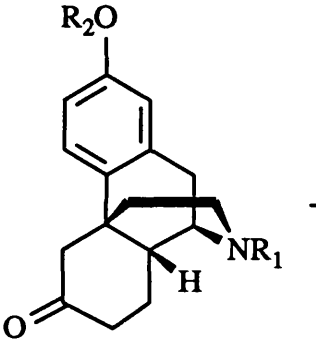
(i) Resolution
(ii) Birch Reduction



(44) R = H

(45) R = CHO

H_2SO_4



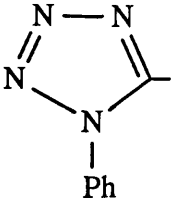
(46), R_1 = CHO, R_2 = H

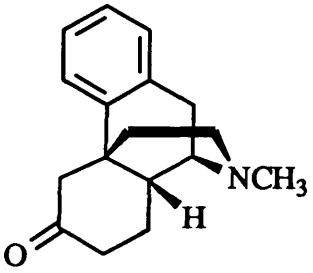
(47), R_1 = R_2 = H

(48), R_1 = CH_3, R_2 = H

(49), R_1 = R_2 = CH_3

(50), R_1 = CH_3, R_2 =



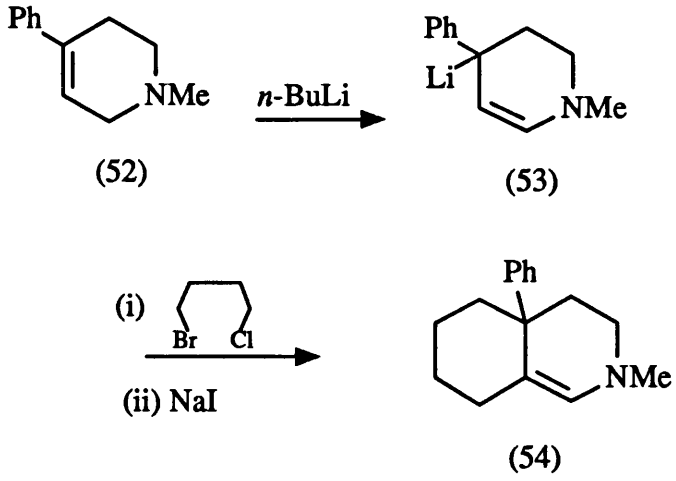


(51)

Scheme 7b

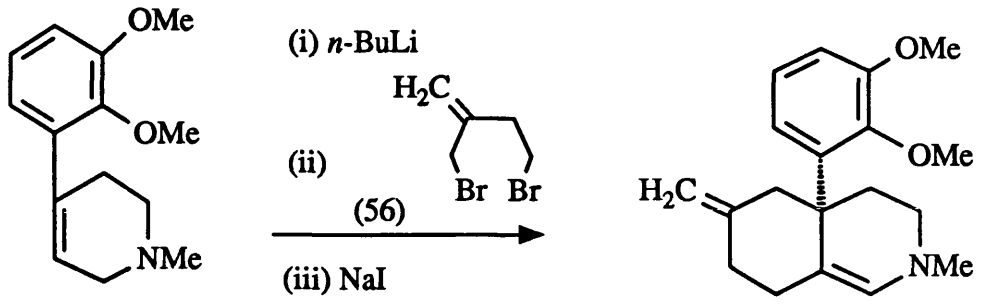
was N-formylated with ethyl formate to form the amide (**45**). Cyclisation of (**45**) proceeded smoothly in 80% sulphuric acid solution at 25°C and afforded N-formyl-2-hydroxymorphinan-6-one (**46**). Acid hydrolysis of (**46**) gave (**47**) which was converted into (**48**) by reductive N-methylation and into the O-methyl ether (**49**) by reaction with phenyltrimethyl ammonium chloride in DMF. A reaction of (**48**) with 5-chloro-1-phenyl-1H-tetrazole afforded the ether (**50**) which on catalytic hydrogenation with Pd/C gave the morphinan (**51**). (Scheme 7b)

Evans and Mitch[47] reported a different approach for the preparation of morphine - related alkaloids. They found that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (**52**) when treated with *n*-butylithium formed the intermediate metalated enamine (**53**) which on reaction with 1-chloro-4-bromobutane formed a 4,4-disubstituted tetrahydropyridine which can be cyclicised to (**54**) (Scheme 8).

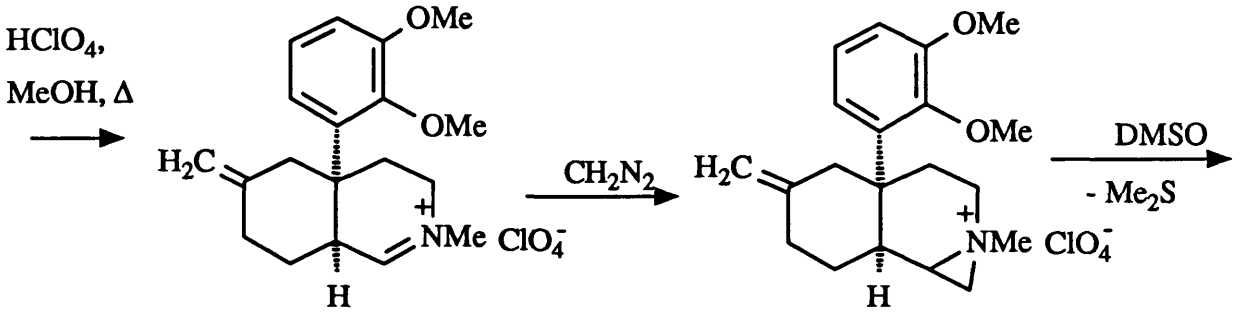


Scheme 8

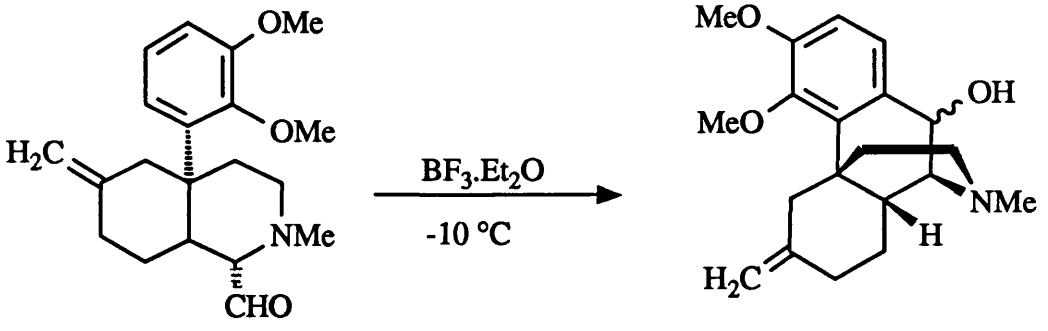
In the studies which followed Evans and Mitch[48] used the tetrahydropyridine (**55**) in conjunction with the dibromide (**56**) (Scheme 9) to afford the bicyclic enamine (**57**).



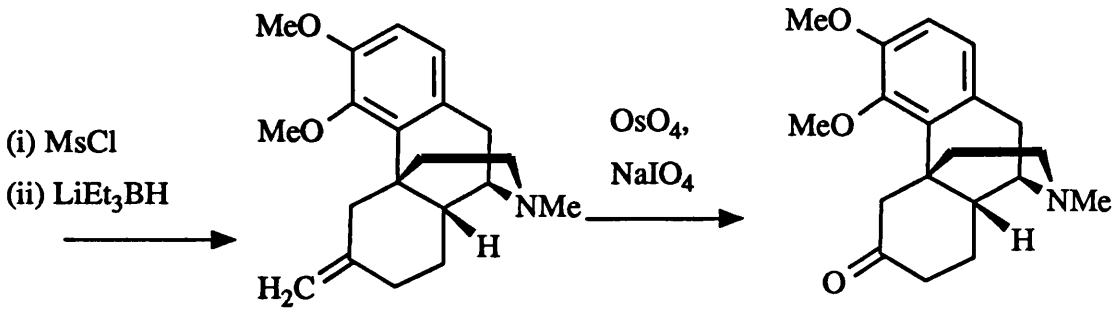
(55) (57)



(58) (59)



(60) (61)



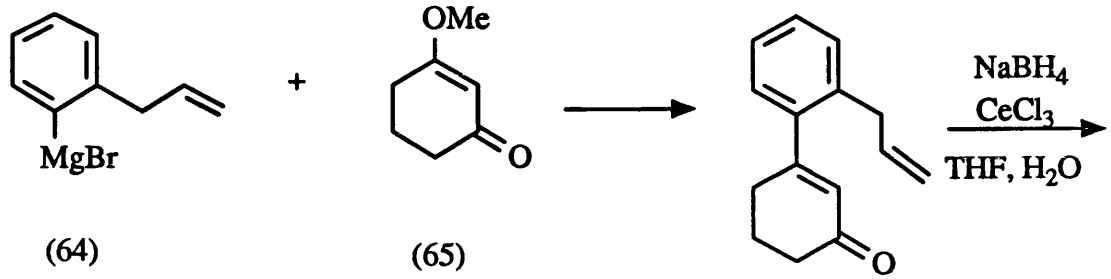
(62) (63)

Scheme 9

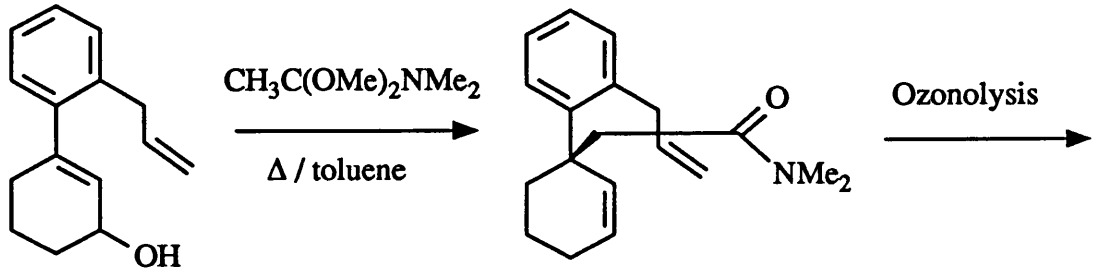
The perchlorate of (**57**) on dissolution in methanol and heating gave the thermodynamically preferred *cis*-isomer (**58**) which with diazomethane afforded the aziridium salt (**59**). This in turn gave the α-aminoaldehyde (**60**) and conversion of (**60**) into the morphinan carbinol (**61**) was effected by Lewis acid catalysed cyclization. Methylsulphonation of (**61**), followed by reduction of the mesylate with $LiBEt_3N$ afforded the morphinan (**62**) which could be oxidized to (**63**) by Lemieux-Johnson oxidation with osmium tetroxide and sodium periodate under acid conditions.

A modern synthesis of the morphinan system has been devised by Chandler and Parsons.[49] They have shown that *o*-allylphenyl magnesium bromide (**64**) adds smoothly to 3-methoxycyclohex-2-enone (**65**) to give the cyclohexenone (**66**). Reduction of (**66**) with $NaBH_4$ and $CeCl_3$, followed by treatment with dimethylacetamide dimethylacetal gave the amide (**68**). Ozonolysis of (**68**) produced the aldehyde (**69**) which on treatment with N-methyl hydroxylamine gave the adduct (**70**). Hydrogenation of (**70**) in acetic acid using Raney nickel catalyst, followed by basification yielded the amine (**71**). Treatment of the amine with hydrogen chloride gas gave a crystalline salt which on fusion furnished the morphinan (**72**). Reduction

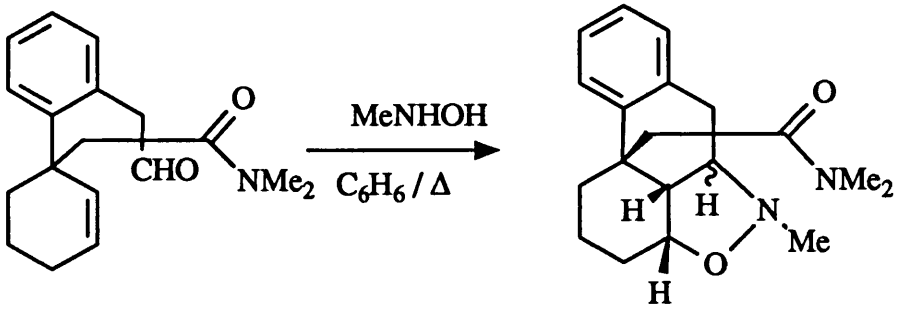
then formed the morphinan (**73**). (Scheme 10)



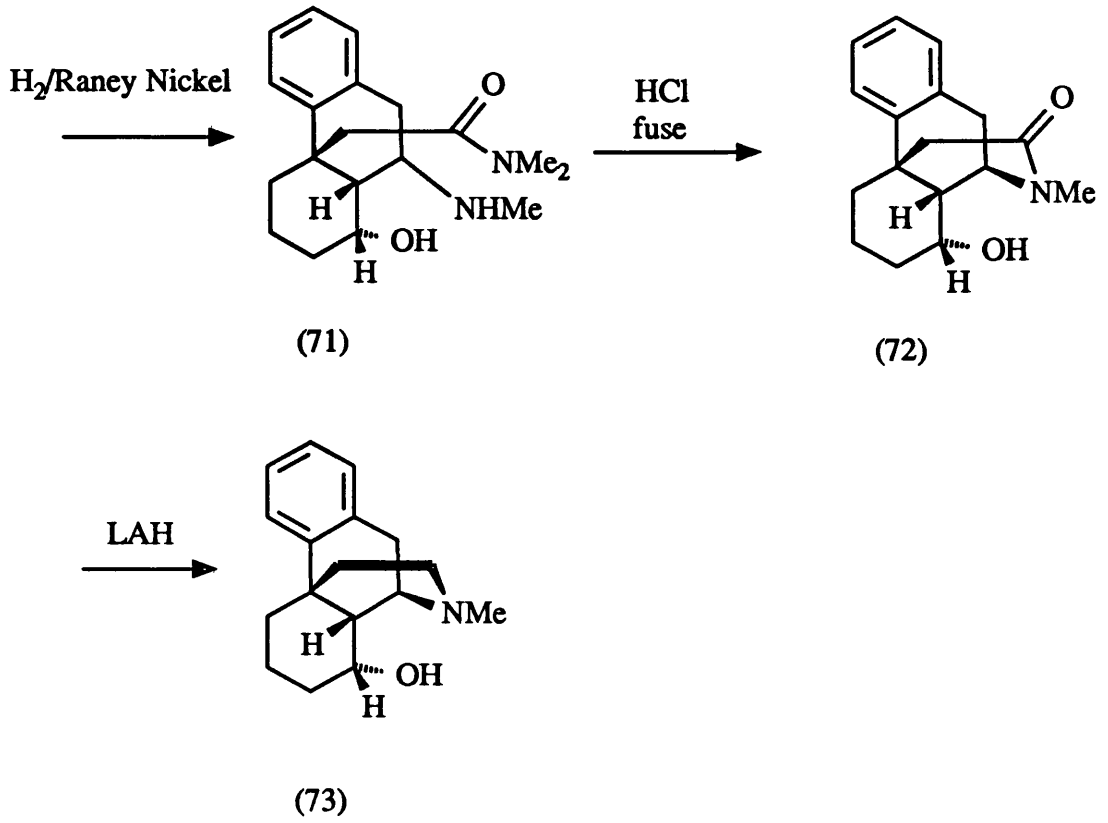
(64) (65) (66)



(67) (68)



(69) (70)

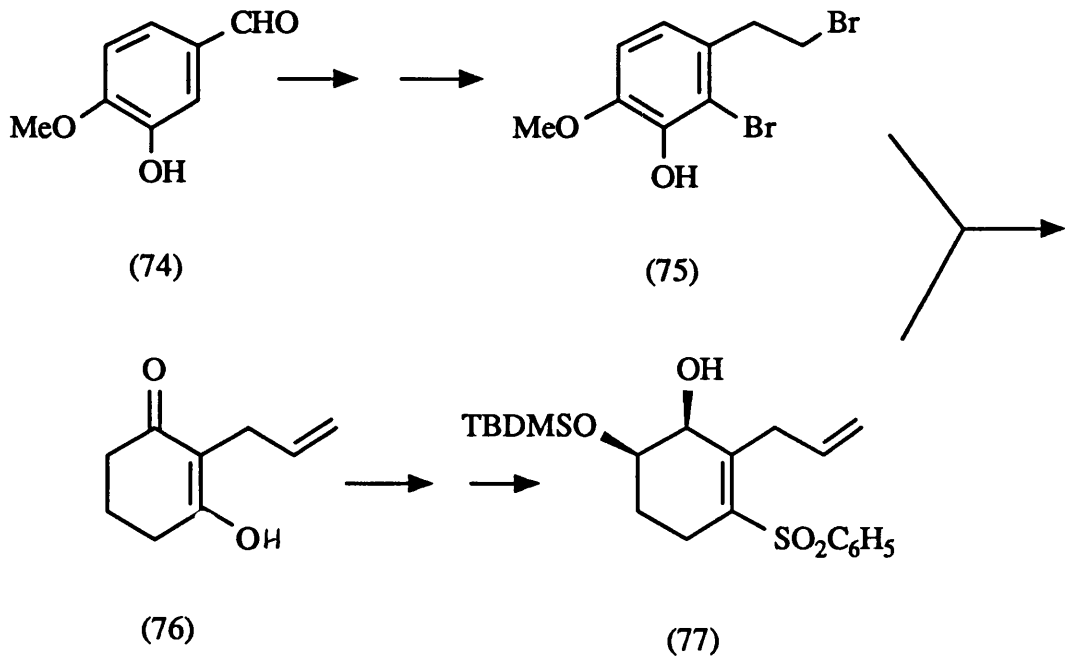


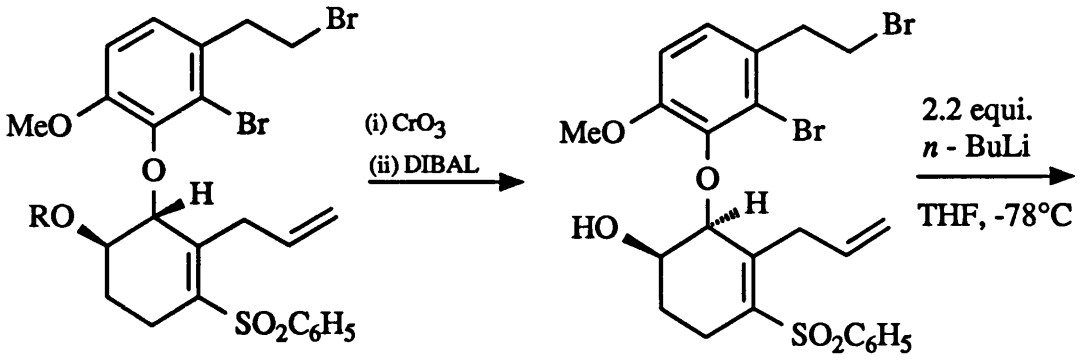
(71) (72) (73)

Scheme 10

In 1987 Toth and Fuchs[50] prepared racemic morphine from 2-allylcyclohexene-1,3-dione and isovanillin in 1.1% overall yield. Isovanillin (**74**) was converted to the dibromophenol (**75**) and 2-allylcyclohexene-1,3,-dione (**76**) was transformed into the alcohol (**77**). Mitsunobu coupling of the phenol (**75**) with the alcohol (**77**) gave the *trans*-silyloxy-aryl ether (**78**) which was desilylated to (**79**) and converted to its epimeric alcohol (**80**). Treatment of the alcohol (**80**) with *n*-butyllithium in THF, followed by quenching with ammonium chloride solution gave tetracyclic sulphone (**81**). Catalytic osmylation, followed by lead tetraacetate cleavage of the resultant diol afforded the aldehyde (**82**). Reaction of (**82**) with methylamine hydrochloride and sodium cyanoborohydride in methanol, and acylation of the resultant secondary amine with (trimethylsilyl)-ethoxychloroformate

(TEOC-Cl) provided the urethane (**83**). Swern oxidation of the alcohol, and next treatment of the resulting ketone with trimethylorthoformate in acidic methanol afforded the enol ether (**84**), which with potassium *tert*-butoxide in THF produced the dienyl ether (**85**). Oxidation of (**85**) provided the racemic dienone (**86**). Reaction of (**86**) with trifluoroacetic acid gave the dienone-ammonium salt (**87**) which upon neutralization spontaneously underwent an intramolecular 1,6-Michael addition to the dienone. The resulting mixture of codeinone (**88**) and neopinone (**89**) was isomerized to codeinone (**88**). Sodium borohydride reduction of racemic codeinone gave racemic codeine (**4**) which on *O*-demethylation gave racemic morphine (**1**). (Scheme 11)

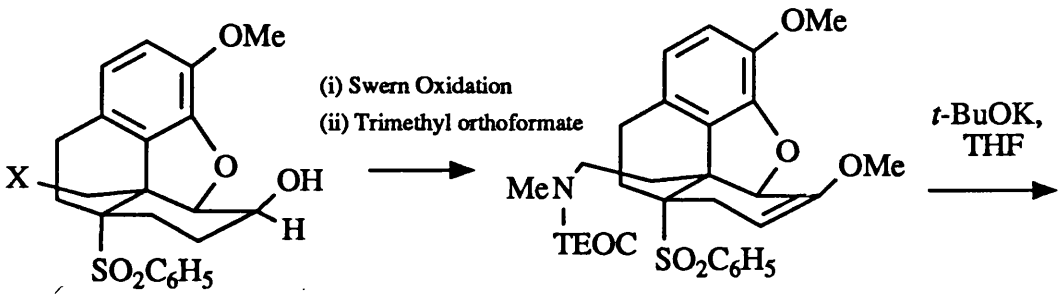




(78) R = TBDMS

(79) R = H

(80)

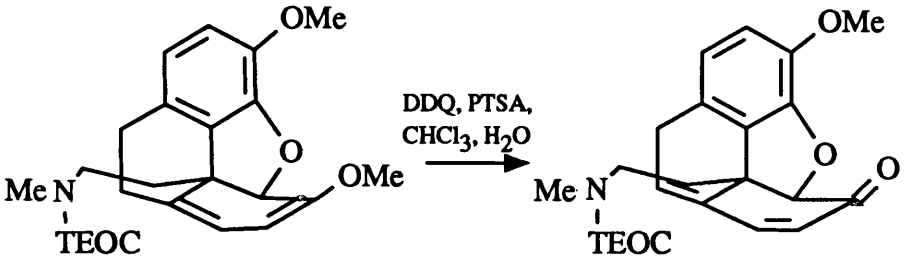


(81), X = $CH{=}CH_2$

(82), X = CHO

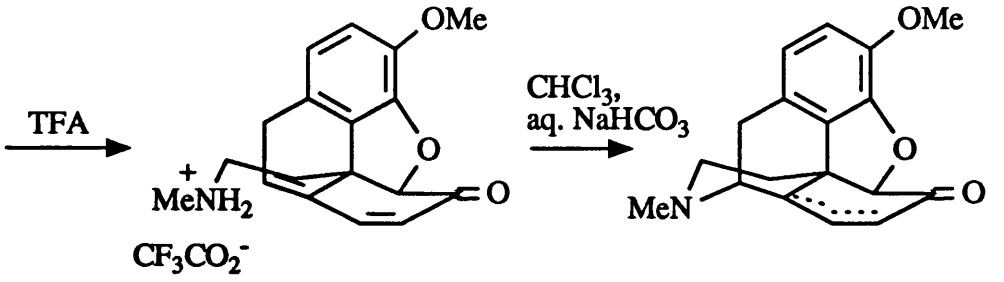
(83), X = $CH_2N(CH_3)CO_2CH_2CH_2TMS$

(84)



(85)

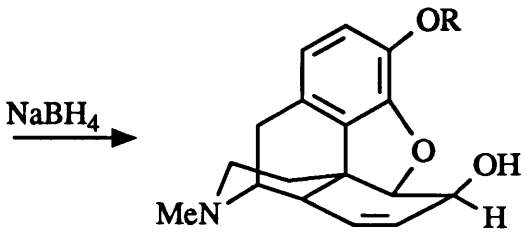
(86)



(87)

(88), Δ^7 Codeinone

(89), Δ^8 Neopinone



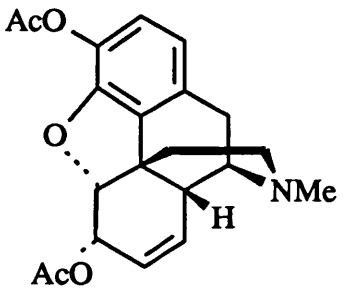
(4) R = Me

(1) R = H

Scheme 11

2.6 Analogues and derivatives of morphine

Despite the valuable analgesic effect of morphine its medical applications are restricted *inter alia* by its addictiveness, which results from its euphoric action, and its respiratory depressing properties. This has stimulated a continuing search for effective and non-addictive replacements. By 1929 there were 150 derivatives and over 300 analogues available. One of the earliest attempts to suppress its undesirable effects was acetylation. Thus 3,6-diacetylmorphine (heroin, **90**, RP = 2.5), which is superior to morphine (RP = 1) as an analgesic and which was thought initially to be non-addictive, was soon found to have a high physical dependence.

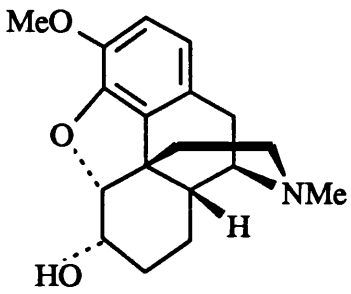


(90)

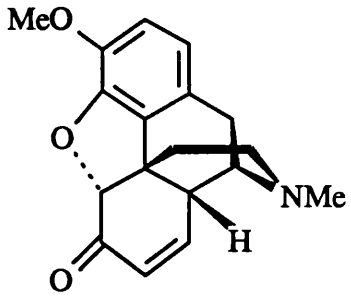
Codeine is used extensively in various applications that require an orally effective, relatively low potency central analgesic (RP = 0.1). It is an effective antitussive as well. Since codeine occurs in opium in relatively small amounts, it is generally prepared commercially by methylation of the more abundant morphine, using methylating agents like dimethyl sulphate, diazomethane and phenyltrimethyl ammonium chloride.

Reduction of the double bond in codeine leads to dihydrocodeine (paracodin,

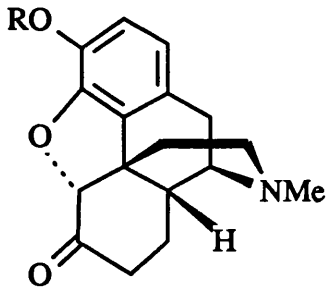
91), a compound that has found some use as an antitussive agent and it is also an analgesic (RP = 0.1). Codeine can easily be converted to dihydrocodeinone (hydrocodone, **92**) by oxidation of codeine (**4**) to codeinone (**40**), followed by catalytic hydrogenation. Hydrocodone (**92**) and its morphine analogue, hydromorphone (**93**) are potential analgesics (RP = 3-4), but fail as drugs because of their relatively higher addiction liability.



(91)



(40)

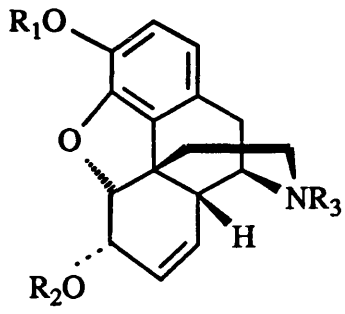


(92), R = Me, Hydrocodone

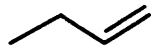
(93), R = H, Hydromorphone

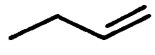
Another modification has been the introduction of small groups at the nitrogen atom of normorphine (**94**).[51] Normorphine itself is found to have a higher analgesic effect than morphine. Substituents like propyl, pentyl, hexyl and

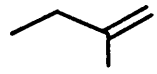
phenylethyl on the nitrogen atom of normorphine give rise to analgesics with higher potency.[52,53] N-Allylnormorphine[54] (nalorphine, **95**) and N-allylnorcodeine[55] (**96**) were found to have powerful morphine antagonist activity and subsequently used clinically in a variety of applications including diagnosis of addiction.

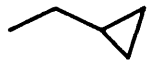


(94), R1 = R2 = R3 = H

(95), R1 = R2 = H, R3 = 

(96), R1 = Me, R2 = H, R3 = 

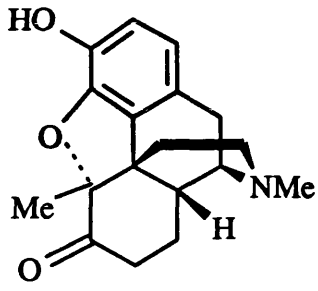
(97), R1 = R2 = H, R3 = 

(98), R1 = R2 = H, R3 = 

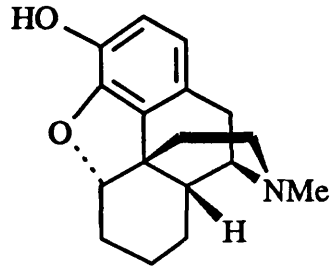
N-(2-Methylallyl) normorphine (**97**) is a more potent antagonist than nalorphine and N-cyclopropylmethyl normorphine[56] (**98**) is about three times as powerful as nalorphine as an antagonist and three times as potent as morphine as an analgesic.

Metopon[57] (5-methyldihydromorphinone, **99**) is another compound of pharmacological interest. It is orally active and it is about three times as active as morphine in relief of severe pain, but usage is restricted because of the expense of manufacture. Some potent analgesics which have 6-substitution are desomorphine (dihydrodesoxymorphine, **100**, RP = 10)[58], 6-methyldihydrodeoxycodeine (**101**)[59,60]

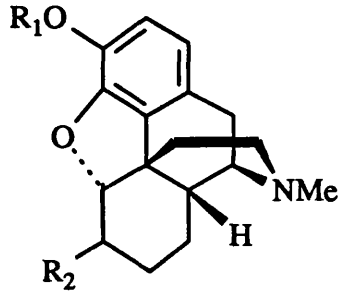
and 6-deoxy-6-azidodihydroisomorphine[61] (**102**), both of which are 25-50 times as active as morphine.



(99)

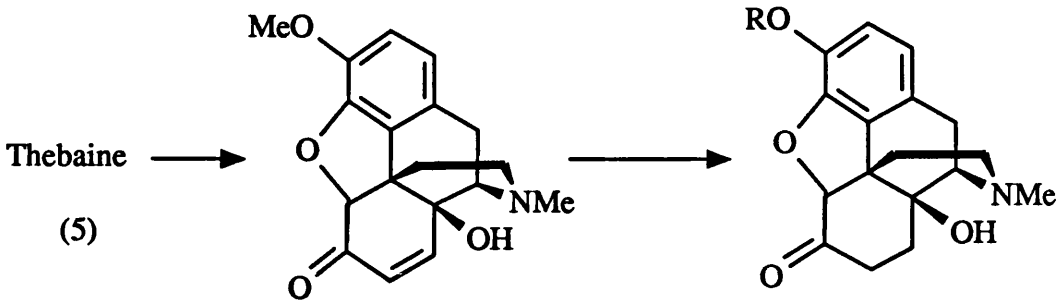


(100)



(101), $R_1 = R_2 = Me$
(102), $R_1 = H$, $R_2 = N_3$

Another series of drugs is derived from 14-hydroxy-4,5-epoxymorphinans. Thebaine (**5**) on oxidation gives 14-hydroxycodeinone (**103**) which is reduced catalytically to 14-hydroxydihydrocodeinone (oxycodone, **104**). *O*-Demethylation of oxycodone gives 14-hydroxydihydromorphinone (oxymorphone,**105**) (Scheme 12). Both oxycodone and oxymorphone are several times more potent than morphine as analgesics.

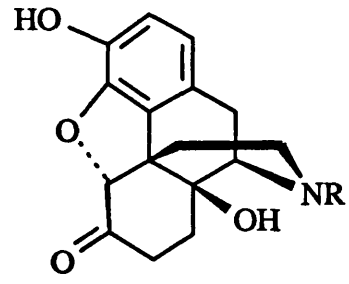


(103)

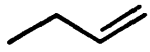
(104), R = Me
(105), R = H

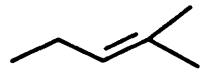
Scheme 12

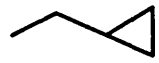
Antagonists are developed from 14-hydroxydihydronormorphinone (noroxymorphone, **106**). Alkylation of noroxymorphone at nitrogen with allyl bromide gives N-allylnoroxymorphone[62] (naloxone, **107**). It is a potent narcotic antagonist. In contrast to nalorphine (**95**) however, naloxone (**107**) fails to show analgesic activity.[63] This property has led to its use as a specific antidote for the reversal of toxic manifestations of narcotics, particularly in cases of overdoses. Analogous compounds, N-dimethylallylnoroxymorphone[64] (nalmexone, **108**), N-cyclopropylmethylnoroxymorphone[65] (naltrexone, **109**) and N-cyclobutylmethyl-noroxymorphone[65] (**110**) show a mixture of agonist and antagonist activities.

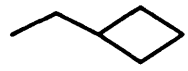


(106), R = H

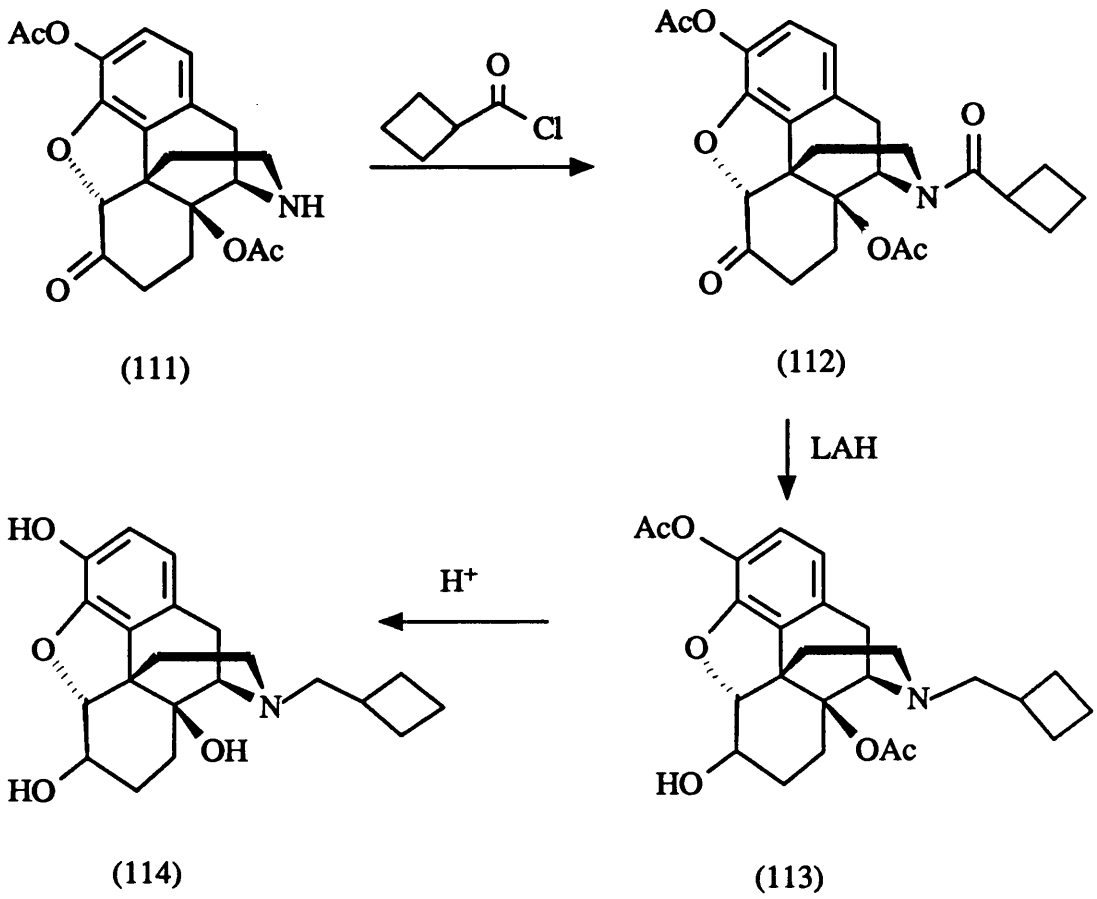
(107), R = 

(108), R = 

(109), R = 

(110), R = 

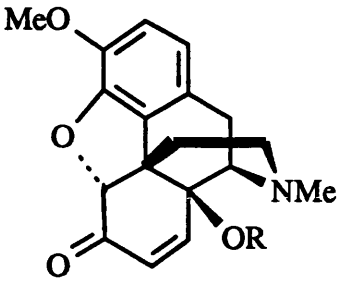
Acylation of 3,14-diacetylnoroxymorphone (**111**) with cyclobutylcarbonyl chloride, followed by reduction of both amide and ketone functions with LAH and deacetylation gives the drug nalbuphine[64] (N-cyclobutylmethyl-14-hydroxy-dihydromorphine, **114**) (Scheme 13). This is used clinically as an analgesic with reduced addiction liability.



Scheme 13

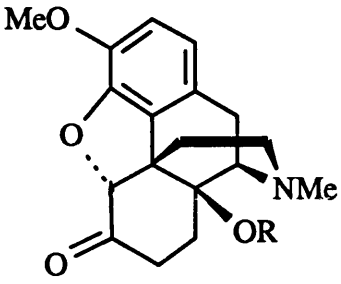
Nalbuphine is as effective as morphine as an analgesic and it has a low incidence of nausea and vomiting, a low frequency of psychotomimetic reactions.[66]

14-Hydroxycodeinone (**103**), on acetylation, gives 14-acetoxycodeinone (**115**) which is reported to be a better analgesic[67] than the hydroxycodeinone (**103**), but it is more toxic. Extending the alkyl chain length in the ester function at the 14-position increases the analgesic potency, with the *n*-pentanoate ester having the highest effect. Cinnamoylation at 14-position of oxycodone (**104**) leads to the ester[68] (**116**) with very high potency (RP = 200). This has led to the speculation that there is a receptor lipophilic site in addition to those previously recognised, extending above and away from the plane of the opiate C-ring.



(103), R = H

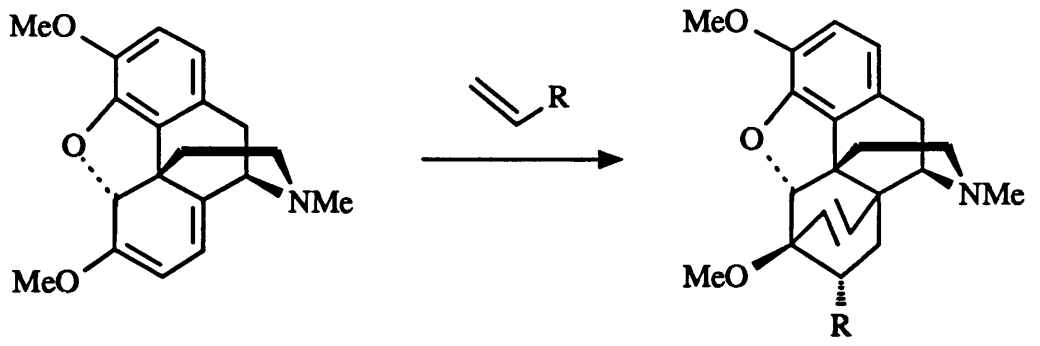
(115), R = Ac



(104), R = H, oxycodone

(116), R = COCH=CHPh

As the above account reveals, early efforts centered around derivatisation of morphine or the synthesis of simpler structures containing what were perceived to be the key pharmacophores.[69,70] In the event this did not lead to a marked separation of desirable and undesirable effects, although some useful drugs were developed from these labours. Lack of success prompted another phase of endeavour this time to construct more complex rigid analogues of morphine (see page 15). In this way it was hoped that the reduced flexibility and subtle differences in overall shape would prevent access to some receptor surfaces but not others and lead to a selectivity of biological action. The prime instigator of this approach was Bentley[71-73] who showed that the addition of dienophiles to thebaine (**5**) gives endo-adducts of the type (**117**) (Scheme 14).

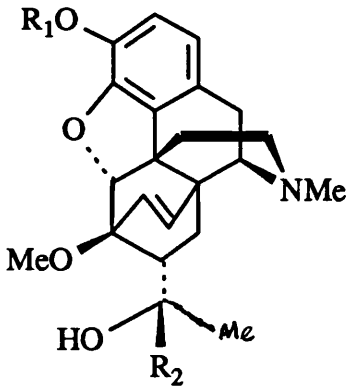


(5)

(117), R = CHO, COMe, COPh, CN, COOR etc.

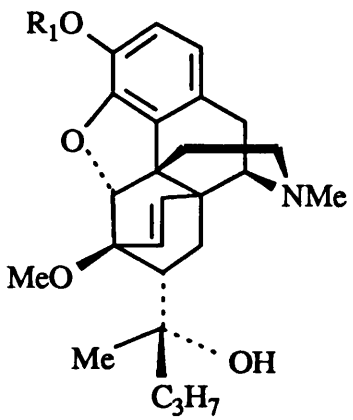
Scheme 14

These adducts (**117**, R = COR_1) react readily with Grignard reagents[74] to give alcohols of general structure (**118**, R_1= CH_3).

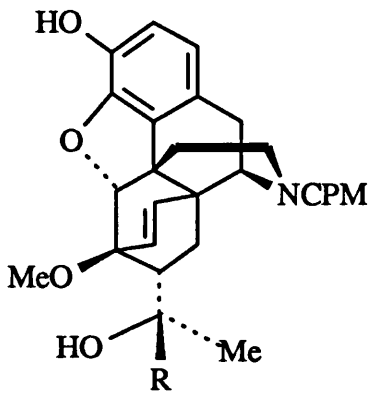


(118), R_1 = Me

O-Demethylation of these compounds (**118**, $R_1 = CH_3$) affords the corresponding oripavines (**118**, R = H) which are more potent than the corresponding thebaines. Substitution of the analgesic (**118**) of N-methyl group by N-alkyl units (up to C5), allyl, dimethylallyl, and cyclopropylmethyl (CPM) gives compounds with either agonist or antagonist activities and varying degrees of potency. Indeed, some of these compounds have analgesic activities many hundred times that of morphine with low addiction potential. One of such compounds is etorphine (**119**) which has exceptionally high analgesic power[75,76] (RP = 10,000).



(119)



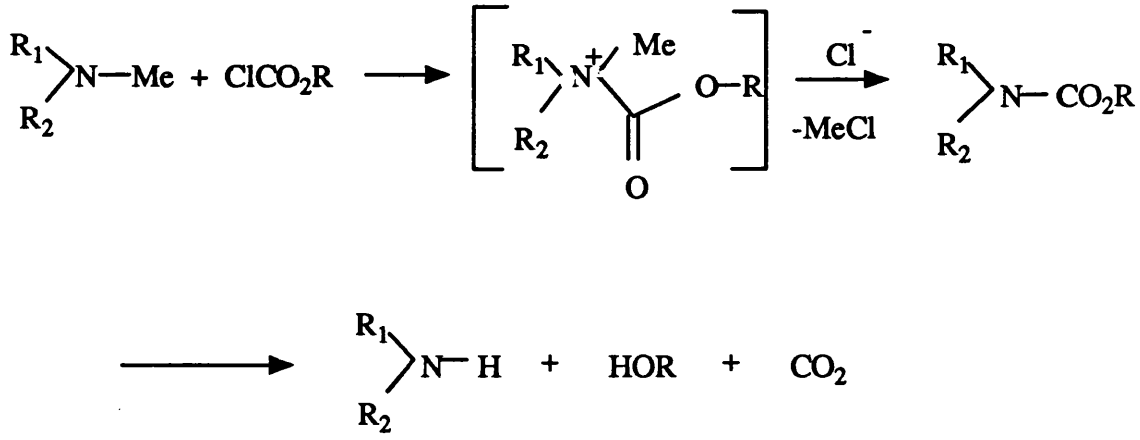
(120), R = Me, diprenorphine

(121), R = t-Bu, buprenorphine

Etorphine is now only used in veterinary practice because it causes considerable respiratory depression in man, even in very small doses. The agonist action of etorphine can be reversed by naloxone (**107**), or diprenorphine (**120**). Diprenorphine is a hundred times as powerful as nalorphine (**95**) as an antagonist.[77] Buprenorphine (**121**) with a *tert*-butyl group in the C-side chain is a powerful agonist (RP = 75) and also an antagonist with four times the efficiency of nalorphine.[78] Buprenorphine is found to be a very effective drug for patients with severe pain. No serious side effects have been reported for it.

2.7 N-Dealkylation

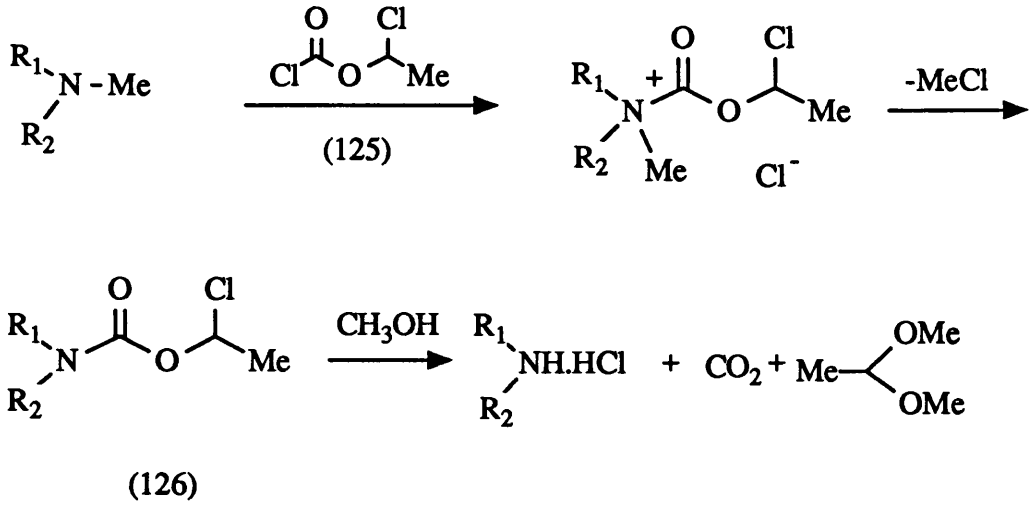
Although most of the preceding drugs are alkylated at nitrogen, this is not always necessary and compounds such as noroxycodone and noroxymorphone are important drugs, or drug intermediates. The synthesis of these compounds often requires a N-demethylation step which is accomplished in many ways. The classic method of N-demethylation is the von Braun reaction[79] in which the tertiary amine, in a suitable solvent, is treated with cyanogen bromide to form the N-cyanonor derivative. This is then hydrolysed and decarboxylated to the corresponding secondary amine. The disadvantage with this method is that cyanogen bromide is very toxic and also the yields are usually only moderate. An improvement uses chloroformates. Thus when a tertiary amine is treated with a chloroformate ester (**123**), a carbamate (**124**) is formed. On hydrolysis this affords the carbamic acid which decarboxylates *in situ* to the secondary amine (Scheme 15).



Scheme 15

This technique was first reported in 1911,[80] and ethyl chloroformate[81,82] and benzyl chloroformate were found to be effective reagents. Later on, however, their use has been superceded[83,84] and in 1975, Rice[85] reported a modified procedure using phenyl chloroformate, in which the intermediate N-carbamate ester was cleaved with a 1:1 mixture of 64% and 95% hydrazine.

Diethyl azodicarboxylate[86] has also been used to N-demethylate thebaine and various derivatives of morphine and codeine. 2,2,2-Trichloro-ethylchloroformate[87] is another reagent used for this purpose and in this case the carbamate ester is cleaved with zinc in acetic acid, or in methanol. In 1970s Olofson *et al.*[88] introduced vinyl chloroformate as a reagent for N-demethylation. Though reaction times are long, cleavage of the carbamate group is easily achieved and clean products and higher yields of products are reported. 1-Chloro-ethylchloroformate[89,90] (**125**) is also recommended, and it is reported to give similar yields to vinyl chloroformate, but it has the advantage that the intermediate carbamate (**126**) is cleaved by simply warming with methanol (Scheme 16).

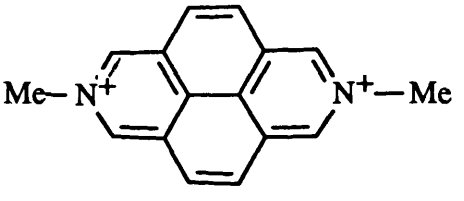


(126)

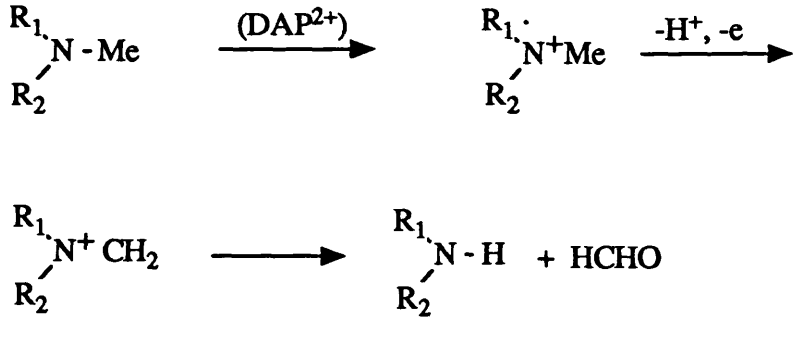
Scheme 16

In 1989, Santamaria *et al.*[91] reported a photochemical N-demethylation procedure for tertiary amines, specifically alkaloidal types. The reaction occurs when the amine, together with a catalytic amount of N,N'-dimethyl-2,7-diazapyrenium ion (DAP^{2+} $2BF_4^-$) in acetonitrile is irradiated while oxygen is bubbled through the solution. A 500W high pressure mercury lamp is recommended with a glass filter to remove ultra violet rays.

DAP^{2+} is an electron acceptor excited by visible light, which is not absorbed by the amines. In its excited form the reagent abstracts an electron from the lone pair of the amine which then undergoes further oxidation to give an immonium ion. Hydrolysis completes the reaction.



DAP^{2+}



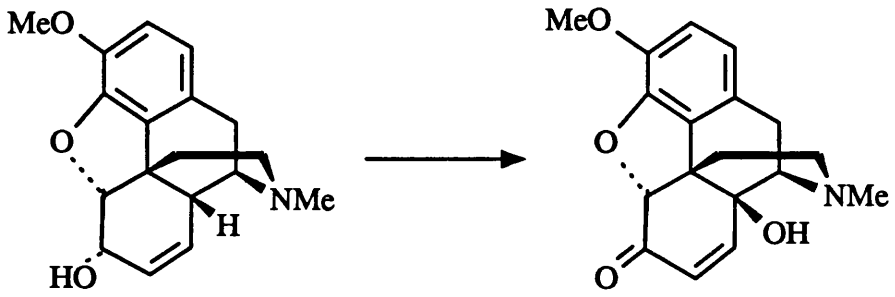
Scheme 17

2.8 O-Demethylation

The conversion of codeine (**4**) to morphine (**1**) or codeine derivatives like oxycodone (**104**), hydrocodone (**92**) etc. to the corresponding morphine analogues requires the cleavage of aromatic 3-0-Me group. Though there are a number of methods available for *O*-demethylation, the reagents used in the past are often toxic and severe reaction conditions and low yields[92,93] (15 - 34%) are commonplace. More modern reagents include lithiumdiphenylphosphide, which has been recommended for the conversion of *trans*-codeine and *trans*-isocodeine into the corresponding morphines,[94,95] but some workers have found that this is unreliable. Boron tribromide is a reagent of choice for many O-demethylation reactions. It has been used previously for the cleavage of methyl aryl ethers[96] and the method has been developed by Rice[97] for the conversion of codeine into morphine. Thioethoxide ion[98] in hot DMF under nitrogen effects the demethylation of aryl-methyl ethers. Other reagents are: sodium benzylselenate,[99] concentrated hydrobromic acid,[100] sodium propylmercaptide[101] and trimethylsilyl iodide.[102,103]

2.9 Synthesis of 14-hydroxy morphine compounds

14-Hydroxymorphines form important semisynthetic drugs, and attempts have been made to effect the allylic oxidation of codeine (**4**) to give 14-hydroxycodeinone (**103**). Reagents tried include chromic acid,[104] manganese (IV) oxide,[105] selenium dioxide and *tert*-butylhydroperoxide.[106] In no case is a satisfactory yield of the product obtained.

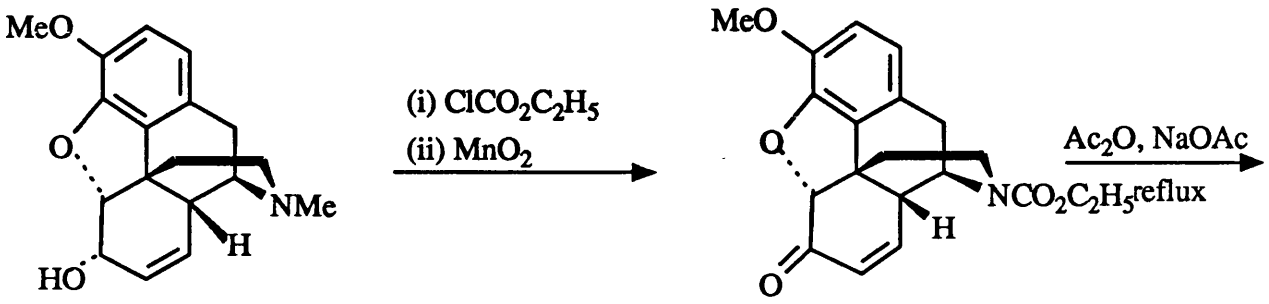


(4) (103)

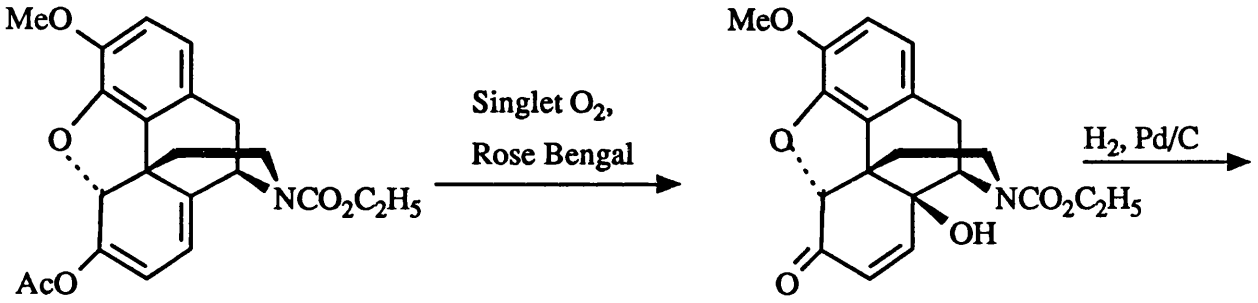
Scheme 18

Schwartz and Wallace[106] reported the conversion of codeine (**4**) into noroxycodone (**131**) and then onto noroxymorphone (**106**). Seven steps were involved and the authors claimed a 43% overall yield. According to their scheme, codeine (**4**) was first converted to its N-ethyl carbamate by treating with ethyl chloroformate. The product was oxidised to the codeinone derivative (**127**) with manganese (IV) oxide and then converted to the dienol acetate (**128**) by heating under reflux with acetic anhydride and sodium acetate. The dienol acetate on oxidation with singlet oxygen in presence of Rose Bengal sensitiser gave 14-hydroxycodeinone (**129**), which was reduced to the corresponding dihydrocodeinone (**130**). Finally the 3-0-methyl group and the N-carbamate

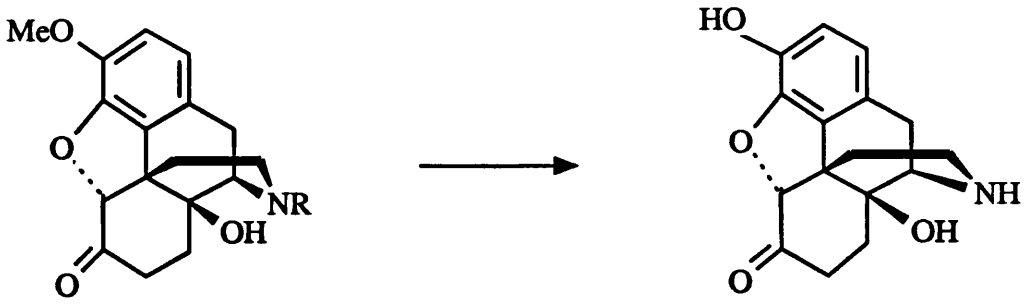
substituent were cleaved in order to obtain the desired product (Scheme 19). The *N*-demethylation step of Schartz and Wallace is, far from satisfactory and the whole process has not found favour in industry.



(4) (127)



(128) (129)

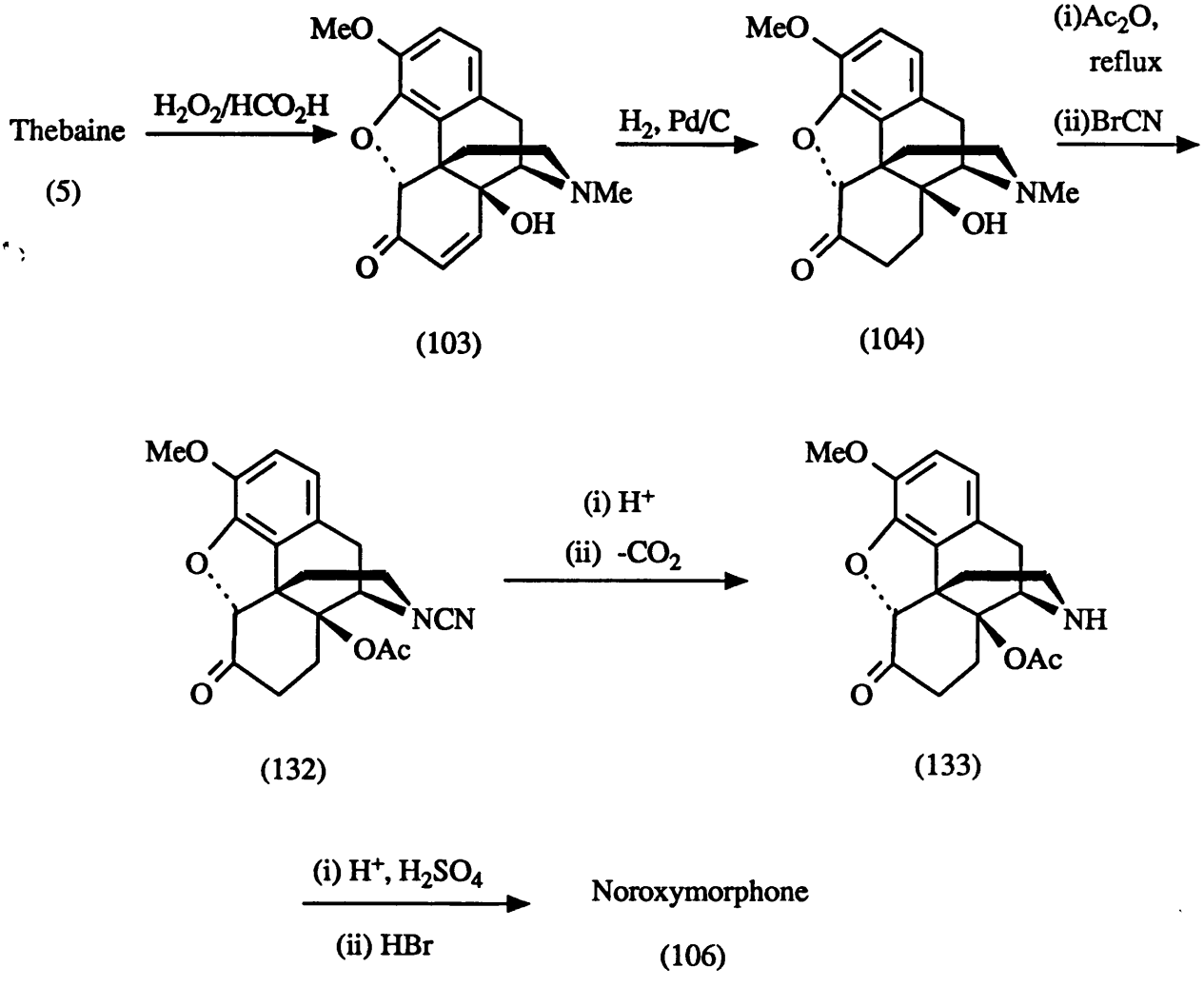


(130), R = CO_2Et
(131), R = H, noroxycodone

(106), noroxymorphone

Scheme 19

The present commercial route to noroxymorphone is from thebaine.[107,108] Thebaine (**5**) is oxidised to 14-hydroxycodeinone (**103**) by hydrogen peroxide - formic acid mixture[109,110] and the enone is selectively hydrogenated catalytically to give the corresponding dihydrocodeinone (**104**). After protection through 14-O-acetylation, N-demethylation is effected by the von Braun reaction with cyanogen bromide.[111] The resultant N-cyanoderivative (**132**) is hydrolysed to give the secondary amine (**133**) and this, on acid hydrolysis and *O*-demethylation by boiling with hydrobromic acid,[112] finally yields noroxymorphone (**106**) (Scheme 20).


Thebaine
(5)
H_2O_2/HCO_2H
MeO
O
NMe
OH
O
(103)
H_2, Pd/C
MeO
O
NMe
OH
O
(104)
(i)Ac_2O,
reflux
(ii)BrCN
MeO
O
NCN
OAc
O
(132)
(i) H^+
(ii) $-CO_2$
MeO
O
NH
OAc
O
(133)
(i) H^+, H_2SO_4
(ii) HBr
Noroxymorphone
(106)

Scheme 20

CHAPTER 3

RESULTS AND DISCUSSION

3.1 An Investigation of the MacFarlan Smith Morphine Extraction Process.

In a recent phase of redevelopment, MacFarlan Smith planned to improve the process for the extraction of the major alkaloids of opium viz; morphine, codeine, thebaine, noscapine and papaverine. They aimed at a process of greater efficiency than the existing one, higher recoveries of thebaine and noscapine and the isolation of the alkaloids from normally discarded side streams. A flow chart (Fig. 4) helps to explain the extraction process showing the inputs, outputs, recycles and effluent streams (labelled 1-14). A brief explanation of the process is given below.

1. Opium is treated with ammoniacal industrial methylated spirit (IMS), the insolubles are removed and the filtrate is partitioned between aqueous sodium hydroxide and a mixture of xylene and amyl alcohol (XAA). The phenolic bases dissolve in the aqueous phase at pH 12 while other alkaloids remain in the organic phase.

2. The aqueous phase is acidified (pH 5) with sulphuric acid to remove a second crop of insolubles which are filtered off. The filtrate is basified to pH 9 with sodium hydroxide in presence of XAA causing morphine to precipitate almost completely. The solvent layer is removed to give 'effluent stream (4)'.

3. The XAA phase from step (1) is acidified with sulphuric acid to pH 2 to extract basic alkaloids. The XAA fraction separated from the acid layer is designated as 'effluent (10)'. The aqueous acid phase is treated with sodium hydroxide until pH 6 is obtained. This treatment precipitates the weak bases -

noscapine and papaverine.

4. The aqueous fraction after removing noscapine and papaverine is brought to pH 10 with alkali and extracted with XAA to remove the remaining non-phenolic alkaloids, mainly thebaine and codeine. The XAA extract is treated with 50% tartaric acid when thebaine is precipitated as the insoluble tartrate salt. Codeine acid tartrate remains in solution. Thebaine base is regenerated from its tartrate by treatment with ammonia. It is then filtered off and the filtrate is labelled 'effluent (12)'.

5. The aqueous phase containing codeine acid tartrate is made alkaline with alkali to pH 10 and extracted with XAA. The organic phase containing (mainly codeine) is treated with sulphuric acid at 80°C. Once the XAA phase is separated from the mixture it is called 'effluent (7)'. The aqueous phase (at pH 3.5) is cooled when codeine sulphate precipitates; the filtrate is known as 'effluent (13)'. Codeine is regenerated from codeine sulphate by treatment with ammonia.

The effluent streams contain quantities of the major and minor alkaloids of opium and are normally discarded. Some of these effluent streams, concentrated or dried, were given to the University for analysis. The author's task was to isolate and identify the alkaloids present in these effluent streams, thus allowing an assessment to be made as to whether they should be reprocessed or not. We have analysed fractions (effluents) (4), (7), (10) and (13).

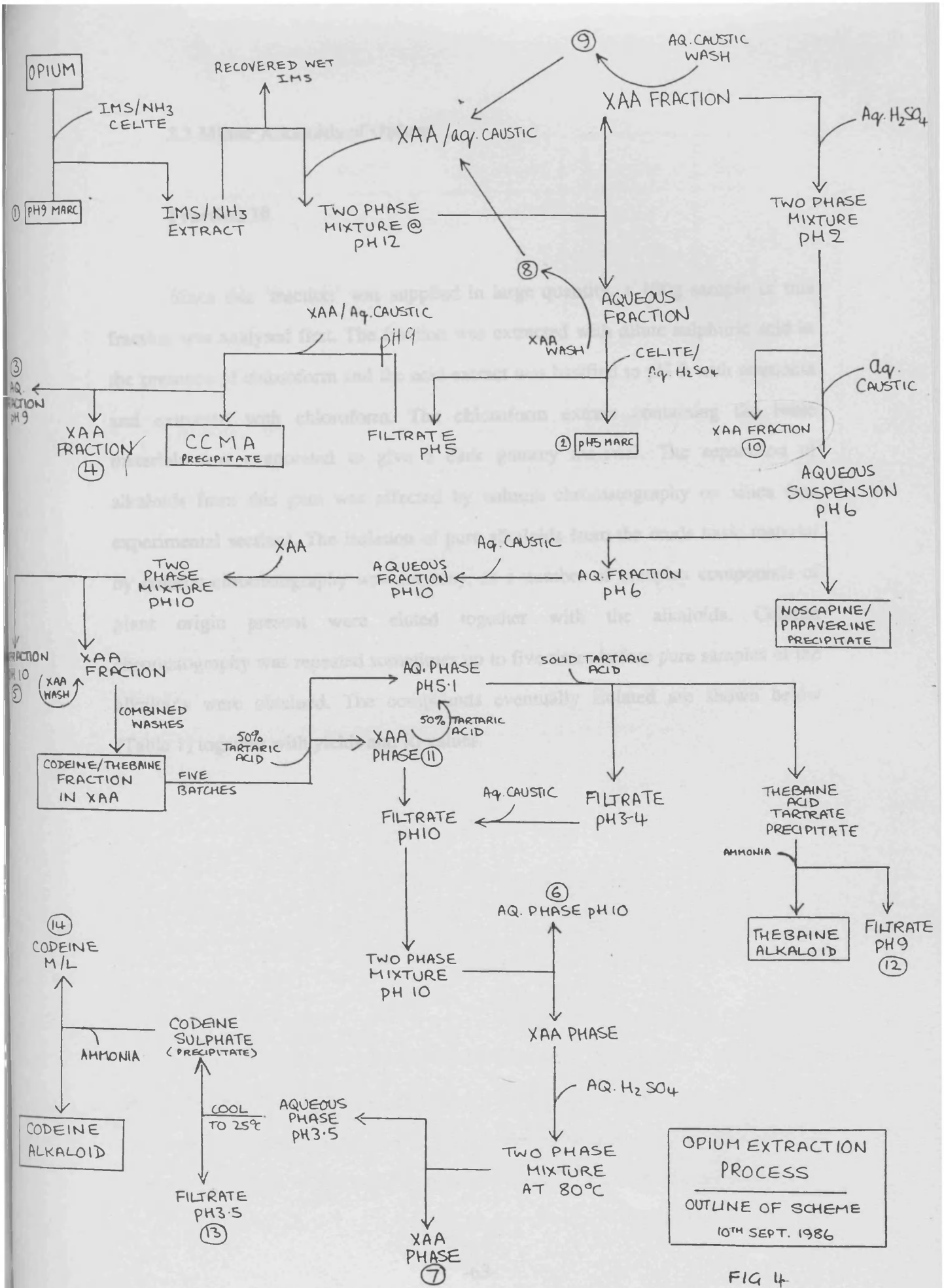

OPIUM
IMS/NH3 CELITE
RECOVERED WET IMS
XAA/aq. CAUSTIC
AQ. CAUSTIC WASH
XAA FRACTION
Aq. H2SO4
① pH9 MARC
IMS/NH3 EXTRACT
TWO PHASE MIXTURE @ pH12
TWO PHASE MIXTURE pH2
⑧
AQUEOUS FRACTION
XAA/Aq. CAUSTIC pH9
XAA WASH
CELITE/ Aq. H2SO4
Aq. CAUSTIC
③ AQ. FRACTION pH9
XAA FRACTION ④
CCMA PRECIPITATE
FILTRATE pH5
② pH5 MARC
XAA FRACTION ⑩
AQUEOUS SUSPENSION pH6
XAA
Aq. CAUSTIC
TWO PHASE MIXTURE pH10
AQUEOUS FRACTION pH10
AQ. FRACTION pH6
NOSCAPINE/ PAPAVERINE PRECIPITATE
XAA FRACTION
XAA WASH ⑤
AQ. PHASE pH5·1
SOLID TARTARIC ACID
50% TARTARIC ACID
COMBINED WASHES
50% TARTARIC ACID
XAA PHASE ⑪
CODEINE/THEBAINE FRACTION IN XAA
FIVE BATCHES
FILTRATE pH10
Aq. CAUSTIC
FILTRATE pH3-4
THEBAINE ACID TARTRATE PRECIPITATE
AMMONIA
⑥ AQ. PHASE pH10
⑭ CODEINE M/L
TWO PHASE MIXTURE pH10
THEBAINE ALKALOID
FILTRATE pH9 ⑫
XAA PHASE
CODEINE SULPHATE (PRECIPITATE)
AMMONIA
AQ. H2SO4
COOL TO 25°C
AQUEOUS PHASE pH3·5
CODEINE ALKALOID
TWO PHASE MIXTURE AT 80°C
FILTRATE pH3·5 ⑬
XAA PHASE ⑦
OPIUM EXTRACTION PROCESS
OUTLINE OF SCHEME
10TH SEPT. 1986

FIG 4.

3.2 Minor Alkaloids of Opium

Fraction 10

Since this 'fraction' was supplied in large quantity, a 100g sample of this fraction was analysed first. The fraction was extracted with dilute sulphuric acid in the presence of chloroform and the acid extract was basified to pH 9 with ammonia and extracted with chloroform. The chloroform extract containing the basic materials was evaporated to give a dark gummy material. The separation of alkaloids from this gum was effected by column chromatography on silica (see experimental section). The isolation of pure alkaloids from the crude basic material by column chromatography was not easy, as a number of complex compounds of plant origin present were eluted together with the alkaloids. Column chromatography was repeated sometimes up to five times before pure samples of the alkaloids were obtained. The compounds eventually isolated are shown below (Table 1) together with yields and R_f values.

Noscapine (α-Narcotine) **(2)**

The next compound isolated was proven to be noscapine (2). It was crystallised from ethyl acetate as colourless crystals. The mass spectrum of the alkaloid gave a base peak at *m/z* 220 corresponding to the fragment shown below.

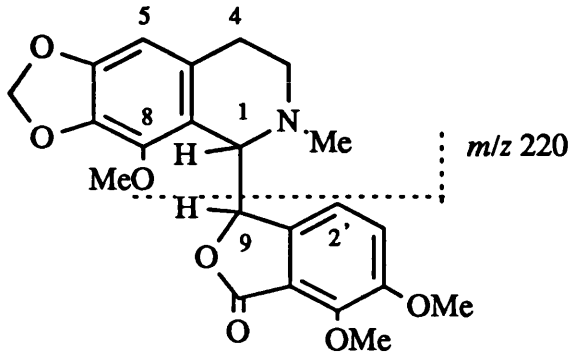


Fig. 5

The molecular ion peak occurs at *m/z* 413 in E.I. and in C.I. at *m/z* 414 ($M+H^+$). The details of the ^1H n.m.r. spectrum of the compound are as follows :

1. Four, three-proton singlets, three at δ 3.86, 4.04 and 4.09 are due to the resonances of the hydrogen atoms of the three methoxy functions and one at δ 2.55 due to that of the N-methyl group.

2. A two-proton singlet at δ 5.94 is characteristic of the resonance of the protons of the methylene dioxy group.

3. The 5-H proton resonates at δ 6.31 as a singlet. Two doublets centered at δ 6.08 and 6.96 (J = 8.25 Hz) are the resonances of *ortho-* oriented aromatic protons 2'-H and 3'-H respectively.

4. A four-proton multiplet at δ 1.91 - 2.61 is characteristic of the proton resonances of the $N\text{-}CH_2\text{-}CH_2$- group.

5. The resonances of 1-H and 9-H give rise to doublets at δ 4.40 and 5.58

respectively with a coupling constant $J_{1,9}$ = 4.0 Hz. This can be used to estimate the dihedral angle as 130° between the two halves of the molecule and hence its preferred conformation.[114]

6. The high field position of 2'-H (δ 6.08) also reflects the fact that the adoption of a dihedral angle of 130° between the upper and lower parts of the alkaloid places 2'-H over the π-system of the isoquinoline benzenoid ring (Fig. 6).

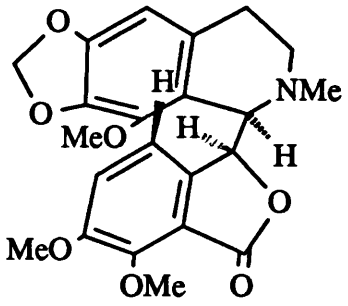


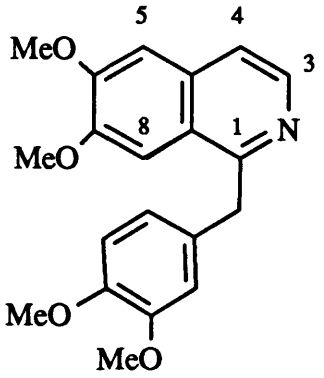
Fig. 6

In the infra red spectrum of the alkaloid there are bands commensurate with methylene and methoxy groups[115] and a carbonyl band at 1708 cm^{-1}. The frequency of the latter agrees with the presence of an aromatic five-membered lactone and together with the rest of the data, and m.p., led us to conclude that the alkaloid was indeed noscapine.[116] This was proved by a direct comparison with an authentic sample.

Papaverine(3)

The next alkaloid proved to be papaverine (3). This alkaloid gives rise to a simpler ^1H n.m.r. spectrum than that of noscapine (2): four three-proton singlets at δ 3.77, 3.82, 3.91 and 4.0 which arise from the resonances of four sets of methoxy protons and a two-proton singlet at δ 4.54 is associated with that of a benzylic

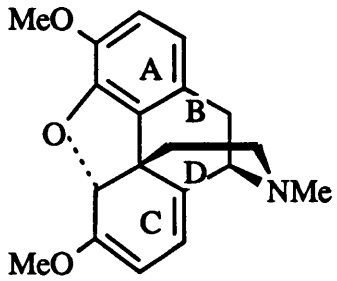
methylene group of the papaverine structure (3). Aromatic protons 5-H and 8-H resonate at δ 7.05 and 7.35 respectively as singlets, while 3-H and 4-H give rise to doublets at δ 8.37 and 7.43 ($J_{3,4}$ = 5.7 Hz) respectively. A three-proton multiplet at δ 6.74 - 6.83 accounts for the aryl proton resonance of the benzylic group. In the mass spectrum, the molecular ion peak is observed at *m/z* 339 and the base peak is at *m/z* 338 [$(M-H)^+$]. Papaverine has m.p. 147 - 148°C[117] and showed no depression in m.p. when mixed with the sample obtained from 'effluent stream (10)'.



(3)

Thebaine (5)

The third alkaloid isolated was shown to be thebaine (5); the ^1H n.m.r. spectrum of which is significantly more complex than that of papaverine. This reflects the rigidity of the chiral molecule and hence the non-equivalence of many of its protons. Thus, the $-CH_2-CH_2-$ group of the D-ring of thebaine gives a complicated pattern of signals between δ 1.5 and 3.0.



(5)

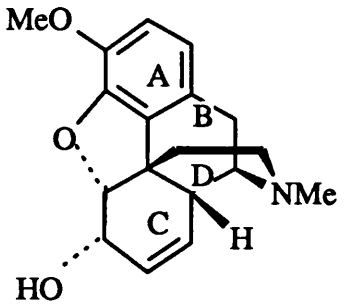
Two 2H multiplets centered at δ 1.95 and 2.80 are due to the resonances of the protons of the C-15 and C-16 methylene groups. The protons of the N-CH_3, 3-OCH_3 and 6-OCH_3 groups give rise to singlets at δ 2.48, 3.85 and 3.61 respectively. A doublet of doublets centered at δ 2.70 is due to the resonance of 10-H_β, this signal couples with that of 10-H_α (δ 3.33, J_{gem} = 18.1 Hz) and with 9-H (δ 3.69, $J_{9,10}$ = 7 Hz). Protons 7-H and 8-H resonate as doublets centered at δ 5.56 and δ 5.07 respectively with $J_{7,8}$ = 6.5 Hz, whereas 5-H resonates as a singlet at δ 5.28. The resonances of 1-H and 2-H give rise to an AB quartet at δ 6.50 - 6.66 ($J_{1,2}$ = 8.0 Hz).

The mass spectrum of thebaine shows the base peak at *m/z* 311 which is also the molecular ion peak. Once again the identity of the sample of thebaine was cross checked by means of an authentic sample.[118,119]

Codeine (4)

The final alkaloid from the effluent was identified as codeine (4). The ^1H n.m.r. spectrum of codeine has similarities to that of thebaine. Thus the resonance of 15-H_α is double multiplet with J_{gem} = 12.8 Hz. The resonance of 15-H_β is observed as a set of doublet of doublets ($J_{15,16}$ = 5.1 Hz). Similarly the signal for 16-H_α is a doublet of doublets (J_{gem} = 12.6 Hz, $J_{16,15}$ = 5.6Hz) whereas that of 16-H_β is a

double multiplet (J_{gem} = 12.5 Hz). The resonance due to 14-H exists as a multiplet at δ 2.67 and couples with the signals of 9-H, 8-H and 7-H. The resonances of 9-H and 10-H are similar to those of thebaine (see experimental section), that of 6-H is a multiplet at δ 4.18 and the signal of 6-OH is a broad singlet at δ 2.9. The resonance of 5-H is a doublet at δ 4.9 ($J_{5,6}$ = 6.6 Hz). The resonances of the ethylenic hydrogens 7-H and 8-H from C-ring form multiplets centered at δ 5.7 and δ 5.3 respectively ($J_{7,8}$ = 9.9 Hz).



(4)

Codeine is of course a familiar alkaloid and one which we expected to find in the effluent stream. We suspected its presence long before it was isolated from TLC evidence.

Fraction 4

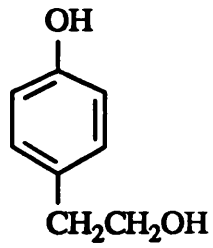
'Fraction 4' (page 61) was analysed in a similar manner to 'Fraction 10'. The details of the separation method are given in the experimental section. Even though only 4.0g of this sample was available for analysis, nine compounds (eight alkaloids) were isolated and identified. These compounds together with the corresponding yields and R_f values are given in Table 2.

	Compound	R_f*	% by weight
1	2-(4-Hydroxyphenyl)ethanol (135)	0.96	0.15
2	Noscapine (2)	0.94	3.0
3	Papaverine (3)	0.93	1.6
4	Thebaine (5)	0.74	0.3
5	Narcotoline (136)	0.64	0.2
6	Pa laudine (137)	0.61	1.4
7	Oripavine (138)	0.58	0.25
8	Codeine (4)	0.54	0.5
9	Morphine (1)	0.22	0.4

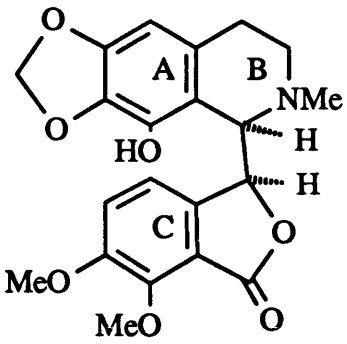
*Solvent : $CHCl_3$: CH_3COCH_3 : CH_3OH : NH_3 = 25:20:5:1

Table 2

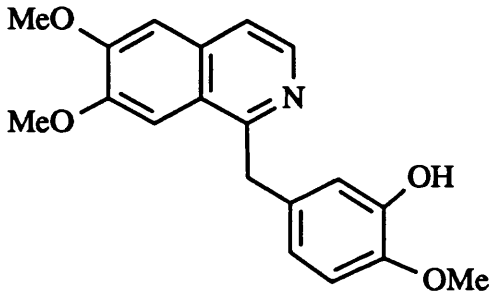
The alkaloids noscapine (**2**), papaverine (**3**), thebaine (**5**) and codeine (**4**) were identified by comparing the ^1H n.m.r., mass and infrared spectra and the R_f values with those of the samples previously identified.



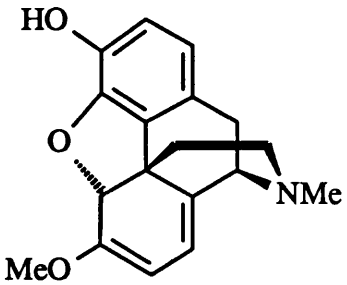
(135)



(136)



(137)



(138)

Narcotoline (136)

This is an uncommon alkaloid clearly related to noscapine (2). Its identity was suspected when the ^1H n.m.r. spectra of the unknown was compared to that of noscapine. The differences in spectra between the two compounds are that there are only two three-proton singlets at δ 3.87 and 4.10 for the resonances of two methoxy groups instead of the three in noscapine and the protons of the methylene dioxy-group in narcotoline give rise to a quartet at δ 5.97 (J_{gem} = 1.1 Hz) while those of noscapine exhibit as a singlet at δ 5.94. The non-equivalence of the methylene protons of narcotoline reflects the chiral nature of the molecule and presumably also the same dihedral angle between the upper and lower fragments as exhibited by

noscapine (Fig. 7).

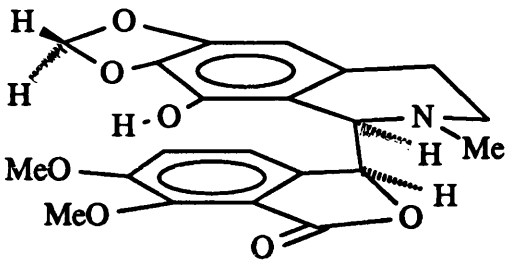
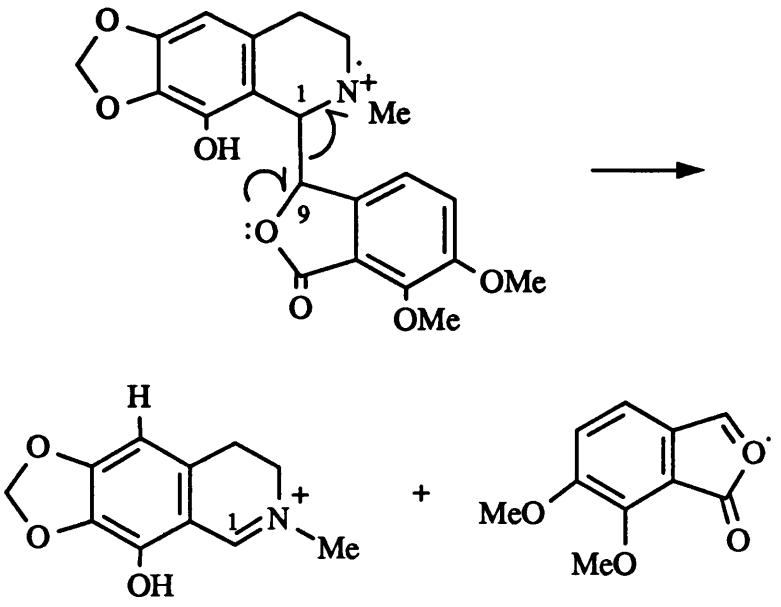


Fig. 7

The mass spectrum of narcotoline also shows a similar fragmentation pattern to noscapine, thus the base peak at *m/z* 206 due to the ion $C_{11}H_{12}O_3N^+$ is formed by the cleavage of the C-1 - C-9 bond. The prominence of the fragment $C_{11}H_{12}O_3N^+$ is due to the ease of formation by fission of a bond which is at the same time doubly benzylic and β to a nitrogen atom.[120]



$C_{11}H_{12}O_3N^+$, *m/z* = 206

Scheme 21

Palaudine (137)

This alkaloid was also readily identified by its close resemblance to papaverine (**3**). A pure sample of palaudine was obtained by flash column chromatography of the crude extract and it was then crystallised from ethanol as colourless crystals (m.p. 174 - 175°C).[121] The ^1H n.m.r. spectrum shows 3H singlets resonating at δ 3.82, 3.89 and 4.10 corresponding to the proton signals of three of the four methoxyl groups of papaverine (**3**). A two-proton singlet at δ 4.49 is associated with a methylene group, and a broad singlet at δ 6.5 (removable by D_2O exchange) is the resonance of a phenolic proton. Seven aromatic proton resonances from an isoquinoline ring and a substituted benzyl group form similar spin-spin patterns to those shown by papaverine. The mass spectrum of the alkaloid shows a molecular ion with *m/z* 325 in line with the required structure and as expected an $[M - 1]^+$ peak was of much greater intensity and reflects the presence of the phenolic

hydroxyl group.

Oripavine (138)

Alkaloid number 6 proved to be oripavine (**138**). Its infra red spectrum exhibited a broad band at ≈ 3200 cm^{-1} due to a phenolic O-H and the ^1H n.m.r. spectrum was very similar to that of thebaine (**5**), except that thebaine has signals for the proton resonances of two methoxyl groups (at δ 3.61 and 3.85). Oripavine has only one which resonates at δ 3.61. This must be located at the terminus of the diene system , otherwise such a unit could not survive. The mass spectrum showed the presence of a molecular ion of *m/z* 297 (100%) and it was immediately clear that the alkaloid we had isolated was O-demethylthebaine i.e. oripavine. This conclusion was verified by comparison with an authentic sample of oripavine.

Morphine (1)

The final alkaloid of 'fraction 4' was morphine. Once again we expected to find this compound and had detected it by TLC at an early stage. Here, as for all the other alkaloids, we needed to know how much was present not merely to detect it, and some pains were taken to minimise losses during the recovery process.

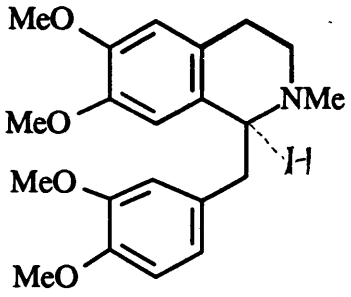
The ^1H n.m.r. spectrum of morphine exhibits multiplets between δ 1.7 and 2.1 which are assigned to the resonances of 15-CH_2. Additional signals at δ 2.40 - 2.55 are due to the resonances of 16-CH_2, whereas a doublet of doublets at δ 2.29 corresponds to the signal of 10-Hα (J_{gem} = 18.8 Hz and $J_{10,9}$ = 6.4 Hz). The protons of the N-methyl group resonate as a singlet at δ 2.37. 14-H resonates as a multiplet at δ 2.59, whereas 10-Hβ generates a doublet at δ 2.96 (J_{gem} = 18.9 Hz). A double doublet centered at δ 3.32 is assigned to the resonance of 9-H ($J_{9,10}$ = 6.4 Hz and $J_{9,14}$ = 3.3 Hz). The 6-OH proton resonance occurs as a broad band at δ 3.07. A multiplet at δ 4.12 is due to the resonance of 6-H. The spin-spin pattern for the signals of 7-H and 8-H centered at δ 5.56 and 5.24 respectively is that expected of

the signal couples to 6-H, 5-H and 14-H ($J_{7,8}$ = 9.9 Hz). Finally aromatic protons 1-H and 2-H resonate as an AB quartet at δ 6.4 - 6.6 (*J* = 8.0 Hz).

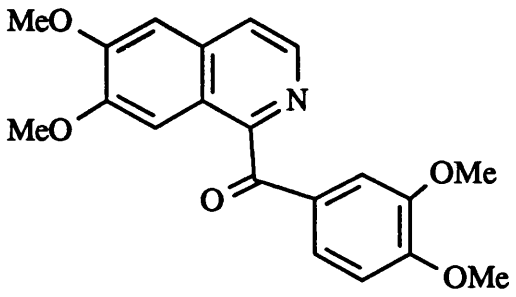
It is not surprising that the phenolic opium alkaloids *viz*, narcotoline (**136**), palaudine (**137**) and oripavine(**138**), together with morphine (**1**), are isolated from 'effluent (**4**)' which is the organic phase separated after precipitating morphine from the extract containing all the phenols (see fig. 4).

Fraction 7

The analysis of 'Fraction 7' (page 61) showed it to contain, in addition to the major alkaloids noscapine (**2**), papaverine (**3**) and codeine (**4**), two minor alkaloids *viz*, xantholine (**139**) and laudanosine (**140**).



(140)



(139)

	Compound	R_f*	% by weight
1	Noscapine (2)	0.75	0.83
2	Papaverine (3)	0.64	0.33
3	Xanthaline (139)	0.63	0.50
4	Laudanosine (140)	0.59	0.80
5	Codeine (4)	0.30	1.20

* Solvent : $CHCl_3$: MeOH : NH_3 = 90 : 10 : 1

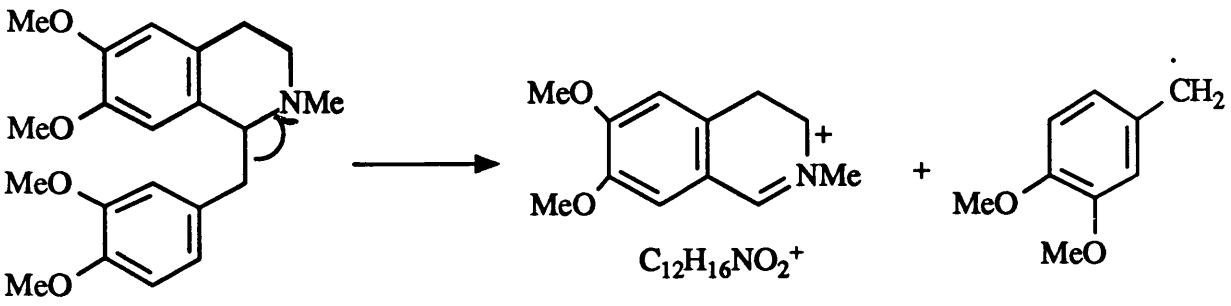
Table 3

Xanthaline (139)

Xanthaline[122], also known as papavaraldine has a carbonyl group in place of the methylene group of papaverine (3). In the infra red spectrum it exhibits ν_{max} 1640 cm^{-1} characteristic of a diaryl ketone. The ^1H n.m.r. spectrum shows four three-proton singlets at δ 3.95, 3.96, 3.97 and 4.06 corresponding to the proton resonances of the four methoxyl groups. Protons 5-H and 8-H resonate at δ 7.15 and δ 7.55 respectively as singlets and the resonances of 3-H and 4-H give rise to doublets centered at δ 8.46 and δ 7.66 respectively ($J_{3,4}$ = 5.6 Hz). A doublet at δ 6.87 is due to the resonance of 5'-H which is coupled to the signal of 6'-H ($J_{5',6'}$ = 8.4 Hz). A doublet at δ 7.12 due to the resonance of 2'-H is also coupled to the signal for 6'-H ($J_{2',6'}$ = 1.8 Hz) which resonates as a doublet of doublets at δ 7.42. Apart from chemical shift differences caused by the substitution of the methylene group by a carbonyl function the spectra of papaverine and xantholine are similar. It is uncertain whether xantholine is a true alkaloid or an oxidation product of papaverine. It is however, a common component of opium which has received much exposure to atmospheric oxygen both in the "field" and in the processing methods.

Laudanosine (140)

The remaining alkaloid of this fraction was shown to be laudanosine which is N-methyl-1,2,3,4-tetrahydropapaverine. The ^1H n.m.r. spectrum of this alkaloid shows a four-proton multiplet between δ 2.48 and δ 2.88 which is due to the resonances of 3-CH_2 and 4-CH_2. A signal for the N-methyl protons and those of four O-methyl protons give rise to five singlets at δ 2.55 (N-CH_3) and δ 3.56, 3.79, 3.84 and 3.85. The benzylic methylene bridge protons resonate as a multiplet centered at δ 3.18 unlike the corresponding signals for papaverine (3) and palaudine (**137**). This is a result of the chiral centre at C-1 and through coupling with the proton signal of 1-H. In the mass spectrum, cleavage of the benzylic fragment leads to the base peak (*m/z* 206 for the ion $C_{12}H_{16}NO_2^+$ (**141**).

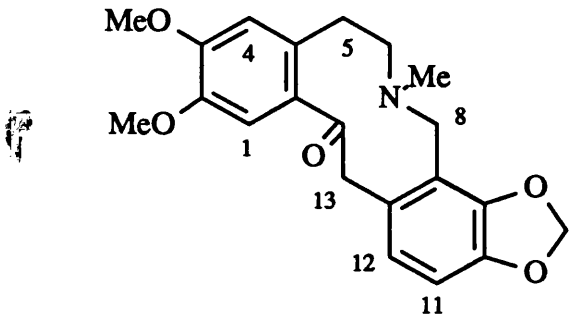


(140) (141)

Scheme 22

Fraction 13

'Fraction 13' is water soluble and in order to investigate its contents it was taken up in dilute acid and extracted with diethyl ether. Evaporation of the organic phase gave no residue. The aqueous phase was then basified and extracted first with diethyl ether and then with chloroform. The ether extract on concentrating and cooling overnight gave colourless crystals. These were subsequently shown to be cryptopine **(142)**.



(142)

The chloroform extract contained, in addition to cryptopine, the alkaloids noscapine **(2)**, papavarine **(3)**, laudanosine **(140)**, thebaine **(5)** and codeine **(4)** (Table 4).

Cryptopine (142)

In the ^1H n.m.r. spectrum of cryptopine, signals due to the resonances of 5-CH_2 and 6-CH_2 are observed as a four-proton multiplet at δ 1.6 - 2.6 and those of 8-CH_2 and 13-CH_2 appear as another four-proton multiplet at δ 3.55 - 3.65. Two methoxyl groups give rise to singlet resonances at δ 3.89 and 3.90 and the resonance of the methylenedioxy group occurs as a two proton singlet at δ 5.94. Signals due to

	Compound	R_f*	% by weight
1	Cryptopine (142)	0.57	2.5
2	Noscapine (2)	0.75	0.5
3	Papaverine (3)	0.64	1.8
4	Laudanosine (140)	0.59	0.3
5	Thebaine (5)	0.56	0.25
6	Codeine (4)	0.30	2.0

* Solvent $CHCl_3$: MeOH : NH_3 = 90 : 10 : 1

Table 4

1-H and 4-H are exhibited as singlets at δ 7.00 and δ 6.70 respectively. The mass spectrum of cryptopine shows a molecular ion at *m/z* 369, and a base peak corresponding to $C_9H_8O_2$ at *m/z* 148.

Crytopine is a well known alkaloid investigated many years ago by Perkin.[123] Like thebaine, cryptopine is something of a chemical 'chameleon' and undergoes a wealth of reactions. Strangely enough Dr. D.W. Brown from this group worked on cryptopine for his doctoral thesis[124] and so the identity of this alkaloid was immediately recognisable to my supervisor who once shared a laboratory bench with Dr. Brown.

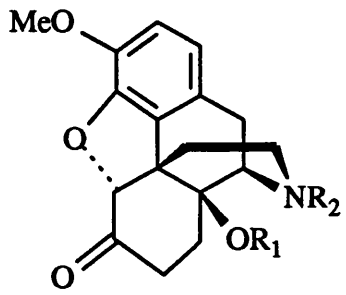
Conclusion

This piece of work represents the first attempt to quantify the 'wasted' alkaloids from the commercial opium extraction process run by McFarlan Smith Ltd. Although the actual percentage yields in the effluent streams are small the scale of the overall process makes their recovery worthwhile provided uses can be made of them.

The remainder of this thesis is devoted to utilising of the opium alkaloid morphine and some of its derivatives as raw materials for other drug substances.

3.3 N-Demethylation of Oxycodone

Many modifications of morphine alkaloids have been undertaken and the semi-synthetic products have been tested for analgesic/ antagonistic properties. For example, N-normorphines serve as important intermediates in the synthesis of many drugs. N-Demethylation has always been a problem since reagents used for this purpose are often toxic, reaction conditions rigorous and yields of the normorphines low to moderate. Several N-demethylation methods are in use of which the von Braun reaction of cyanogen bromide with tertiary amines is one of the oldest. Other reagents such as diethyl azodicarboxylate[125] and various chloroformate esters are recommended as replacements for cyanogen bromide and the next project undertaken by the author was to assess such reagents applied to the N-demethylation of oxycodone (**104**). This is an important reaction because noroxycodone is an important intermediate *en route* to several commercially valuable drugs.



(104), R_1 = H, R_2 = Me, oxycodone
(131), R_1 = R_2 = H
(143), R_1 = COMe, R_2 = Me

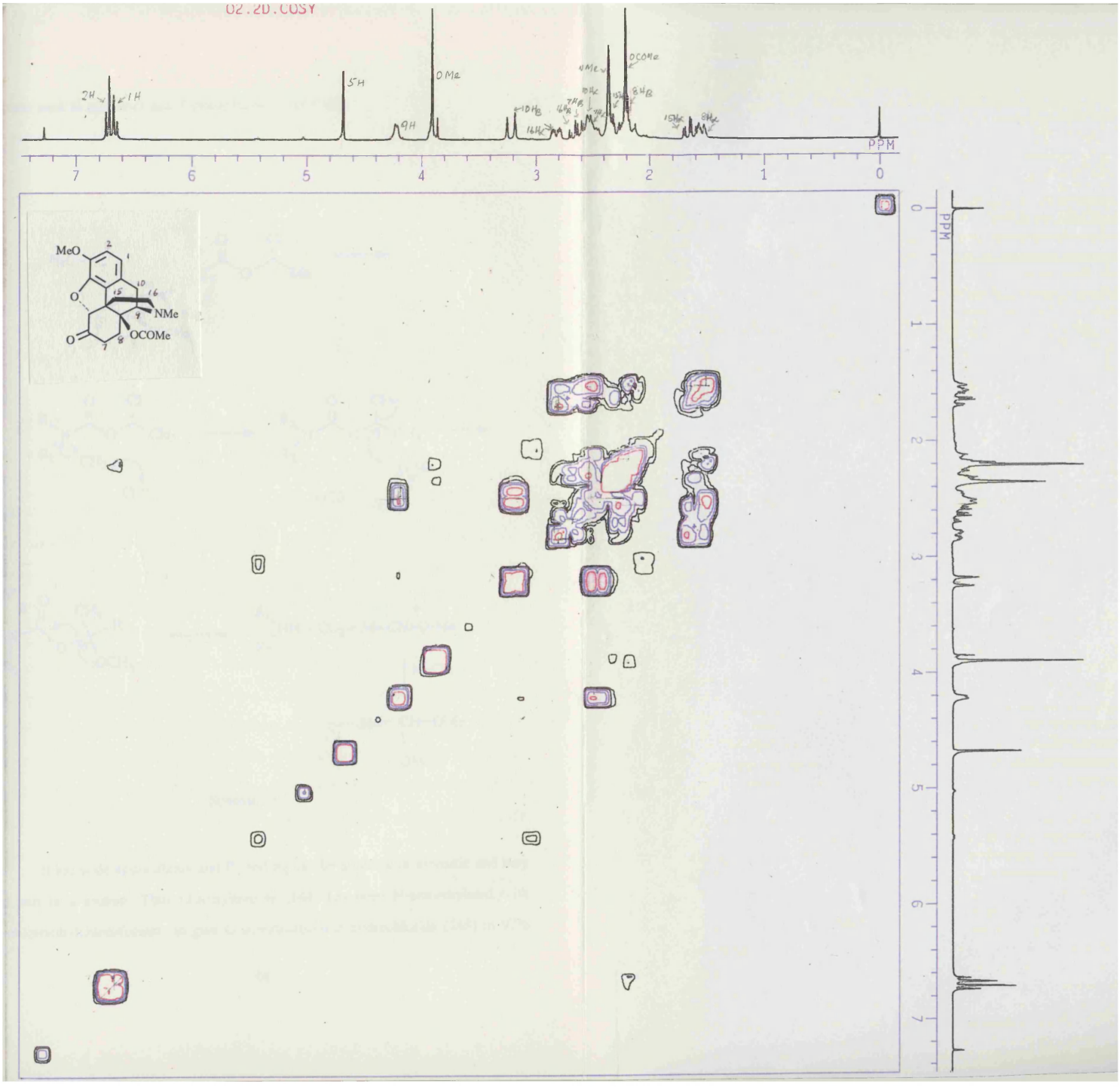
Oxycodone (**104**) has a free hydroxyl group at C-14 and it is necessary to protect this group before attempting N-demethylation reactions. This can be done, for example, by acetylation. Thus 14-acetyloxycodone (**143**) was prepared by

heating oxycodone under reflux with acetic anhydride.

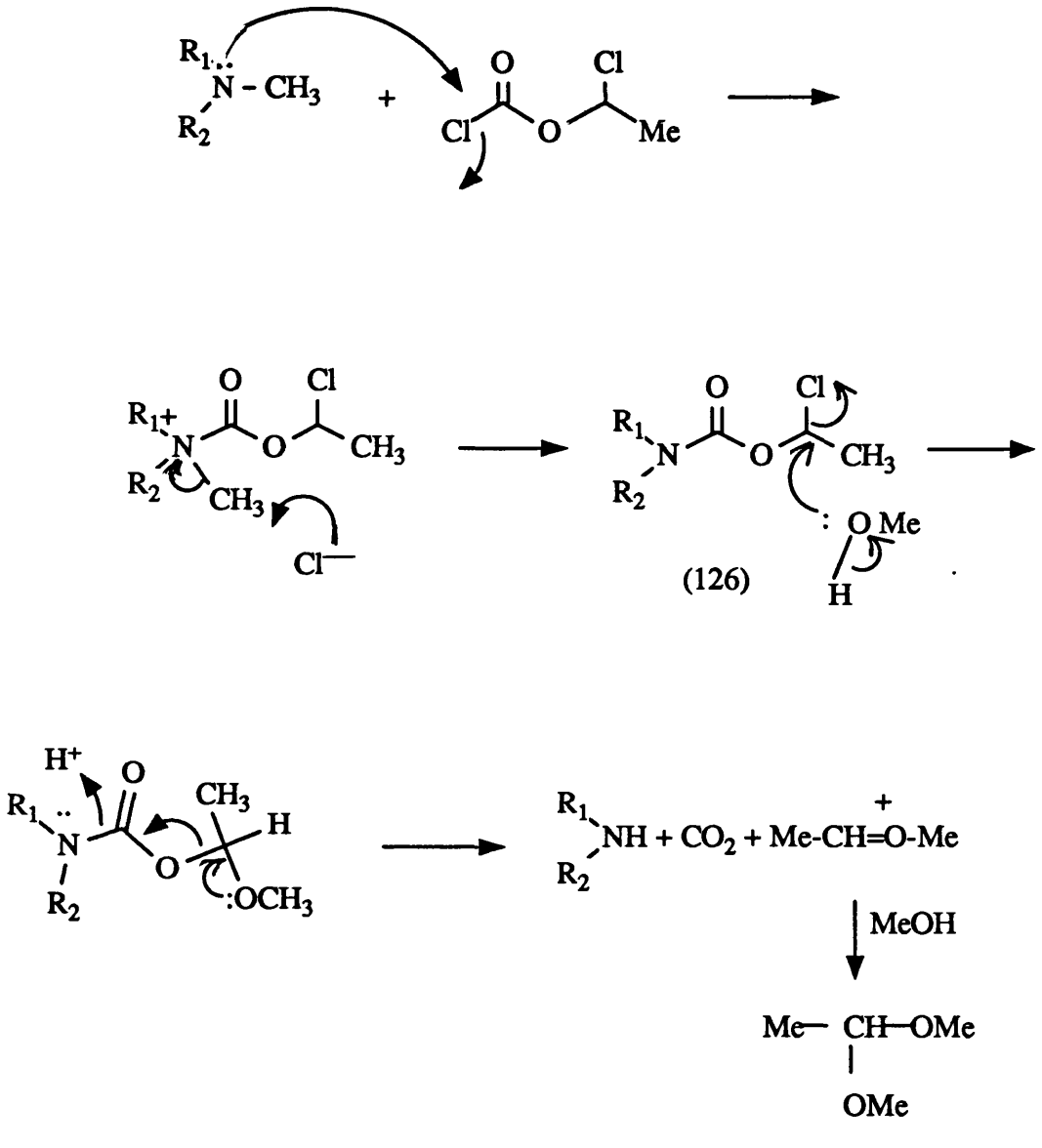
An ^1H n.m.r. spectrum of 14-acetyloxycodone (**143**) was recorded at 400 MHz. The three-proton singlets at δ 2.19, 2.32 and 3.89 were assigned to the resonances arising from the N-CH_3, $COCH_3$ and OCH_3 groups respectively. A one-proton singlet at δ 4.67 is due to the resonance of 5-H and the two-proton double doublet at δ 6.64 - 6.72 (J = 8.0 Hz) is that due to the resonances of the 1-H and 2-H protons of the aromatic ring. The rest of the spectrum is quite complex due to the presence of two ethano bridging groups forming part of C-ring and D-ring. The protons of the -CH_2-CH- group of B-ring also resonate in this region. A double multiplet at δ 1.54 is due to the resonance of 8-H_α which is coupled to 8-Hβ (J_{gem} = 11.9 Hz) and also to 7-H_α and 7-H_β. The resonance of 8-H_β forms a multiplet at δ 2.18 (J_{gem} = 11.6 Hz). A triplet of doublets centered at δ 1.64 is due to the resonance of 15-H_α (J_{gem} = 14.6 Hz, $J_{15,16}$ = 3.7 Hz).

When the signal at δ 1.64 was irradiated the triplet of doublets at δ 2.28 collapsed to a simple quartet. This double doublet of doublets at δ 2.28 is assigned to the resonance of 15-H_β. The resonance of 16-H_α is observed as a triplet of doublets at δ 2.64 (J_{gem} = 14.6 Hz and $J_{16,15}$ = 5.2 Hz), while that of 16-H_β is exhibited as another double doublet of doublets. The signal of 10-H_β is a doublet at low field (δ 3.21) with a large geminal coupling constant (J_{gem} = 18.6 Hz). Proton 10-H_α resonates at δ 2.5 as a doublet of doublets (J_{gem} = 18.3 Hz and $J_{10,9}$ = 5.2 Hz). The signal of 9-H is a doublet at δ 4.19, which couples with 10-H_α ($J_{9,10}$ = 5.5 Hz). An irradiation of the peak at δ 3.2 changed the quartet at δ 2.5 into a doublet. Also, when the peak at δ 4.2 was irradiated the quartet at δ 2.5 collapsed into a doublet. The final proton assignments were confirmed by a 2D cosy analysis, backed up with data from assignments previously made for similar compounds earlier in the project.

For our first experiments to N-demethylate acetyloxycodone we selected 1-chloroethylchloroformate (**125**). This reagent[89] reacts with tertiary amines to form a carbamate (**126**). This product undergoes scission on treatment with hydroxylated


02.2D.COSY
2H
1H
5H
OMe
9H
NMe
OCOMe
PPM
7
6
5
4
3
2
1
0
MeO
NMe
OCOMe

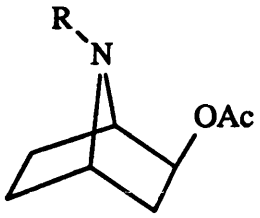
solvents such as methanol and N-dealkylation is achieved.



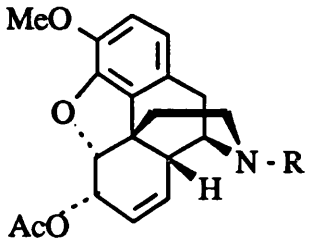
Scheme 23

It has wide applicability and R_1 and R_2 can be aliphatic or aromatic and may be part of a system. Thus O-acetyltropine (**144**) has been N-demethylated with 1-chloroethylchloroformate to give O-acetylnortropine hydrochloride (**145**) in 97%

yield, 6-acetylcodeine (**146**) to 6-acetylnorcodeine (**147**) in 97% yield, and oxycodone (**104**) to noroxycodone (**131**) in 86% yield.



(144), R = Me
(145), R = H



(146), R = Me
(147), R = H

14-Acetyloxycodone (**143**) dissolved in 1,2-dichloroethane was heated with 1-chloroethylchloroformate at 65°C for about 20 hours and then at reflux for 2 hours. After evaporation of the volatiles under reduced pressure, the residue was column chromatographed on silica to give the carbamate (**148**) in about 70% yield. An accurate mass determination of the product indicated the molecular formula to be $C_{22}H_{24}NO_7Cl$. The methyl group of $-NCO_2CHClCH_3$ resonates at δ 1.85 as a doublet while the proton of -CHCl- resonates in the aromatic region together with the signals of the 1-H and 2-H protons (δ 6.40 - 6.90). The $N-CH_3$ peak of 14-acetyloxycodone at δ 2.45 was not present in the spectrum.

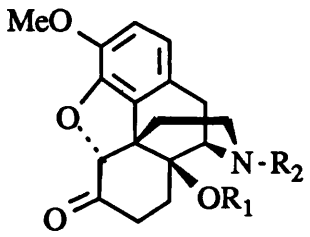
Since the yield of the product (**148**) was less than that expected, the reaction was repeated a number of times under several reaction conditions. Unfortunately we have not achieved any better results by changing the solvent, temperature, the concentration of the reagent or the reaction times.

The carbamate group was next cleaved by treating N-(1-chloro-ethoxycarbonyl)-14-acetylnoroxycodone (**148**) at reflux in methanol. This gave 14-acetylnoroxycodone (**149**) which was then heated with 6M hydrochloric acid at

100°C for 4-5 hours to hydrolyse the acetyl group and to give noroxycodone (**131**).

The ^1H n.m.r. spectrum of noroxycodone (**131**) exhibits multiplets between δ 1.56 and 3.2 for the resonances of eleven protons (7-H_2, 8-H_2, 9-H, 10-H_2, 15-H_2 and 16-H_2). Spin-spin coupling patterns were similar to those of 14-acetyl oxycodone described on page (83). The methoxyl protons resonate as a singlet at δ 3.90 and the resonance of 5-H gives rise to another singlet at δ 4.66. The 14-OH proton resonates at a broad singlet at δ 4.94 and a double doublet at δ 6.62 - 6.73 (J = 8.2 Hz) is due to the resonance of 1-H and 2-H. The IR spectrum of noroxycodone shows a broad peak at 3200-3500 cm^{-1} (OH and NH) and a sharp band at 1718 cm^{-1} (CO).

The best overall yield we obtained for the conversion of oxycodone to noroxycodone was 68 - 69%, though the literature claim is 86%. However, we find that if the N-demethylation experiment is carried out without purifying any of the intermediate compounds, an overall return of material representing 85 - 88% of the starting material can be obtained, but this is a mixture of oxycodone and noroxycodone.



(148), R_1 = COMe, R_2 = $CO_2CHClCH_3$

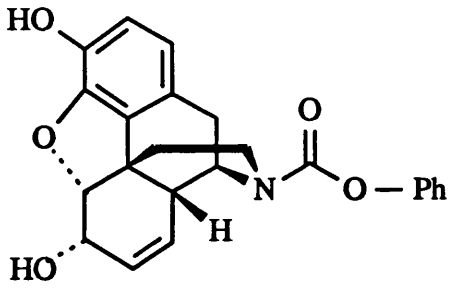
(149), R_1 = COMe, R_2 = H

(150), R_1 = COMe, R_2 = $CO_2CH{=}CH_2$

R.A.Olofson *et al.*[127] used vinyl chloroformate[128,129] for the selective N-demethylation of tertiary amines. We tried this reagent for the N-demethylation of oxycodone. First 14-acetyloxycodone (**143**) was prepared and a solution of it in 1,2-dichloroethane was treated with vinyl chloroformate at 50°C. The reaction is very slow. So heating the mixture for 4-5 days with 10 molar equivalents of vinyl chloroformate became necessary for the completion of the reaction. Eventually, however, N-vinyloxycarbonyl-14-acetylnoroxycodone (**150**) was obtained in high yield and this was dissolved in dichlormethane and reacted with hydrogen chloride gas. When the solvent was removed and residue heated at reflux with methanol the carbamate group was cleaved off. Eventually the O-acetyl group was removed by the procedure described earlier, or by heating the product 14-acetylnoroxycodone with 25% sulphuric acid at 100°C for 5 hours. In either case noroxycodone was prepared in ≈ 88% yield.

In 1972 Abdel-Monem and Portoghese[130] reported the use of phenyl chloroformate[131] for the N-demethylation of morphine and codeine. They treated morphine with phenyl chloroformate in presence of potassium carbonate in boiling chloroform to obtain N-phenoxycarbonylnormorphine (**151**). The carbamate group of this compound was then removed by reaction with ethanolic potassium hydroxide. This method was revised by Rice[132] who used a 1:1 mixture of 64% and 95% hydrazine to cleave the N-phenoxycarbonyl group.

Later, Rice and May[133] found that either normorphine or norcodeine prepared by this method were contaminated with a small quantity of the corresponding dihydro derivatives formed by reduction with hydrazine. They then modified the procedure and according to their revised method, a mixture of morphine, potassium carbonate and chloroform was heated under reflux for 20 hours. After filtration, the solvents were evaporated and the product mixture was



(151)

treated with 95% hydrazine under reflux for 7-8 hours. The final product was then isolated from the reaction mixture.

Oxycodone was thus N-demethylated by using phenyl chloroformate according to the modified procedure of Rice, a 56% yield of noroxycodone was obtained.

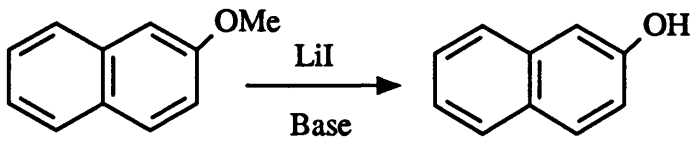
Ethyl chloroformate,[81] benzyl chloroformate and 2,2,2-trichloroethyl chloroformate[87] are three other chloroformates used for N-demethylation. When we tried to demethylate oxycodone by heating it under reflux with a mixture of ethyl chloroformate, potassium carbonate and chloroform for a week, we found that the N-carbamate ester was formed only in 15 - 20% yield.

Montzka *et al.*,[134] recommended 2,2,2-trichloroethyl chloroformate as a demethylating agent, employing a procedure similar to that used with phenyl chloroformate.[130] Here the intermediate carbamate is cleaved by reduction with zinc in acetic acid or methanol. In our hands, this method gave only a 10% yield of noroxycodone.

3.4 O-Demethylation

Many natural products contain aryl rings bearing methoxy groups and although phenols are metabolised first either by the 'shikimate' or the 'acetate' biosynthetic pathways, O-methylation of the products through the agency of S-adenosyl methionine (or an equivalent) is a frequent final step. Often the methyl ether is then released from the assembling enzyme system without further elaboration.

O-Demethylation of aryl methyl ethers is not normally a biosynthetic process, but it is one often required synthetically. In our case we were asked to find a commercially viable means of converting oxycodone (**104**) into oxymorphone (**105**). The latter compound is a very useful starting material for a range of opiate drugs. Clearly the need was for a high yielding reaction involving a relatively non-toxic reagent. From the long list of possible O-demethylating agents our first selection was lithium iodide,[135] which under anhydrous conditions is known to cleave aryl methyl ethers. This reagent is easily handled and is normally used in conjunction with a base, such as 2,4,6-collidine. Harrison,[136] for example, claims a quantitative yield for the conversion of 2-methoxylnaphthalene (**152a**) into 2-naphthol (**152b**).

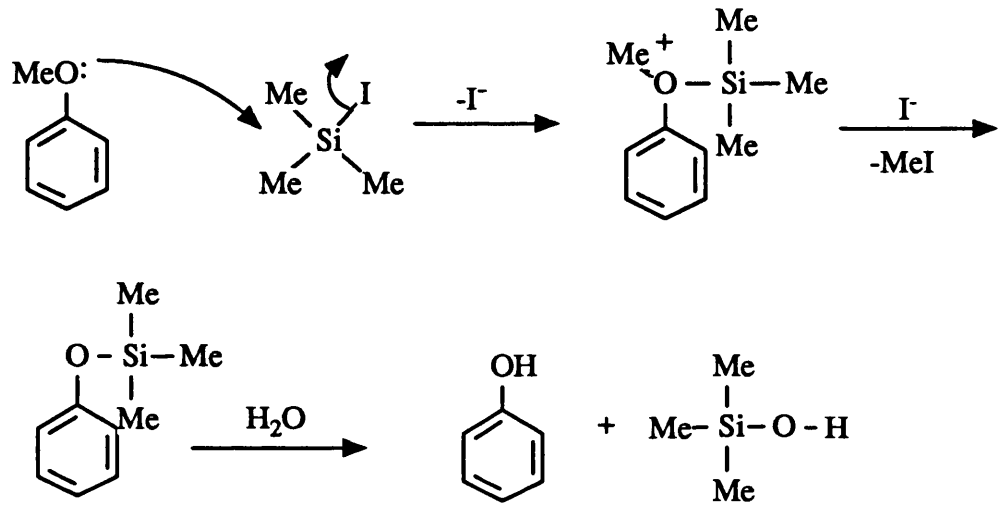


(152a) (152b)

Scheme 24

When we applied this reaction to oxycodone, however, only starting material was recovered.

Trimethylsilyl iodide[137] is another recommended reagent. It is known to cleave alkyl aryl ethers and alkyl esters when they are heated together in an aprotic solvent such as carbon tetrachloride or deuteriochloroform at about 50°C. Yields are claimed to be very high (80 - 95%). It was observed by other workers that the reaction is less successful for aryl methyl ethers although phenols have been obtained in moderate to low yields.[138] The mechanism of the reaction is as follows.



Scheme 25

When applied to oxycodone, however, the maximum yield of oxymorphone obtained was 15 - 20%, the remainder being recovered starting material.

A modification of the reaction, due to Olah,[138] requires that trimethylsilyl iodide is replaced by phenyltrimethylsilane and iodine. This has been superceded, however, by the use of a mixture of chlorotrimethyl silane and sodium iodide.[139] Disappointingly, neither process is satisfactory for the demethylation of oxycodone.

Lithium diphenylphosphide[140] was tried next. The reagent was prepared by treating chlorodiphenylphosphine with lithium metal in dry THF and stirring the mixture for 2 hours. The recommended literature procedure[141] for demethylation of aryl ethers is to heat the ether in dry THF with lithium diphenylphosphide reagent.

$$PhOMe + Ph_2P^- Li^+ \longrightarrow PhO^- + Ph_2OPMe + Li^+$$

When reacted with oxycodone lithium diphenylphosphide produced at least five compounds as seen by TLC analysis of the product mixture, none of which corresponded to required oxymorphone (**105**).

Of course, hydrogen bromide[100] has proved to be an effective reagent for the fission of many type of ethers and it is claimed to be effective for the conversion of oxycodone (**104**) into oxymorphone (**105**). When we repeated the reaction with oxycodone, the yield of oxymorphone was 61% with 17% unchanged oxycodone recovered.

Boron tribromide[142-145] is another reagent widely used for the purpose of O-demethylation. Rice[97] reports that codeine can be O-demethylated to morphine in 90% yield by treatment with boron tribromide in chloroform at room temperature. The reaction time is only 20 minutes. When we tried the reaction upon oxycodone we obtained oxymorphone in 50% yield and it was not possible to improve upon this productivity by altering the conditions. Boron tribromide, like hydrogen bromide, is toxic and corrosive and one reason we were commissioned to do this study was to attempt to avoid the use of such reagents.

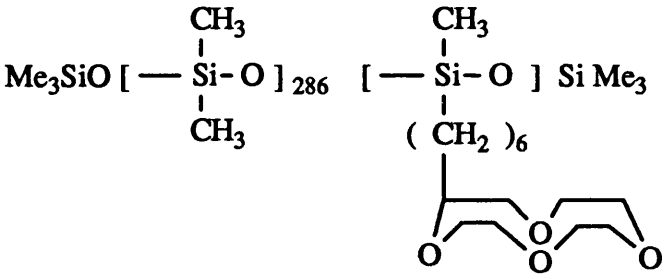
Fusion of codeine with pyridine hydrochloride at 190°C provides morphine in low yield. This method has been used by Rapport[44], by Gates[37] and by Goto[146] in

synthetic routes to morphine. Unfortunately, the separation of the phenol from the spent reagent is not simple and this tends to limit the yield of morphine to 15 - 34%. Applied to the conversion of oxycodone to oxymorphone we obtained only to a 10% yield of the required compound. A similar yield was recorded when oxycodone was treated with propane-thiol in dimethylformamide a procedure recomended by Lawson and DeGraw[101] for similar molecules.

At the end of this investigation we found that for the O-demethylation process we were unable to recommend any better reagent than hydrogen bromide, and even so a mixture of product and starting material was produced. A similar situation was presented by N-demethylation, although here, at least, the reagent 1-chloroethylchloroformate seemed to offer a reasonable yield of noroxycodone from oxycodone.

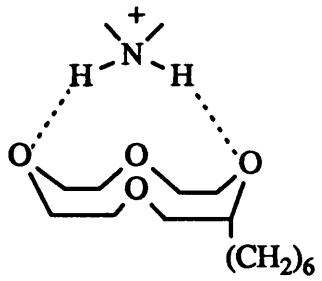
3.5 Separation of noroxycodone (131) from a mixture containing oxycodone (104)

Separation of products and starting materials is a common enough problem to industrial companies and frequently unreacted compounds are simply recycled. We used column chromatography to separate our mixtures but this technique is not viable on a commercial scale except for very valuable chemicals. Drs. Brisdon and England[147] at Bath have shown that it is possible to separate protonated secondary amines from tertiary amines by liquid-liquid extraction. A dilute solution of the amines is acidfied and extracted with 12-crown-4 functionalised polysiloxanes **(153)**.



(153)

The polysiloxane provides a mobile hydrophobic phase and the crown ether bonded to it 'captures' the conjugate acid of the secondary amine by hydrogen bonding (Fig. 8). This technique has been used at Bath to separate codeine and norcodeine.



Protonated secondary amine - polysiloxane complex

Fig 8..

The method works best for solutions containing 1% of the bases, but it can be made continuous and in principle as pure materials are removed, more mixture can be added. We sought to use the technique to separate oxycodone and noroxycodone, but we were very disappointed to find that using HPLC to analyse the extent of separation only 6% of the noroxycodone was taken up by the polysiloxane/crown after a period of 24 hours as against the 25% separation reported of norcodeine from a codeine-norcodeine mixture.

A variant of the method uses a membrane of the polysiloxane/crown to separate two aqueous phases. One of these contains the amine mixture, but with time the secondary amine, which in its protonated form binds initially to the membrane surface, translocates through the membrane and passes into the hitherto amine free compartment. In a sense, this has analogies with osmotic separations and it is necessary to continually remove the secondary amine by solvent extraction so as to maintain a concentration gradient between the solutions.

We have as yet not fully investigated this procedure, but our initial attempts were not encouraging and probably reflect differences in basicity between noroxycodone and norcodeine itself.

3.6 A New Synthesis of Noroxymorphone

The introduction of 14-hydroxyl group into morphines enhances their analgesic activity. 14-Hydroxydihydromorphinone (oxymorphone, **105**) is a powerful analgesic and its N-nor analogue, 14-hydroxydihydronormorphinone (noroxymorphone, **106**) is an important intermediate for naloxone (**107**), nalmexone (**108**), naltrexone (**109**) etc. Some of these products are pure antagonists, while others have mixed agonist-antagonist properties.

There are two established methods for the preparation of noroxymorphone, one due to Schwartz and Wallace (Scheme 19) (see p. 58) utilizes codeine as the starting material, while the other begins with thebaine (Scheme 20) (see p. 59). The latter is used commercially, despite the fact that thebaine is expensive and relatively unstable. This uses toxic cyanogen bromide method also.

Our aim was to prepare noroxymorphone by a method suitable for industrial use from another source other than thebaine. Since O-demethylation of codeine is difficult to achieve, the obvious choice of starting material is morphine. Morphine is also the most abundant alkaloid of opium and hence the cheapest.

If morphine is selected then the following steps were envisaged:

(1) Selective protection of the phenolic hydroxyl group.

(2) Oxidation of the alcoholic group to the corresponding ketone.

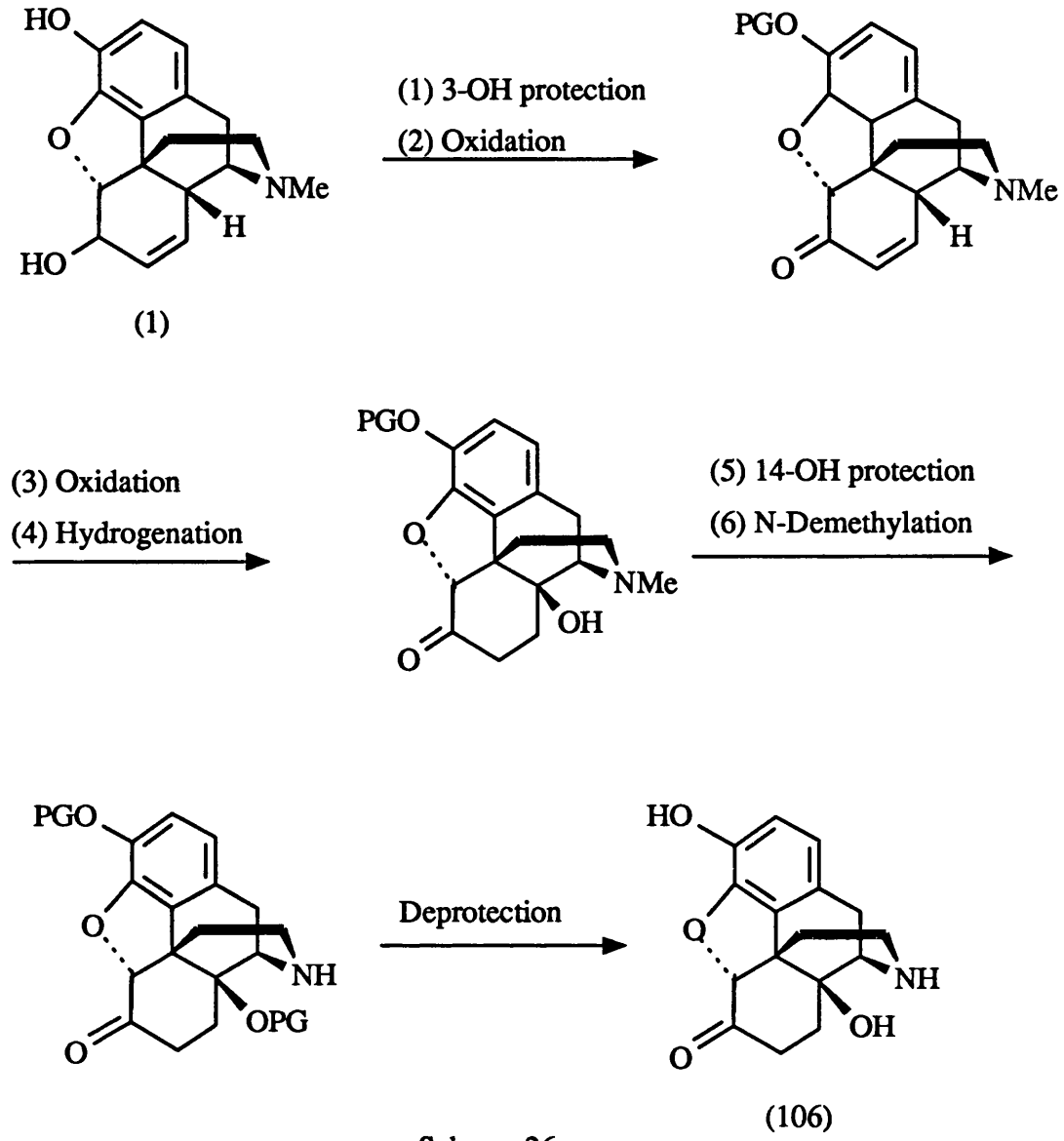
(3) Reduction of double bond of ring C.

(4) Introduction of hydroxyl group at C-14.

(5) N-Demethylation, perhaps after protection of the C-14 hydroxyl group.

(6) Deprotection.

A summary of these steps is shown in scheme 26.



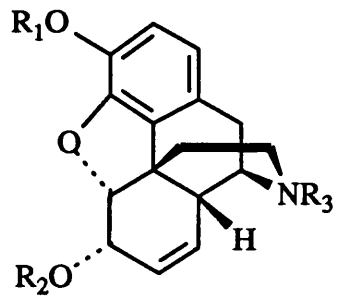
Scheme 26

Hydroxyl Protection

Step 1 is required since oxidation of morphine is known to give complex mixtures. The problem is the phenolic nature of the alkaloid, a fact substantiated by the observation that its O-methyl ether, codeine, is oxidised without difficulty. We have commented already that codeine is not a good starting material yet we were precluded from O-acylation since this gives rise to schedule 1 derivatives.

3,6-Diacetyl morphine, for example, is better known as "heroin".

Our choice was thus a silyl protecting group which has the advantage of easy removal. One widely used reagent is *t*-butyl dimethylsilyl chloride which reacts with both alcoholic and phenolic hydroxyl groups in the presence of a base to yield the appropriate *t*-butyldimethylsilyl (TBDMS) ether. This has been used by Arzeno *et al.*[148] and by Matthews and Sainsbury[149] to protect the 6-OH group of codeine. In practice the reaction works well and in the presence of two equivalents of imidazole in dimethylformamide solution a 70% yield of 3,6-*bis* (TBDMS) morphine (**154**) and 22% yield of 3-TBDMS morphine (**155**) were obtained. Here two equivalents of TBDMS chloride were used; but when this concentration was raised to three equivalents and the proportion of imidazole was increased to five equivalents the isolated yield of the disilyl ether (**154**) was 98%. Furthermore, no heating is required and simply stirring the reaction mixture under a nitrogen atmosphere overnight is sufficient. Physical data for the product are provided in the experimental section.



154, $R_1 = R_2$ = TBDMS, R_3 = Me

155, R_1 = TBDMS, R_2 = H, R_3 = Me

156, $R_1 = R_2 = CH_2$=CHCO, R_3 = OCOCH=CH_2

157, $R_1 = R_2$ = TBDMS, R_3 = OCOCH=CH_2

94, $R_1 = R_2 = R_3$ = H

Normorphine

With this doubly protected compound to hand we tried to change the order of reactions previously outlined and attempted a N-demethylation experiment upon it. Olofson *et al.*[150] have effected N-demethylation of morphine itself using vinyl chloroformate as reagent. This gave 3,6-dihydroxy protected N-vinyl carbamoyl morphine derivative (**156**) in 91 % yield, but this compound had to be N-deprotected by treatment with hydrogen bromide, prior to the removal of the 3-0- and 6-O-substituents by hydrolysis with dilute hydrochloric acid. The last reaction required 8 hours. When we reacted the disilyl ether (**154**) with vinyl chloroformate we were pleased to find that 3,6 *bis* (TBDMS)-N-vinyloxycarbonylnormorphine (**157**) was obtained in quantitative yield. This product could be converted into normorphine by either of the following methods.

(a) The carbamate (**157**) in dichloromethane solution was treated with hydrogen chloride gas and the solvent removed by evaporation under reduced pressure. The residue was then warmed with methanol.

(b) The carbamate was simply heated with methanol containing a few drops of concentrated hydrochloric acid.

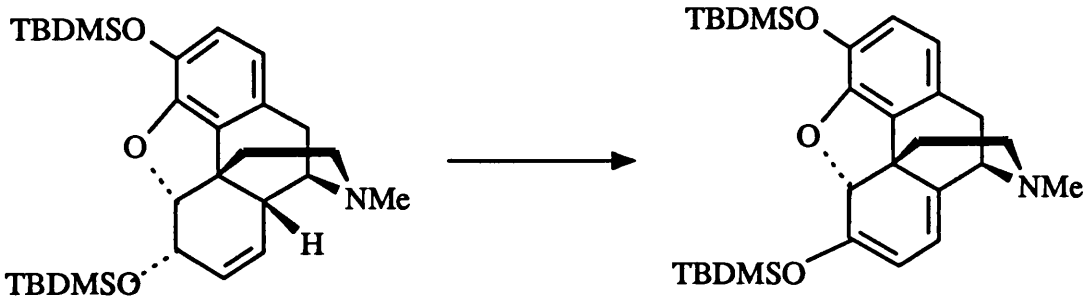
Either way the product normorphine (**94**) was isolated in greater than 95% yield. In a separate experiment, 1-chloroethyl chloroformate was used as the demethylating agent and a 80% yield of normorphine was obtained, details of the experiment are given in the experimental section.

In some other reactions an attempt was made to N-demethylate the disilyl ether (**154**) with *t*-butyl hydroperoxide in the presence of a catalytic amount of ruthenium (II) tri(triphenylphosphine)dichloride [$RuCl_2(PPh_3)_3$]. This reagent combination has recently been introduced by Murahashi *et al.*[151] for the demethylation of N-methyl tertiary amines. However, it totally failed to effect any N-demethylation of the disilyl ether (**154**), even after it was heated under reflux with

the reagent and catalyst in benzene solution for 3 hours.

Attempt to introduce diene system in C-ring

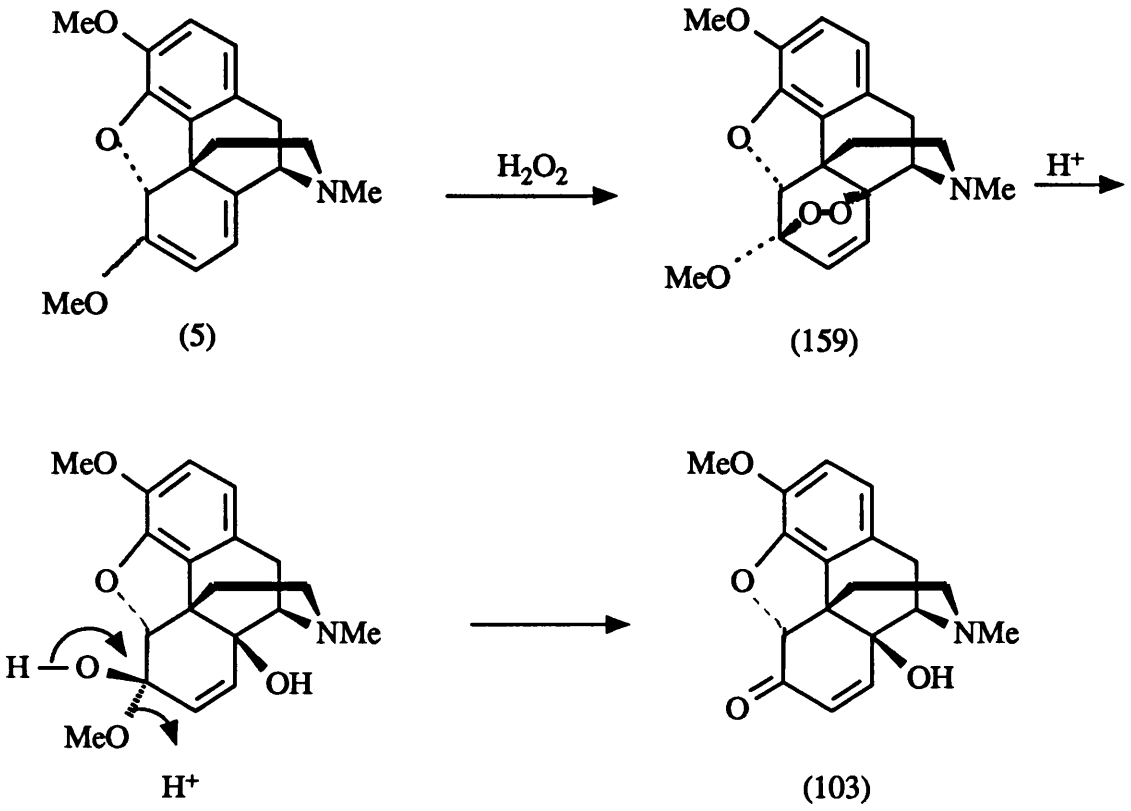
We also considered the possibility of introducing a diene system into ring-C of the 3,6-*bis* (TBDMS) morphine (**154**) in the anticipation that we might be able to hydroxylate the derivative (**158**) at C-14 through reaction with hydrogen peroxide.



(154) (158)

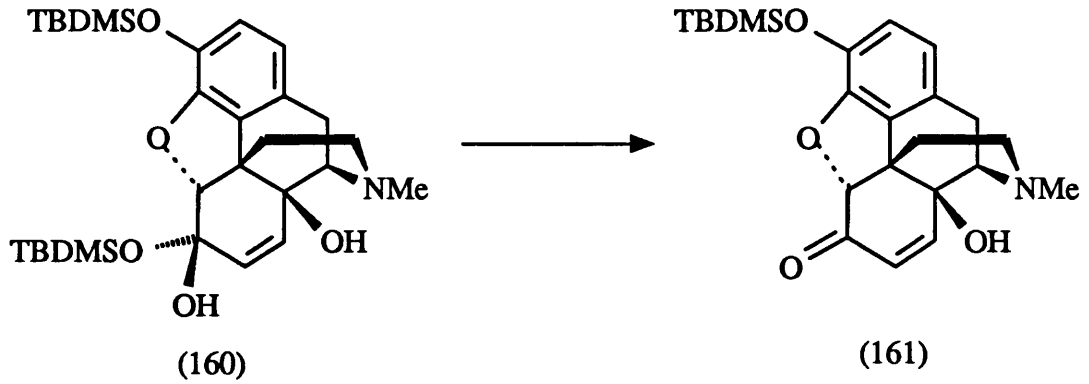
Scheme 27

This type of reaction is known to occur with thebaine (**5**) where it is proposed that the initial product is an endoperoxide (**159**), which then cleaves and eliminates methanol.



Scheme 28

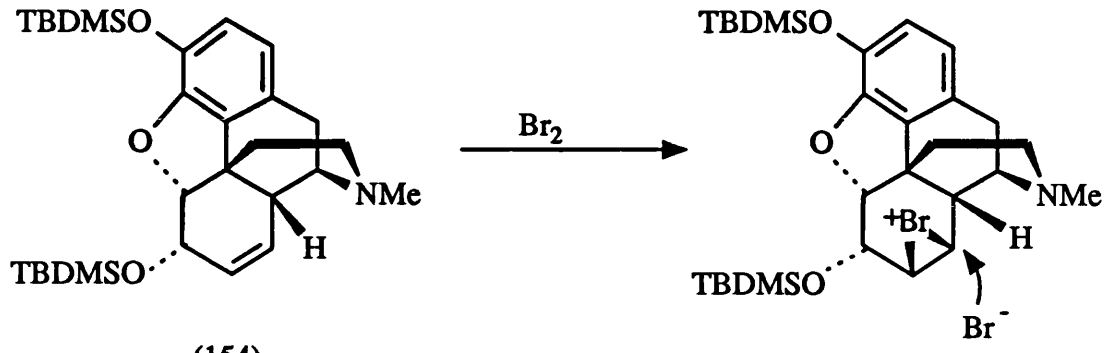
If successful this should afford the corresponding silyloxydiol (**160**) which on further reaction would give 3-TBDMS-14-hydroxymorphinone (**161**).



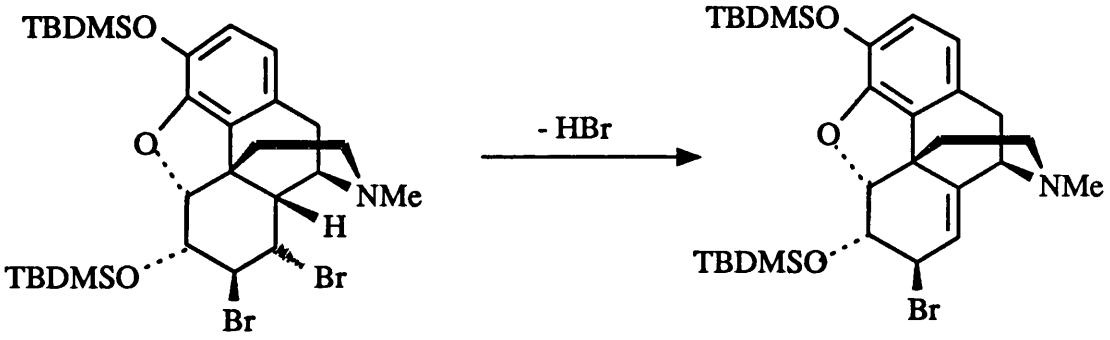
Scheme 29

One way to insert the diene system would be to brominate the disilyl ether at

C-7 and then to cause elimination of hydrogen bromide by treatment with base.

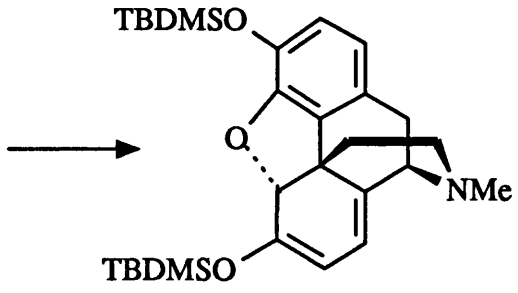


(154)



(162)

(163)

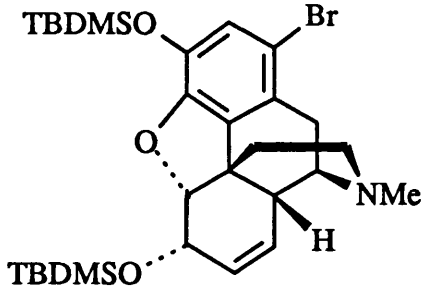


(158)

Scheme 30

One problem with this approach, is highlighted in the above scheme, namely the α-orientated bulky silyloxy group at C-6 would dictate the formation of a β-bromonium ion intermediate. If bromine itself was the reagent then this would lead to the *trans*-dibromide and thus the expected product would be the monobromo compound (**164**) rather than the diene (**158**) since it is not possible to attain the usual *trans* antiperiplanar transition state geometry for the elimination of the second molecule of hydrogen bromide.

In the event, bromination of the disilyl morphine (**154**) with N-bromoacetamide in methanol at 0°C gave a monobromo derivative $C_{29}H_{46}Si_2BrNO_3$ in 33% yield. The ^1H n.m.r. spectrum of this compound exhibited a one proton singlet at δ 6.84 in place of the AB double doublet (δ 6.4 - 6.8) expected for the 1-H and 2-H resonances of the disilyl ether. No other significant changes in the spectra of the starting material and product were noted suggesting that the product is 1-bromo-3,6 *bis* (TBDMS) morphine (**164**).

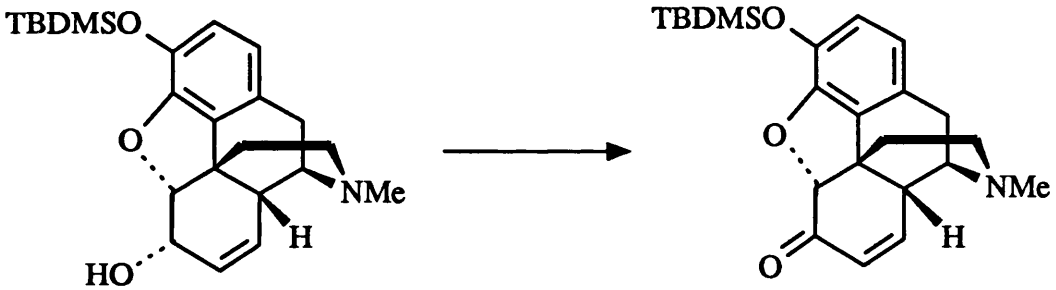


(164)

The formation of the 1-bromoderivative (**164**) did not encourage us to proceed with this route.

Oxidation

At this point we returned to our original plan namely to oxidise 3-(TBDMS) morphine (**155**) to 3-(TBDMS)morphinone (**165**) (Scheme 31). This requires selective deprotection of the disilyl ether (**154**) and this posed a problem. This difficulty was solved by forming the anion of morphine, through reaction with sodium ethoxide, and treating it with 1.5 molar equivalents of TBDMSCl. No imidazole was added. The yield of 3-(TBDMS) morphine (**155**) obtained was 99% and it is noteworthy that if only 1.1 molar equivalent of TBDMSCl are used the yield falls to 91%. The ^{1}H n.m.r. spectrum of the product exhibits the 6-hydroxyl proton signal as a broad doublet at δ 2.81, but in other respects the chemical shifts and spin-spin coupling patterns are similar to that shown in the spectrum of 3,6 *bis* (TBDMS) morphine (**154**).



(155) (165)

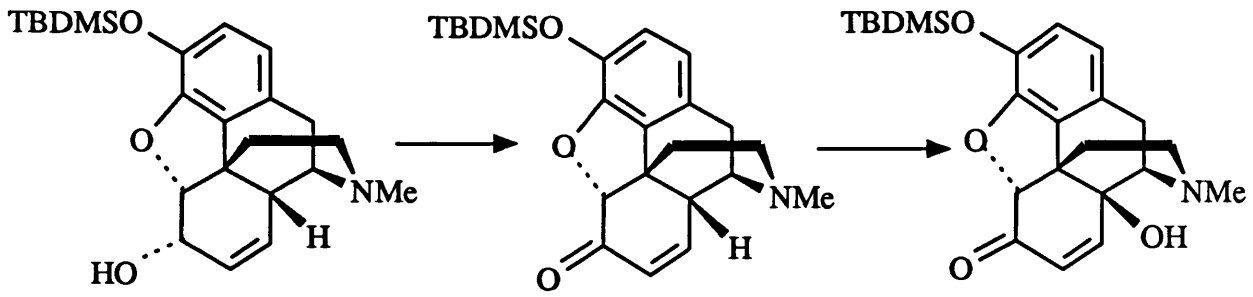
Scheme 31

Oxidation of 3-(TBDMS) morphine

A mild cheap oxidising agent for allylic alcohols is manganese (IV) oxide, a reagent which is easily removed at the end of the reaction and which is far less of an environmental hazard than, say, a chromium based oxidant.

When a chloroform solution of 3-(TBDMS) morphine (**155**) was stirred for 30 minutes with 'activated' manganese (IV) oxide, TLC analysis (Silica, $CHCl_3$: MeOH = 9 : 1) showed that two compounds had been formed. After 48 hours, however, a single product was present. This compound exhibited a molecular ion peak at *m/z* 413, 16 mass units greater than expected for the morphinone (**165**). Hydroxylation as well as oxidation to the 6-hydroxyl group was indicated and the ^1H n.m.r. spectrum revealed a simplified set of resonances for the signals of 7-H and 8-H. In the starting compound these occur as multiplets centered at δ 5.30 and 5.70 while in the new compound they form two simple AB related doublets (J = 10.1 Hz) at δ 6.16 and 6.61.

The multiplicity of 8-H resonance in the starting material is in part due to spin-spin coupling to the signal of 14-H, thus since we were anticipating oxidation of the 6-hydroxyl group to a carbonyl group with the evitable loss of 6-H, the cause of the spectroscopic change must be the formation of the hydroxyenone (**166**). The formation of such a product would, of course, explain the downfield shift of the signals of 8-H and particularly 7-H.



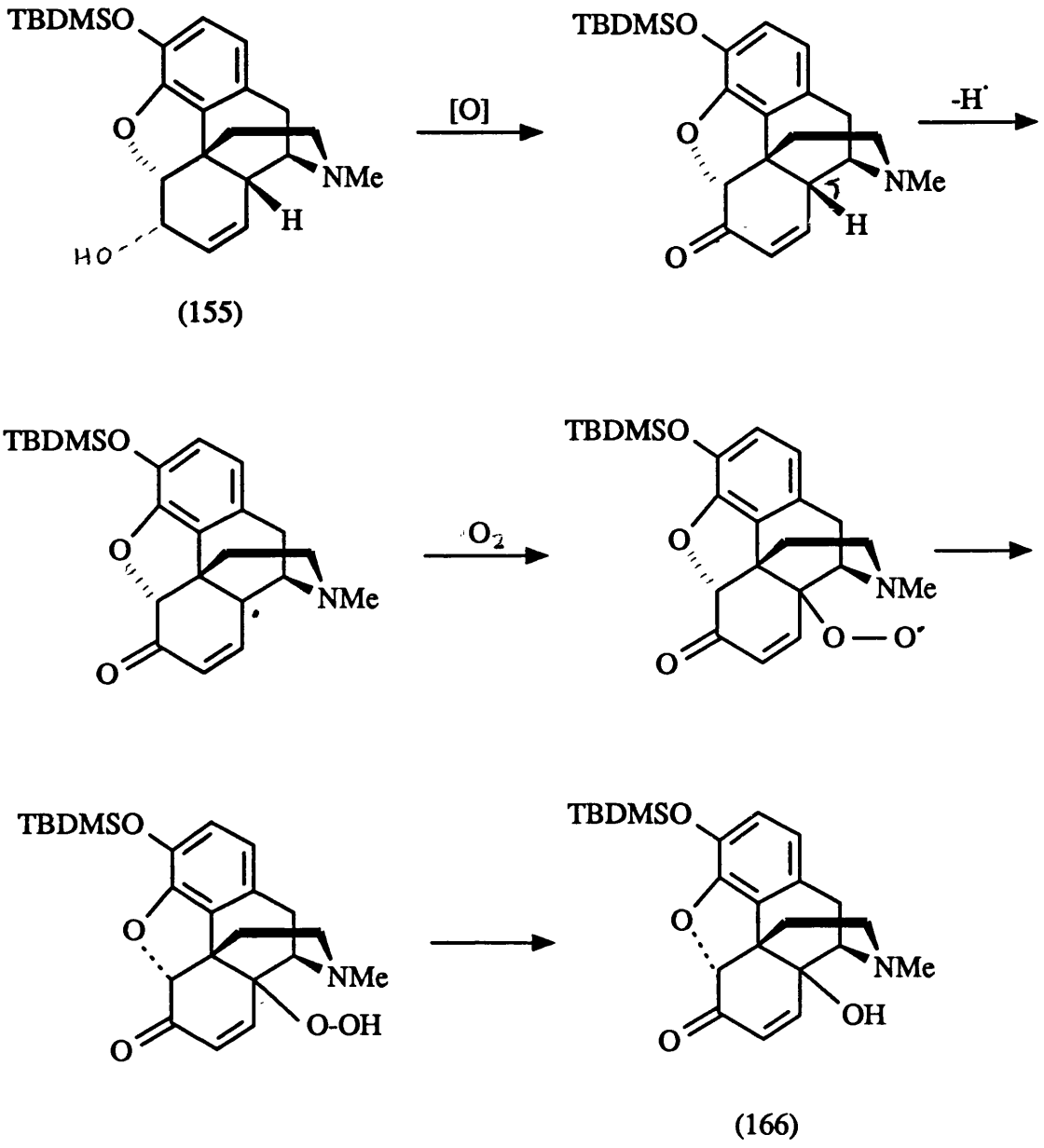
(155) (165) (166)

Scheme 32

Indeed reference to the spectrum shows that a signal for 14-H is absent and that of 9-H is now a doublet at δ 3.03 (J = 5.9 Hz) coupled only to the signal of 10-H. A broad exchangeable (1H) resonance is present at δ 5.4 due to the 14-hydroxyl proton and further proof that we have made the correct structure assignment comes from the infra red (ν_{max}3340, 1670 cm^{-1}) and the ^{13}C n.m.r. spectra. In the latter a new singlet peak occurs at δ 68 whereas normally the resonance of C-14 occurs as a doublet at δ 40 - 41.

This result was extremely pleasing for we had succeeded in bringing about what we might have anticipated as the single most difficult step in the synthesis of 14-hydroxydihydronormorphinone.

We envisage that this must be a radical mediated reaction and that after oxidation at C-6, the C-14 position is oxidised. Perhaps a hydroperoxy radical is formed which then decomposes to a hydroxyl group. Such allylic oxidation processes are common in lipid peroxidation.



(155)

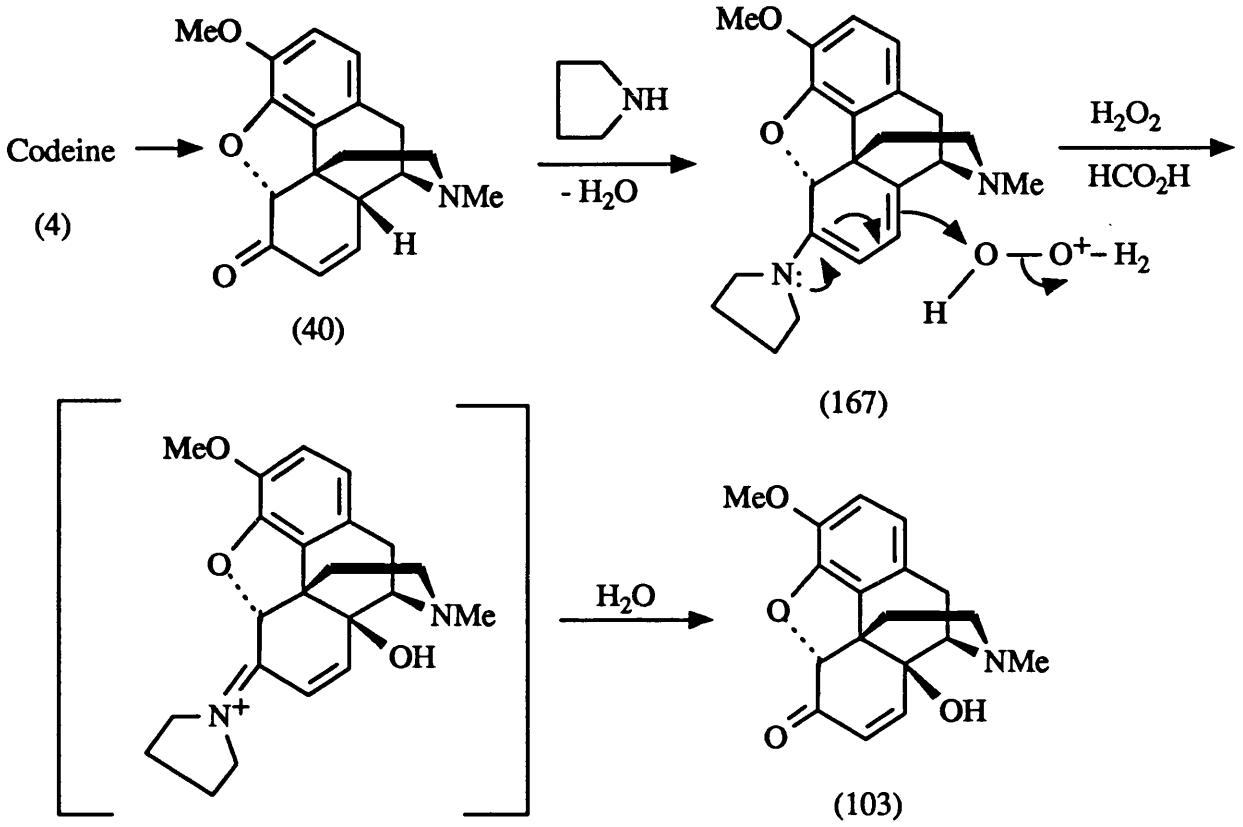
(166)

Scheme 33

Our enthusiasm for this chemistry was only tempered by the low yield of 35%. Two options were open either: (a) to try and improve the oxidation step, or (b) to seek an alternative route.

We noted that codeine (**4**) can be easily oxidised to codeinone (**40**) by treatment with chromic acid. The ketone can then be converted into the dienamine

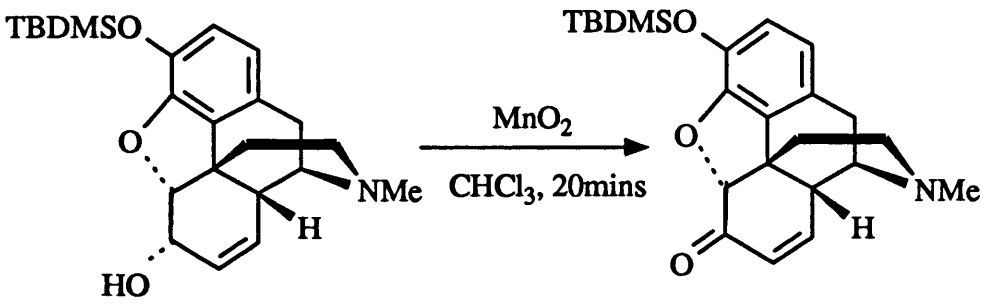
(**167**) by reaction with pyrrolidine in the presence of *p*-toluene sulphonic acid;[152] and this product may then be oxidised with 30% hydrogen peroxide-formic acid to 14-hydroxycodeinone (**103**) (Scheme 34).



Scheme 34

We were encouraged by this result and considered applying to the oxidation of 3-(TBDMS) morphinone (**165**). The starting material was prepared by treating 3-TBDMS morphine (**155**) in chloroform with manganese (IV) oxide. When the reaction mixture was stirred at room temperature for 15-20 minutes it was noted that most of the starting material was converted into the corresponding ketone. (R_f = 0.43, $CHCl_3$: MeOH = 9:1) together with a small amount of the

14-hydroxymorphinone (**166**) (R_f = 0.55, same solvent system). These could be separated by flash column chromatography to give approximately 90% yield of 3-TBDMS morphinone (**165**). The IR spectrum of this compound showed a strong carbonyl band at 1667 cm^{-1} and in the ^1H n.m.r. spectrum the 5-H proton resonance is seen as a singlet at δ 4.66. The signal for 7-H is a doublet at δ 6.63 ($J_{7,8}$ = 10.4 Hz) and that of 8-H is a doublet of doublets at δ 6.07 ($J_{8,7}$ = 10.3 Hz and $J_{8,14}$ = 2.8 Hz). Other features of the spectrum are similar to those of the starting compound.



(155) (165)

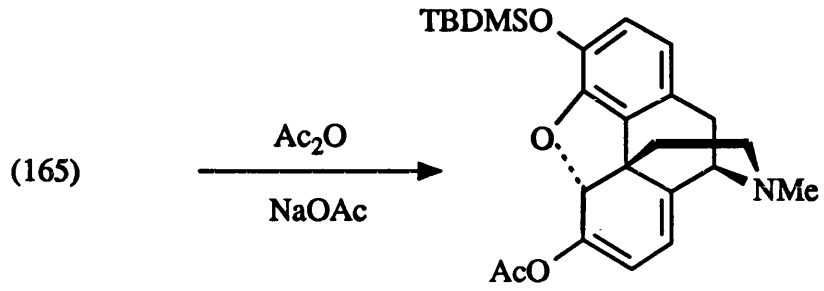
Scheme 35

Alternative ways of generating 3-TBDMS morphinone were also tried, but were generally far less satisfactory. For example, an oxidation with selenium dioxide gave only 15% of product, but a combination of selenium dioxide and *t*-butyl hydroperoxide afforded 43% of the morphinone (**165**), plus 10% of 14-hydroxy-3-TBDMS morphinone (**166**).

Tetra-*n*-propyl ammonium perruthenate (TPAP) has received much publicity as an oxidant[153,154] for alcohols. An oxidation using this reagent in the presence of N-methylmorpholine-N-oxide gave an 86% yield of the morphinone (**165**), but overall this is less efficient than using the inexpensive manganese (IV) oxide.

3-TBDMS morphinone (**165**) was next converted to the dienol acetate (**168**)

by heating it under reflux with freshly fused sodium acetate and acetic anhydride for 1 hour. The yield was 84%.



(168)

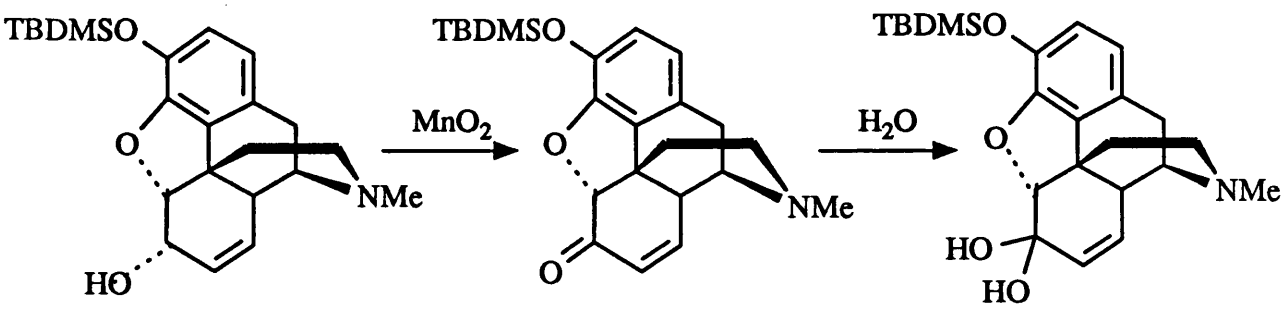
Scheme 36

An attempted oxidation of the dienol acetate (**168**) with hydrogen peroxide in a sulphuric acid - formic acid mixture did not give the 14-hydroxymorphinone (**166**) or any other tangible product.

We thus returned to the direct oxidation of 3-TBDMS morphine (**155**) to (**166**) with manganese (IV) oxide, and sought to improve upon the previous yield. This reaction was repeated under a number of different reaction conditions, thus different solvents such as dichloromethane, tetrahydrofuran, acetone etc., were tried, but it was found that no advantage was to be gained over the use of chloroform. When carefully dried chloroform was used as solvent and the reaction was carried out under nitrogen, we discovered that oxidation had taken place only to a limited extent, even after stirring the reaction mixture for two days.

Activated manganese (IV) oxide (Attenburrow oxide) was next prepared according to the literature method[155] and used in the reaction. This proved less efficient than the commercial sample of activated manganese (IV) oxide as supplied by Aldrich Chemicals. This gave a better yield and a cleaner product.

The conversion of 3-TBDMS morphine(**155**) to 3-TBDMS-14-hydroxymorphinone (**166**) takes about two days to complete with ordinary stirring of the reaction mixture. When the reaction was carried out with an ultrasonic vibrator, the starting material decomposed. Repetition with varying amounts of manganese (IV) oxide showed that at least 8-10 times (the weight of morphine) oxidant was necessary to minimise the reaction time and to optimise the yield. Interestingly, when 2-3 drops of hydrogen peroxide were added to the reaction mixture and the reaction was followed by TLC for 3 days only partial conversion to the 3-TBDMS morphinone was noted. No 14-hydroxyl-3-TBDMS morphinone (**166**) was formed. Manganese (IV) oxide and hydrogen peroxide react to produce water and it seems possible that the morphinone may be protected as its hydrate. (Scheme 37)



Scheme 37

Indeed when the mixture containing 3-TBDMS morphine and 3-TBDMS morphinone was stirred with some 4Å molecular sieves and left stirring overnight both compounds were oxidised to 14-hydroxy-3-TBDMS morphinone (**166**).

When the oxidation process, without hydrogen peroxide, was carried out in presence of molecular sieves, oxidation to the 14-hydroxymorphinone was complete within a day and the yield was increased to about 40%. Some anhydrous sodium

carbonate present in the reaction mixture did not favour the formation of 14-hydroxymorphinone, but the addition of silica gel increase the speed of reaction as well as the yield of 3-TBDMS-14-hydroxymorphinone.

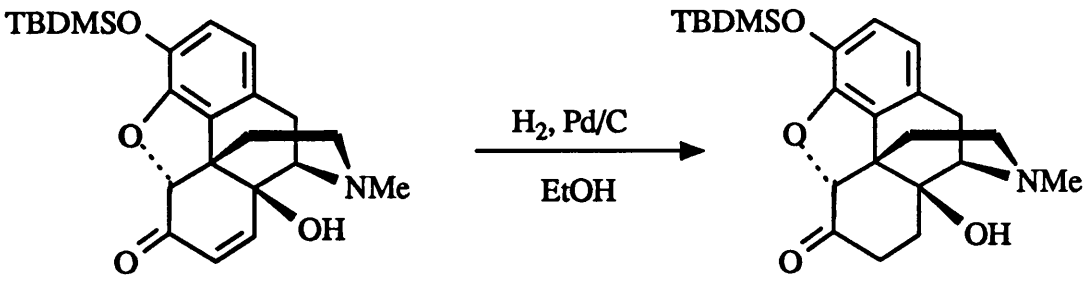
We noted that the oxidation reaction is temperature dependent. Increasing the temperature increases the rate so that in chloroform at reflux 3-TBDMS-14-hydroxymorphinone was formed quickly, but the yield was lowered through decomposition. Repeating the experiment at various temperatures showed that the maximum yield of 14-hydroxymorphinone was achieved at a temperature of 35-38°C in the course of 3-4 hours.

These experimental results helped us to define the optimal conditions for the preparative method:

3-TBDMS morphine (**155**) dissolved in excess chloroform was stirred with 10 equivalents by weight of activated manganese (IV) oxide for 15-20 minutes at about 38°C. Silica gel (Merck No. 7736, type 6OH), (five equivalents by weight) was then added and stirring continued for 3-4 hours at the same temperature until the reaction was complete. The mixture was filtered through a thin pad of silica gel and evaporation of the filtrate gave almost pure 3-TBDMS-14-hydroxymorphinone (**166**) which can further be purified by flash chromatography, or crystallisation from ethyl acetate. By this method a 60% yield of the desired compound was obtained. We consider this to be satisfactory since all other options seem to involve many more steps and so far none had actually worked for us.

Reduction of 3-TBDMS-14-hydroxymorphinone

Hydrogenation of 3-TBDMS-14-hydroxymorphinone (**166**) to the corresponding 7,8-dihydro derivative (**169**) took place without problems. The silyl hydroxymorphinone (**166**) was dissolved in absolute ethanol containing catalytic amounts of Pd/C (10%) and stirred under hydrogen for 2 hours to give the hydrogenated product in quantitative yield.



(166) (169)

Scheme 38

The expected molecular ion peak of the compound occurred at *m/z* 415 together with the base peak at *m/z* 358 corresponding to the ion formed by the loss of *t*-butyl group from the molecule. In the ^1H n.m.r. spectrum the resonances of 7-H_2 and 8-H_2 are seen as multiplets centred at δ 1.67 and 2.60.

14-Hydroxyl Protection

It remained to N-demethylate 7,8-dihydroxy-14-hydroxy-3-(TBDMS)-morphinone (**169**). Prior to this we considered that protection of the 14-hydroxyl group might be necessary. Since O-silyl units are easily removed, an obvious choice for protection is the TBDMS group which we have already shown to withstand N-demethylation conditions using chloroformates.

The 14-hydroxy group is tertiary and sterically crowded thus, we were not surprised to find that O-silylation proved difficult. No reaction occurred between the dihydromorphinone (**169**) dissolved in DMF and TBDMS chloride in presence of imidazole.

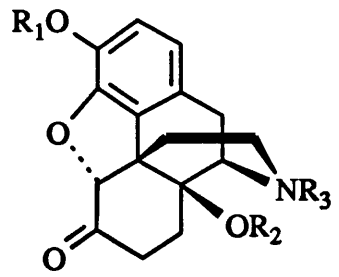
Barton and Tully[156] report that TBDMS perchlorate is a more effective reagent which can be used in difficult cases. However, when this compound was

reacted with the dihydromorphinone (**169**) in acetonitrile containing pyridine, only starting material was recovered. Another failure was experienced in a similar reaction, this time with TBDMS triflate[157] and 2,6-lutidine.

A smaller silyl unit might be inserted, but these are normally less stable than TBDMS. In view of this we turned to O-acetylation. This was achieved without difficulty by heating the dihydromorphinone with acetic anhydride at reflux for 1 hour. The acetoxy derivative (**170**) was thus obtained as a crystalline solid which in its infra red spectrum showed carbonyl bands as well as an ester band at 1735cm^{-1}. In the ^{1}H n.m.r. spectrum the acetoxy methyl protons resonate as a singlet at δ 2.32.

Demethylation of 3-TBDMS-14-acetoxydihydromorphinone

The acetoxymorphinone (**170**) was treated in boiling dichloroethane with excess vinyl chloroformate for 3 days. Removal of solvent and excess reagent afforded 14-acetoxy-3-(TBDMS)-N-vinyloxycarbonyldihydronormorphinone (**171**) in 98% yield. It is a white powder which can be purified by column chromatography. The presence of the vinyl function in this compound is recognisable from the presence of an AMX spin-spin system in the ^{1}H n.m.r. spectrum with 1H multiplets at δ 4.81, 5.51 and 7.2. Significantly the chemical shift of the last multiplet is shifted downfield because the methine carbon is bonded to an oxygen atom.



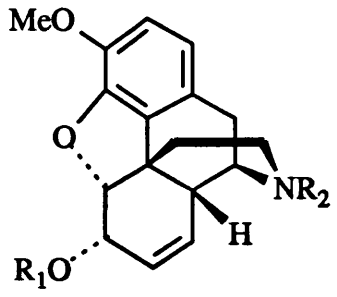
(170), R_1 = TBDMS, R_2 = Ac, R_3 = Me

(171), R_1 = TBDMS, R_2 = Ac, R_3 = $CO_2CH{=}CH_2$

(174), R_1 = R_3 = H, R_2 = Ac

(106), R_1 = R_2 = R_3 = H

Despite the long reaction time and the requirement for a large excess of reagent (10 molar equivalents) the productivity of the process is excellent. Interestingly, Kwiatkowski[158] has claimed that 6-acetylcodeine (**172**) is N-demethylated by 5 equivalents of vinyl chloroformate simply by stirring the mixture in dichloromethane at room temperature for 2 days. The reported yield of N-vinyloxycarbonylnorcodeine (**173**) was 82%. When these conditions were applied to our compound no reaction occurred.



(172), R_1 = Ac, R_2 = Me

(173), R_1 = Ac, R_2 = $CO_2CH{=}CH_2$

The carbamate (**171**) was dissolved in dichloromethane and the solution was saturated with hydrogen chloride. Evaporation of the solvent gave a hydrochloride salt which when warmed with methanol afforded 14-acetoxydihydronormorphinone (**174**) in 96% yield.

An alternative procedure is to reflux a solution of the carbamate in methanol containing a few drops of concentrated hydrochloric acid. This gave the same product in 98% yield. We also tried Kwiatkowski's method for the decarbamoylation of similar compounds by stirring the carbamate (**173**) with a mixture of glacial acetic acid and concentrated hydrochloric acid. This reaction also failed.

Noroxymorphone

Finally 14-acetyl noroxymorphone (**174**) was heated with 6M hydrochloric acid under a nitrogen atmosphere at 100°C for 5 hours. The reaction mixture was then chilled and basified (pH = 9) with ammonia to precipitate noroxymorphone (**106**) as a dark coloured precipitate. This was collected by centrifugation, dissolved in dilute hydrochloric acid and reprecipitated with ammonia. The product is a

colourless solid which was obtained in 88% yield.

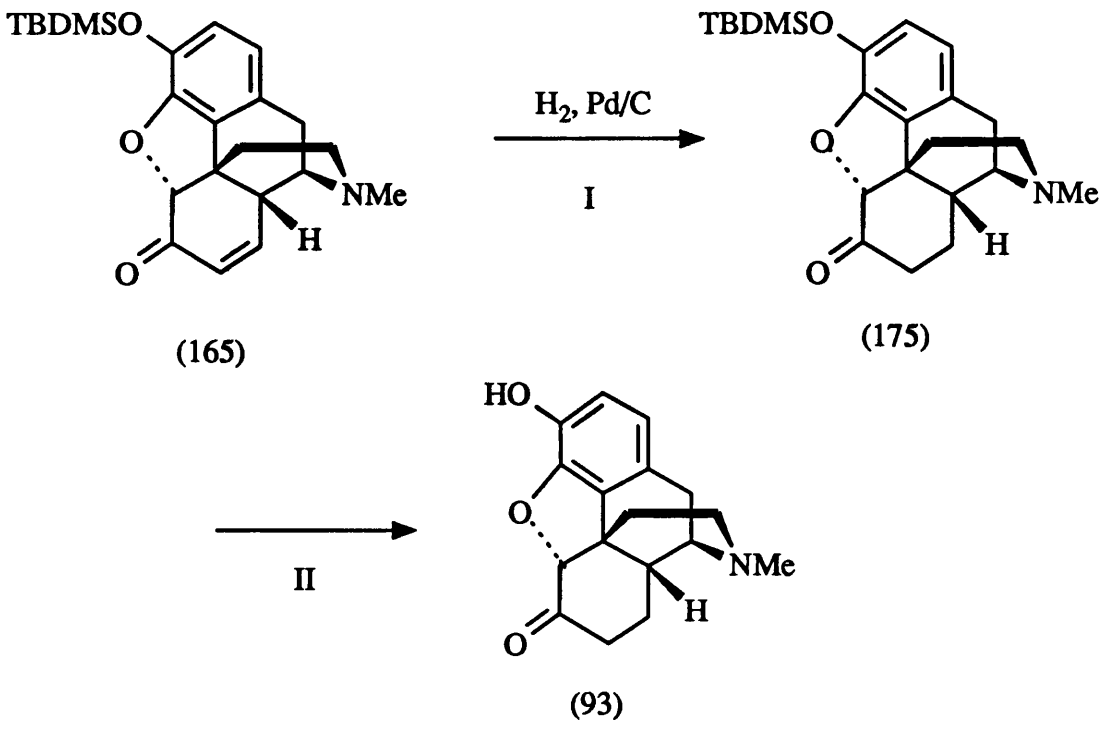
Noroxymorphone (**106**) was characterised as its hydrochloride salt and compared with an authentic sample. Full details of the spectroscopic data are recorded in the experimental section.

Overall, the new synthesis requires seven steps and the yield is 45%. This represents a considerable improvement on existing routes particularly in brevity and economy. It is currently being evaluated on a larger scale by MacFarlan Smith Ltd..

Hydromorphone

As an extension to this work we were advised that hydromorphone (dihydromorphinone) (**93**) is a more potent analgesic than morphine (3-4 times as effective). MacFarlan Smith were interested in the preparation of this drug. We were able to prepare this compound easily from 3-(TBDMS) morphinone (**165**) by reduction and desilylation (Scheme 38).

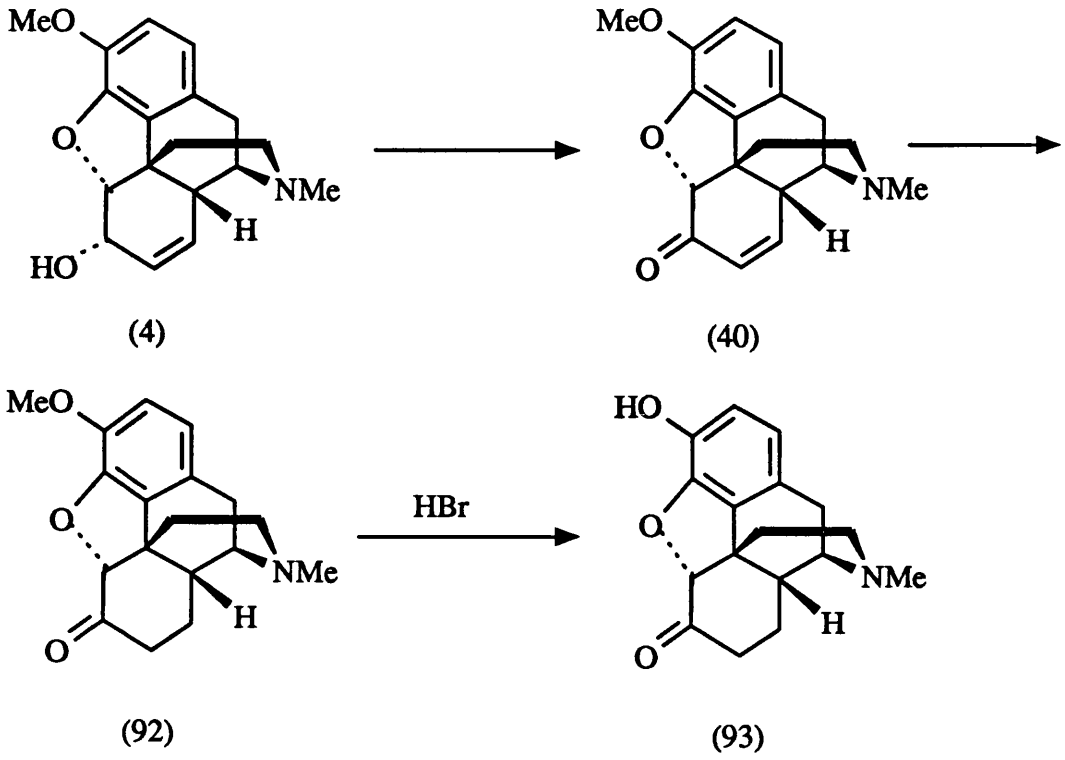
In this approach step one can be effected by hydrogenation at atmospheric pressure in ethanol over 10% palladium on carbon. The yield was 92%. The deprotection, step 2, is carried out by treating the dihydro derivative with tetrabutyl ammonium fluoride in tetrahydrofuran. This gave the required product in 90% yield.



Scheme 38

Overall hydromorphone can now be synthesized in four steps from morphine in 75% yield.

Previously the commercial route started from codeine (**4**) which is first oxidised to codeinone (**40**) and then hydrogenated to dihydrocodeinone (**92**). This product is O-demethylated by heating with hydrogen bromide to give hydromorphone (**93**) (Scheme 39).



Scheme 39

CHAPTER 4

EXPERIMENTAL

4.1 General procedures

Melting points were recorded on an Electrothermal Mark II apparatus and were uncorrected. Infrared spectra are recorded on Perkin-Elmer 197 or 1310 grating spectrophotometers. ^{1}H n.m.r. spectra were run at 60 MHz on Perkin-Elmer R24B and Varian EM360 spectrophotometers; at 270 MHz on a JEOL JNM Fourier Transform spectrometer. ^{13}C n.m.r. spectra were recorded at 67.8 MHz on a JEOL JNM Fourier Transform spectrometer. Chemical shifts are expressed in parts per million downfield from trimethylsilane (TMS) as internal standard. Mass spectra and high resolution accurate mass measurements were determined on a VG 7070E instrument with a VG 2000 data system. TLC analysis was performed on Merck DC-Alufolien plates coated with Kieselgel 60 F_{254}. Visualisation of reaction components was by u.v. light. Column chromatography was performed in short path columns packed with Merck 7736 Kieselgel and the solvent was eluted under pressure provided by hand bellows. Dry column chromatography was performed in cylindrical sinters packed with Merck 7736 Kieselgel and the solvent was eluted under water pump vacuum. Evaporations were carried out under water pump vacuum unless otherwise stated. Ethyl acetate, dichloromethane and pet. ether used for chromatography were distilled prior to use. The term pet. ether refers to light petroleum ether boiling at 60 - 80°C.

Reagents

Tetrahydrofuran was dried by distillation from sodium/ benzophenone ketyl. Diethyl ether and benzene were dried by standing over sodium wire for at least one day. Dichloromethane was dried by distillation from calcium hydride. Methanol and ethanol were dried by distillation from magnesium turnings. Dimethylformamide was dried by standing over activated 4Å molecular sieves. Molecular sieves were activated by heating to at least 150°C overnight. Unless otherwise stated all other solvents and reagents were used as supplied.

4.2 Experimental to Chapter 1.

The powdered bark of *Mimosa tenuiflora* (100 g) was defatted by repeated extraction with petroleum ether (60 - 80°C), (4 x 1ℓ) at reflux. The defatted material was then extracted with boiling methanol (4 x 1.5ℓ). The methanol extract on evaporation under reduced pressure gave a brown solid (Solid 1, 42g). The residue was then extracted with boiling water (3 x 1ℓ) and the extract was evaporated under reduced pressure to give a light brown solid (Solid 4, *ca* 12g). 'Solid 1' was partitioned between 2M hydrochloric acid and chloroform (200 cm^3) and the mixture was extracted with dilute hydrochloric acid (4 x 50 cm^3). The organic phase together with the insolubles was evaporated to get 'Solid 2' (11.5 g). The acid extracts were combined and basified with concentrated NH_3. An off-white solid was precipitated, this was not separated. Instead, the mixture was extracted with chloroform (5 x 100cm^3) until the chloroform extract no longer gave a positive alkaloid test. The aqueous mixture was filtered to collect the chloroform insoluble basic material which was then dried (Solid 3, 14g). The chloroform extract was evaporated under reduced pressure to give the crude alkaloid. This was column chromatographed on silica using a chloroform - ethyl acetate - methanol mixture as the eluent. The fractions which contained the alkaloid were combined, evaporated and again purified by flash column chromatography on silica. Evaporation of the solvent gave a sample of the alkaloid which was then crystallised from ethyl acetate to give colourless crystals of *N,N*-dimethyltryptamine (0.42 g). R_f = 0.34 ($CHCl_3$: EtOAc : MeOH = 4:5:6); m.p. = 48 - 49°C (lit.[3], 48 - 49°C); ν_{max} (NaCl) 3220, 1560, 1250, 1100, 1000, 960 cm^{-1}; δ_H ($CDCl_3$) 2.35 (6H, s, NMe_2), 2.65 (2H, t, *J* = 7Hz, N-CH_2-CH_2-), 2.96 (2H, t, *J* = 7Hz, N-CH_2-CH_2-), 6.99 (1H, s, 2-H), 7.08 - 7.63 (4H, m, 4-H, 5-H, 6-H, 7-H), 8.16 (1H, br.s, indolic N-H); $\delta^{13}C$ ($CDCl_3$) 23.68 (-CH_2-CH_2-N), 45.44 (N-($\underline{C}H_3$)$_2$), 60.33 (-CH_2-CH_2-N), 111.1, 118.8, 119.2, 121.4, 121.9 (5 indolic $\underline{C}$-H) 126.9, 132.0, 136.4 (3 indolic

tert-C); *m/z* (E.I.) 58 (100%, $[CH_2NMe_2]^+$), 188 (40, M^+), 144 (35, $[M - NMe_2]^+$); *m/z* (C.I.) 189 (100%, $[M + H]^+$).

Carbohydrate Analysis

A methanolic solution of 'Solid 1' (20 mg/cm^3 methanol) and solutions of glucose, fructose, galactose, xylose, maltose, glucuronic acid, ribose, mannose, raffinose and sucrose (10mg/cm^3 of methanol) were prepared. These solutions were spotted on to TLC plates (silica) and developed using the following solvent systems.

Solvent 1 : *n*-butanol-acetic acid-diethyl ether-water (9:6:3:1)

Solvent 2 : ethyl acetate-acetic acid-water (6:3:2)

Solvent 3 : *n*-butanol-acetone-water (4:5:1)

The developed plates were dried in air and sprayed with *p*-aminobenzoic acid reagent*, dried and heated at 110°C for a few minutes. R_f values were noted and compared with those of reference compounds. Thus glucose and fructose were identified.

	Solvent 1	Solvent 2	Solvent 3
R_f : Glucose	0.48	0.46	0.62
R_f : Fructose	0.42	0.57	0.64

Table 1.2

* *p*-Aminobenzoic acid reagent: *p*-aminobenzoic acid (3g) was dissolved in hot phosphoric acid (5cm^3) and the solution was added to 300 cm^3 of a mixture of *n*-butanol, acetone and water (10:5:2).

4.3 Minor Alkaloids of Opium

FRACTION 10

'Fraction 10' a dark coloured, viscous liquid (100 g) was treated with dilute sulphuric acid (2M, 200 cm^3) and the mixture extracted with chloroform (3 × 200 cm^3). The combined dry chloroform extracts on evaporation gave a residue (56 g) which contained no alkaloids. The aqueous layer was made alkaline with concentrated ammonia and extracted with chloroform (6 × 100 cm^3). The chloroform extracts were combined, dried (Na_2SO_4) and evaporated under reduced pressure to give a dark brown residue. This was dissolved in methanol and evaporated with silica (*ca* 10g), the material obtained was added to the top of a column of silica and chromatographed using petroleum ether - ethyl acetate mixtures as the eluent. The fractions obtained were grouped by TLC analysis and evaporated individually and rechromatographed. Each compound obtained from the column was further purified by crystallisation or flash column chromatography. The analytical data of the identified compounds is given below and the yields and R_f values in Table 1.

Analytical data

Bis [4-(N,N - dimethylamino) phenyl] methane **(134)**

M.p. 90 - 92°C, (lit.,[126] 91°C); υ_{max}: 3010, 1600, 1500, 1445, 1360, 1220 and 1050 cm^{-1}; δ_H ($CDCl_3$) 2.89 (12H, s, 4 × N-CH_3), 3.80 (2H, s, CH_2), 6.67 - 7.02 (8H, dd, J = 8.8 Hz, 8 × Ar-H); δ_C ($CDCl_3$) 39.9 ($\underline{C}H_2$), 40.9 (N-$\underline{C}H_3$), 113.4 (Ar-$\underline{C}$), 128.1 (Ar *tert* -C), 129.4 (Ar-C); *m/z* (E.I.) 134 (100%) , 253 (32), 254 (30,

M^+); (C.I.) 254 (100, M^+), 255 (78), 134 (75). (Found M: 254.1754, calculated for $C_{17}H_{22}N_2$: 254.1783)

Noscapine (2)

M.p. 174 - 176°C (EtOAc), (*lit.*,[159] 176°C); R_f = 0.75 ($CHCl_3$: MeOH : NH_3 = 90 : 10 : 1); υ_{max} 3500, 2860, 1750, 1708, 1610, 1445, 1370, 1263, 1203, 1180, 1120, 1050, 1010, 972, 860, 810 and 782 cm^{-1}; δ_H ($CDCl_3$) 1.91 - 2.61 (4H, m, N-CH_2-CH_2-), 2.55 (3H, s, N-CH_3), 3.86, 4.04 and 4.09 (3 × 3H, 3 × s, 3 × O-CH_3), 4.40 (1H, d, *J* = 4.0 Hz, 1-H), 5.58 (1H, d, *J* = 4.0 Hz, 9-H), 5.94 (2H, s, O-CH_2-O), 6.08 (1H, d, *J* = 8.25 Hz, 5'-H), 6.31 (1H, s, 5-H), 6.96 (1H, d, *J* = 8.25 Hz, 6'-H); *m/z* (E.I.) 220 (100%);(C.I.) 220 (100), 414 (95, M^++1), 412 (20).

Papaverine (3)

M.p. 147 - 148°C (lit.,[160] 147 -148°C); R_f = 0.64 ($CHCl_3$: MeOH : NH_3 = 90 : 10 : 1); υ_{max} 3400 - 3100 br, 2900, 2820, 1585, 1560, 1490, 1450, 1410, 1342, 1250 - 1180 (br.), 1142, 1130, 1020, 980, 880, 850 cm^{-1}; δ_H ($CDCl_3$) 3.77, 3.82, 3.91 and 4.0 (4 × 3H, 4 × s, 4 × OCH_3), 4.54 (2H, s, -CH_2-), 6.74 - 6.83 (3H, m, 2'-H, 5'-H and 6'-H), 7.05 (1H, s, 8-H), 7.35 (1H, s, 5-H), 7.43 (1H, d, $J_{3,4}$ = 5.7 Hz, 4-H), 8.37 (1H, d, *J* = 5.7 Hz, 3-H); *m/z* (E.1.) 338 (100%, M - 1), 324 (98, M - CH_3), 339 (63, M^+); (C.1.) 340 (100, M + 1).

Thebaine (5)

M.p. 190 - 192°C (EtOH), (lit.,[161] 193°C); υ_{max} 2895, 2820, 1597, 1490, 1300,

1163, 1140, 1100, 1029, 1010, 970, 910 and 860 cm^{-1}; δ_H ($CDCl_3$) : 1.7 - 2.2 (2H, m, 15-H_2), 2.48 (3H, s, N-CH_3), 2.70 (1H, dd, J_{gem} = 18.2 and $J_{9,10}$ = 7.0 Hz, 10-H_α), 2.7 - 2.9 (2H, m, 16-H_2). 3.33 (1H, d, J = 18.1 Hz, 10-H_β), 3.61 (3H, s, 6-OCH_3), 3.69 (1H, d, $J_{9,10}$ = 7.0 Hz, 9-H), 3.85 (3H, s, 3-O-CH_3), 5.07 (1H, d, J = 6.5 Hz, 8-H), 5.28 (1H, s, 5-H), 5.56 (1H, d, J = 6.4 Hz, 7-H), 6.50 - 6.66 (2H, dd, J = 8.0 Hz, 1-H and 2-H) ; *m/z* (E.1.), 311 (100%, M^+), 255 (40).

Codeine (4)

M.p. 155 - 156°C (lit.,[162] 156 - 157°C); υ_{max} 3540, 1640, 1616, 1510, 1330, 1320, 1280, 1250, 1230, 1180, 1152, 1140, 1105, 1080, 1060, 1030, 980, 949, 890, 865 and 830 cm^{-1}; δ_H ($CDCl_3$) 1.88 (1H, dm, J_{gem} = 12.8 Hz, 15-H_α), 2.06 (1H, td, J_{gem} = 12.8 and $J_{15,16}$ = 5.1 Hz, 15-H_β), 2.30 (1H, dd, J_{gem} = 18.7 and $J_{10,9}$ = 6.2 Hz, 10-H_α), 2.36 (1H, dd, J_{gem} = 12.6 and $J_{16,15}$ = 5.6 Hz, 16-H_α), 2.44 (3H, s, N-CH_3), 2.59 (1H, dm, J = 12.5 Hz, 16-H_β), 2.67 (1H, m, 14-H), 2.9 (1H, br.s, 6-OH), 3.05 (1H, d, J_{gem} = 18.6 Hz, 10-H_β), 3.35 (1H, dd, $J_{9,10}$ = 5.9 and $J_{9,14}$ = 3.3Hz, 9-H), 3.84 (3H, s, O-CH_3), 4.18 (1H, m, 6-H), 4.90 (1H, d, $J_{5,6}$ = 6.6 Hz, 5-H), 5.30 (1H, dt, $J_{8,7}$ = 9.9 Hz and $J_{8,14}$ = 2.6 Hz, 8-H), 5.71 (1H, dm, $J_{7,8}$ = 9.9 Hz, 7-H), 6.56 - 6.68 (2H, dd, AB system, J = 8.2 Hz, 1-H and 2-H); *m/z* (E.1.) 299 (100%, M^+); (C.1.) 282 (100, M - OH), 299 (80, M^+), 300 (70, M+1).

FRACTION 4

'Fraction 4' is a dark coloured sticky solid insoluble in water, but soluble in methanol. A methanolic solution of a sample of 'fraction 4' (4.0 g) was prepared and evaporated with silica (10 g). This was added to the top of a column of silica and chromatographed with petroleum ether (40 - 60°C) - chloroform mixture as eluant first and then with chloroform - methanol mixture, progressively increasing the

polarity of each solvent mixture. Fractions (25 cm^3) were collected and analysed by TLC on silica with chloroform - acetone - methanol - ammonia (25 : 20 : 5 :1) mixture as eluant. The first twenty-five fractions contained no alkaloid, but evaporation and purification gave a colourless liquid which was identified as 2-(4-hydroxyphenyl) ethanol (**135**), (6 mg, 0.15%). The next few fractions contained two alkaloids and these fractions were combined and the alkaloids separated by flash column chromatography on silica with petroleum ether - ethyl acetate solvent mixture. The alkaloids were identified as noscapine (**2**), (120 mg, 3%) and papaverine (**3**) (64 mg, 1.6%). In similar manner the remaining components were separated and purified by flash column chromatography and identified as thebaine (**5**), (12 mg, 0.3%), narcotoline (**136**), (8 mg, 0.2%), palaudine (**137**), (56 mg, 1.4%), oripavine (**138**), (10 mg, 0.25%), codeine (**4**), (20 mg, 0.5%) and morphine (**1**), (12 mg, 0.3%). Noscapine, papaverine, thebaine and codeine were identified by comparing their spectral data with those of the samples previously characterised (p.124 - 125).

Analytical data

2-(4-Hydroxphenyl)ethanol (**134**)

δ_H ($CDCl_3$) 1.59 (1H, br.s, $-CH_2O\underline{H}$), 2.81 (2H, t, J = 6.6 Hz, $CH_2-C\underline{H}_2OH$), 3.83 (2H, t, J = 6.4 Hz, $C\underline{H}_2-CH_2OH$), 4.84 (1H, s, phenolic-OH), 6.78 (2H, d, J = 8.6 Hz, 2 x Ar-H), 7.1 (2H, d, J = 8.4 Hz, 2 x Ar-H); *m/z* (E.I.) 107 (100%, M - CH_2OH), 138 (22, M^+); (C.I.) 121 (100, M - OH), 107 (60), 138 (40).

Narcotoline (**136**)

M.p. 200 - 202°C (lit.,[163] 202°C); R_f = 0.64 ($CHCl_3$: CH_3COCH_3 : CH_3OH : NH_3 = 25 : 20 : 5 : 1); ν_{max} 3250, 2900, 1740, 1620, 1470, 1365, 1250, 1190, 1065, 1000, 895, 840, 805, 755, 710, 650 and 620 cm^{-1}; δ_H ($CDCl_3$) 1.95 - 2.70 (4H, m, N-CH_2-CH_2-), 2.54 (3H, s, N-CH_3), 3.87 and 4.10 (2 x 3H, 2 x s, 2 x O-CH_3), 4.40 (1H, d, *J* = 4.4 Hz, 1-H), 5.66 (1H, d, *J* = 4.2 Hz, 9-H), 5.97 (2H, q, *J* = 1.1 Hz, O-CH_2-O), 6.21 (1H, d, *J* = 8.1, 2'-H), 6.3 (1H, s, 5-H), 6.98 (1H, d, *J* = 8.4 Hz, 3'-H); *m/z* (%) : (E.I.) 206 (100), 399 (5, M^+); (C.I.) 206 (100), 400 (7, $[M+H]^+$).

Palaudine (**137**)

R_f = 0.61 ($CHCl_3$: CH_3COCH_3 : CH_3OH : NH_3 = 25 :20 : 5 : 1); m.p. = 174 - 175°C (lit.,[164] 175 - 176°C); $\nu_{max}cm^{-1}$: 3430, 300, 2870, 1620, 1590, 1480, 1463, 1450, 1385, 1350, 1273, 1235, 1200, 1080, 1050, 1030, 960, 860, 824; δ_H ($CDCl_3$) 3.82, 3.89 and 4.00 (3 x 3H, 3 x s, 3 x OCH_3), 4.49 (2H, s, -CH_2-), 6.5 (1H, br.s, 3'-OH), 6.75 - 6.81 (3H, m, 2'-H, 5'-H, 6'-H), 7.03 (1H, s, 5-H / 8-H), 7.32 (1H, s, 5-H / 8-H), 7.39 (1H, d, *J* = 5.7 Hz, 4-H), 8.29 (1H, d, *J* = 5.7 Hz, 3-H); *m/z* (%): (E.I.) 324 (40, $[M-H]^+$), 325 (25, M^+); (C.I) 326 (100, $[M+H]^+$), 325 (40, M^+).

Oripavine (**138**)

R_f = 0.58 ($CHCl_3$: MeCOMe : MeOH : NH_3= 25 : 20 : 5 : 1); m.p. = 198 - 199°C (lit.,[165] 201 - 202°C); $\nu_{max}cm^{-1}$ 3520, 3200 (br.), 2895, 2820, 1597, 1440, 1360, 1320, 1300, 1130, 1100, 1010, 970, 910, 860; δ_H ($CDCl_3$) 1.74 (1H, dd, *J* = 12.5 and 2.1 Hz, 15-H_α), 2.24 (1H, td, *J* = 12.5, 5.1 Hz, 15-H_β), 2.48 (3H, s, N-CH_3),

2 .70 (1H, dd, J = 18.2 and 7.0 Hz, 10-H_α), 2.65 - 2.70 (1H, m, 16-H_α), 2.90 (1H, td, J = 12.8 and 3.5 Hz, 16-H_β), 3.33 (1H, d, J = 18.0Hz, 10-H_β), 3.61 (3H, s, 6-OCH_3), 3.69 (1H, d, J = 7.0Hz, 9-H), 5.07 (1H, d, J = 6.6 Hz, 8-H), 5.30 (1H, s, 5-H), 5.58 (1H, d, J = 6.4 Hz, 7-H), 6.53 - 6.66 (2H, dd, J = 8.1 Hz, Ar 1-H and 2-H); *m/z* (%) 57 (100), 148 (80), 297 (55, M^+); (low E.V.E.I.) 297 (100, M^+).

Morphine (**1**)

R_f = 0.22 ($CHCl_3$: MeCOMe : MeOH : NH_3 = 25 : 20 : 5 : 1), m.p. = 250 - 253°C (lit.,[166], 253 - 254°C); $\nu_{max}cm^{-1}$: 3460, 3310, 3120, 2300, 1590, 1300, 1230, 1110, 1075, 1010, 930, 820, 790, 750; δ_H (CD_3OD): 1.70 - 2.10 (2H, m, 15-H_2), 2.29 (1H, dd, J = 18.8 and 6.4 Hz, 10-H_α), 2.37 (3H, s, NCH_3), 2.40 - 2.55 (2H, m, 16-H_2), 2.59 (1H, m, 14-H), 2.96 (1H, d, J_{gem} = 18.9 Hz, 10-H_β), 3.07 (1H, br.s, 6-OH), 3.32 (1H, q, $J_{9,10}$ = 6.4 Hz and $J_{9,14}$ = 3.3 Hz, 9-H), 4.12 (1H, m, 6-H), 4.75 (1H, d, $J_{5,6}$ = 6.2 Hz, 5-H), 5.24 (1H, ddd, J = 9.9, 2.8 and 2.6 Hz, 8-H), 5.56 (1H, dm, J = 9.9 Hz, 7-H), 6.40 - 6.60 (2H, dd, J = 8.1 Hz, 1-H and 2-H); *m/z* (%): (E.I.) 285 (100, M^+), 162 (40), 215 (30).

FRACTION 7

A sample of 'fraction 7' (3.0 g) was column chromatographed on silica using chloroform - methanol solvent system and the alkaloids isolated were purified further by flash column chromatography or by crystallisation (as described in the case of 'fraction 4'). Five alkaloids were identified from this fraction. They are noscapine (**2**), papavarine (**3**), codeine (**4**), laudanosine (**140**) and xanthaline (**139**). Noscapine (**2**), papaverine (**3**) and codeine (**4**) were identified by IR, NMR and MS spectra as described earlier (p.124 - 125).

Analytical data

Laudanosine **(140)**

R_f = 0.59 ($CHCl_3$: CH_3OH : NH_3 = 90 : 10 : 1); m.p. = 87 - 89°C (lit.,[168] 89°C); ν_{max}, cm^{-1}: 2890, 2820, 1585, 1495, 1430, 1330, 1315, 1230-1180 (br.), 1120, 1090, 1000, 850; δ_H ($CDCl_3$) : 2.48 - 2.88 (4H, m, N-CH_2-CH_2-), 2.55 (3H, s, NCH_3), 3.18 (2H, m, CH_2), 3.69 (1H, q, J = 5.1 and 2.6 Hz, 1-H), 3.56, 3.79, 3.84 and 3.85 (4 × 3H, 4 × s, 4 × OCH_3), 6.05 (1H, s, 5-H), 6.56 (1H, s, 8-H), 6.60 - 6.78 (3H, m, 2'-H, 5'-H, 6'-H); *m/z* (%): (E.I.) 206 (100), 207 (20); (C.I.) 206 (100), 358 (30, $[M+H]^+$).

Xanthaline **(139)**

R_f = 0.79 ($CHCl_3$: CH_3OH : NH_3 = 90 : 10 : 1). m.p. = 207 - 209°C (lit.,[167] 208 - 209°C); ν_{max} cm^{-1}: 2920, 2820, 1640, 1615, 1578, 1490, 1455, 1400, 1335, 1260-1180 (br), 1130, 1010, 935, 875, 850; δ_H ($CDCl_3$) : 3.95, 3.96, 3.97, 4.06 (4 × 3H, 4 × s, 4 × OCH_3), 6.87 (1H, d, $J_{5',6'}$ = 8.4 Hz, 5'-H), 7.12 (1H, d, $J_{2',6'}$ = 1.8 Hz, 2'-H), 7.15 (1H, s, 5-H), 7.42 (1H, dd, $J_{6',5'}$ = 8.4 Hz, $J_{6',2'}$ = 1.8 Hz, 6'-H), 7.55 (1H, s, 8-H), 7.66 (1H, d, $J_{4,3}$ = 5.5 Hz, 4-H), 8.46 (1H, d, $J_{3,4}$ = 5.7 Hz, 3-H); *m/z* (E.I.) 353 (100, M^+), 324 (80), 165 (80); (C.I.) 354 (100, $[M+H]^+$), 353 (40, M^+)

FRACTION 13

'Fraction 13' is a black spongy solid, insoluble in organic solvents but soluble in water. A sample (12 g) of the material was dissolved in water, acidified with dilute H_2SO_4 and extracted with diethyl ether. Ether extract on evaporation gave no

residue. Aqueous layer was basified with concentrated NH_3 and extracted first with diethyl ether (6 × 50 cm^3) and then with chloroform (6 × 50 cm^3). The ether extract was dried, concentrated and kept in a fridge overnight when colourless crystals of a substance were formed. This was recrystallised from methanol and identified as cryptopine (**142**) (0.245 g, 2.5%). The chloroform extract was evaporated and the compounds in the residue were isolated by short column chromatography (silica, petroleum ether - ethyl acetate first and then ethyl acetate - methanol mixture as eluant). The fractions were evaporated and purified. The alkaloids identified are noscapine (**2**), (0.062 g, 0.5%), papaverine (**3**) (0.21 g , 1.8%), laudanosine (**140**), (0.033 g, 0.3%), thebaine (**5**) (0.03 g, 0.25%) and codeine (**4**), (0.249 g, 2%).

Analytical data

Cryptopine (**142**)

R_f = 0.57 ($CHCl_3$: CH_3OH : NH_3 = 90 : 10 : 1) m.p. = 220 - 221°C (lit.,[169] 223°C); ν_{max} cm^{-1} 3510 - 3400 (br.) 2860, 2820, 1640, 1592, 5485, 1440, 1335, 1180 - 1240 (br.), 1110, 1030 (br), 970, 930, 850; δ_H ($CDCl_3$): 1.6 - 2.6 (4H, m, 5-CH_2-, 6-CH_2-), 3.55 - 3.65 (4H, m, 8-CH_2-, 13-CH_2-), 3.89 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 5.94 (2H, s, O-CH_2-O), 6.70 (1H, s, 4-H), 7.00 (1H, s, 1-H); *m/z* (%): (E.I.) 148 (100), 369 (5, M^+); (C.I.) 148 (100), 370 (82, $[M+H]^+$).

4.4 N-Demethylation of Oxycodone

14- Acetyloxycodone (**143**)

Oxycodone (**104**), (3.15 g, 10 mmol) was heated under reflux with acetic anhydride (15 cm^3) for 1 hour. The mixture was then cooled, poured into ice (60g) and stirred to room temperature to hydrolyse the excess anhydride. It was again cooled to O°C and basified with concentrated ammonia to pH 9. A white precipitate of 14-acetyloxycodone (**143**) was formed and this was collected by filteration, washed with water and dried in the vacuum oven at 65°C. Yield = 3.55 g (quantitative). It was crystallised from 95% ethanol. R_f = 0.5 (CH_2Cl_2 : CH_3OH = 9 : 1); m.p. 206 - 208°C (lit.,[109] 206 - 210°C); ν_{max} 3520, 1720, 1630, 1600, 1430, 1360, 1310, 1150, 1098, 1010, 950 and 880 cm^{-1}; δ_H ($CDCl_3$), (400 mHz), 1.54 (1H, dm, *J* = 11.9 Hz, 8-H_α), 1.64 (1H, ddd, *J* = 14.6 and 3.7 Hz, 15-H_α), 2.19 (3H, s, N-CH_3), 2.16 - 2.20 (1H, m, *J* = 11.6 Hz, 8-H_β), 2.28 (1H, dt, *J* = 14.9 and 3 Hz, 15-H_β), 2.32 (3H, s, -$COCH_3$), 2.45 (1H, m, *J* = 12.2 and 5.5 Hz, 7-H_α), 2.5 (1H, dd, *J* = 18.3 and 5.2 Hz, 10-H_α), 2.54 (1H, m, *J* = 12.2 and 5.2 Hz, 7-H_β), 2.64 (1H, td, *J* = 14.6 and 5.2 Hz, 16-H_α), 2.81 (1H, ddd, *J* = 14.3, 5.2 and 2.75 Hz,16-H_β), 3.21 (1H, d, *J* = 18.6 Hz, 10-H_β), 3.89 (3H, s, O-CH_3), 4.19 (1H, d, *J* = 5.5 Hz, 9-H), 4.67 (1H, s, 5-H), 6.64 - 6.72 (2H, dd, AB system, *J* = 8.0 Hz, 1-H and 2-H); δ_C ($CDCl_3$) : 22.2 ($\underline{C}H_3CO$), 22.3 (C-8), 27.0 (C-7), 29.9 (C-10), 35.5 (C-15), 42.6 (CH_3-N), 45.6 (C-16), 56.8 (CH_3O), 57.8 (C-9), 76.5 (C-13), 77.0 (C-14), 77.5 (C-11), 82.4 (C-12), 89.9 (C-5), 115.2 (C-1), 119.5 (C-2), 143.0 (C-3), 146.0 (C-4), 162.0 (C-6), 170.0 ($\underline{C}OCH_3$); *m/z* (%) : (E.I.) 357 (100, M^+), 314 (45, M - CH_3CO).

N-(1-Chloroethoxycarbonyl)-14-acetylnoroxycodone (**148**)

1-Chloroethyl chloroformate (1.4 cm^3; 1.85 g, 13 mmol) was added slowly to a cold solution of 14-acetyloxycodone (**143**), (1.4 g, 3.8 mmol) in 1,2-dichloroethane (12 cm^3) at 0°C. The mixture was then heated at 65°C under nitrogen for 20 hours and then at reflux for 2 hours. The volatiles were removed under reduced pressure to give a colourless solid which was flash chromatographed on silica with chloroform as eluant to give N-(1-chloroethoxycarbonyl)-14-acetylnoroxycodone (**148**), (1.25 g, 71%). R_f = 0.78 (CH_2Cl_2 : CH_3OH = 9 : 1); ν_{max}: 1745, 1715, 1630, 1605 and 1513 cm^{-1}; δ_H ($CDCl_3$) : 1.85 (3H, d, *J* = 5.9 Hz, -CHCl-C<u>H</u>$_3$), 2.18 (3H, s, CO-CH_3), 3.90 (3H, s, OCH_3), 6.40 - 6.90 (3H, m, 1-H, 2-H and -C<u>H</u>Cl-CH_3).

Deprotection of N-carbamate and 14-acetyl groups from N-(1-chloroethoxy-carbonyl)-14-acetylnoroxycodone (**148**)

A solution of N-(1-chloroethoxycarbonyl)-14-acetylnoroxycodone (**148**), (1.2 g, 2.7 mmol) in methanol (20 cm^3) was heated under reflux for 2 hours. The mixture was cooled and the solvent was evaporated to give 14-acetylnoroxycodone (**149**). This was dissolved in dilute hydrochloric acid (6M, 15 cm^3) and heated at 100 - 102°C for 5 hours. The mixture was cooled to 0°C, basified with concentrated ammonia to pH 8.5 and extracted with dichloromethane (10 x 10 cm^3). The combined organic extracts were washed with water, dried (Na_2SO_4) and evaporated to yield noroxycodone (**131**), (0.78 g, 97% yield; 68.9% from 14-acetyloxycodone). The product which contains both secondary amine and ketone groups cannot be crystalised without decomposition as reported by Seki.[171] M.p. 160 - 165°C foaming, then 306°C dec. (lit.,[171] 160°C foamimg, then 310°C dec.); R_f = 0.065 (CH_2Cl_2 : MeOH = 9 : 1); ν_{max}: 3350 - 3200 (br.), 1718 and 1598 cm^{-1}; δ_H ($CDCl_3$) 1.56 - 3.19 (1H, m, 7-H_2, 8-H_2, 9-H, 10-H_2, 15-H_2, 16-H_2), 3.90 (3H, s, OCH_3),

4.66 (1H, s, 5-H), 4.94 (1H, br.s, 14-OH), 6.62 - 6.73 (2H, dd, AB system, J = 8.2 Hz, 1-H and 2-H); *m/z* (%): (E.I.) 301 (100, M^+), 83 (63), 216 (45).

The preparation of noroxycodone from acetyl oxycodone was repeated without purifying the intermediate N-carbamate. The product obtained however was found to be a mixture of noroxycodone and oxycodone. Column chromatographic separation on silica gave 68% of noroxycodone as the best yield. About 23% of oxycodone was also recovered.

N-Demethylation with vinyl chloroformate

A mixture of 14-acetyloxycodone (**143**), (0.71 g, 2 mmol) in 1,2-dichloroethane (20 cm^3) and vinyl chloroformate (0.35 cm^3; 0.43 g, 4 mmol) was heated at 50°C under nitrogen for 120 hrs. Further portions of vinyl chloroformate were added after 72 hrs and 96 hrs (0.35 cm^3 each). The mixture was poured into saturated sodium hydrogen carbonate and extracted with dichloromethane. The extract was dried and evaporated to give N-vinyloxycarbonyl-14-acetylnoroxycodone (**150**). It was purified by column chromatography on silica eluting with chloroform - methanol (100 : 1) mixture to yield a colourless foam of the carbamate (**150**). This product was dissolved in dry dichloromethane (10 cm^3) and hydrogen chloride gas was passed through the solution for one hour. The solvent was evaporated under reduced pressure, and the residue was heated under reflux with methanol for one hour. The solvent was evaporated under reduced pressure, the residue was mixed with saturated sodium hydrogen carbonate solution and extracted with dichloromethane, the extract was dried (Na_2SO_4) and evaporated to give 14-acetylnoroxycodone (**149**), (0.6 g, 88%) as a glassy solid. The acetyl group was hydrolysed to give noroxycodone (**131**) as explained in the previous experiment.

N-Demethylation with phenyl chloroformate

A mixture of 14-acetyloxycodone (**143**), (0.71 g, 2 mmol) dissolved in chloroform (50 cm^3), sodium hydrogen carbonate (4.2 g, 50 mmol) and phenyl chloroformate (2.5 g, 15 mmol) was refluxed with efficient stirring under nitrogen for 20 hours. The mixture was cooled, filtered and evaporated. Anhydrous hydrazine (5 cm^3) was added slowly to the product, followed by 64% hydrazine (2 cm^3) and the mixture was heated under reflux in the atmosphere of nitrogen for 24 hours. The mixture was cooled, water (20 cm^3) was added and the water was removed in vacuo. The addition and removal of water was repeated twice more. Phenol was then removed from the mixture under high vacuum at 120°C. The residue was dissolved in a mixture of water (100 cm^3) and chloroform (200 cm^3), and the mixture was made alkaline with concentrated ammonia, and the chloroform layer was separated, washed with 10% KOH solution and, then with water, dried (Na_2SO_4) and evaporated to give 14-acetylnoroxycodone (**149**), (0.45 g, 66%) which on purification by column chromatography on silica with chloroform - methanol (9:1) gave pure product (**149**), (0.38 g, 56%).

N-Demethylation with 2,2,2-trichloroethyl chloroformate

A mixture of 14-acetyloxycodone (**143**) (0.71 g, 2 mmol), anhydrous potassium carbonate (0.6 g, 4 mmol) and 2,2,2-trichloroethyl chloroformate (2.9 cm^3; 4.26 g, 20 mmol) in chloroform (100 cm^3) was refluxed under nitrogen for three days. The mixture was cooled, washed with water, dried (Na_2SO_4) and evaporated and the residue obtained was dissolved in glacial acetic acid (15 cm^3) and stirred with zinc dust (1 g) at room temperature for 4 hours. The zinc dust was filtered off and the filtrate was basified with concentrated ammonia and extracted with chloroform. The chloroform extract on evaporation gave acetylnoroxycodone (**149**), which was

purified by column chromatography on silica using chloroform-methanol (9:1) to elute. (0.14 g, 20.5%).

N-Demethylation with ethyl chloroformate

A mixture of 14-acetyloxycodone (**143**) (0.71 g, 2 mmol), ethyl chloroformate (1.9 cm^3, 2.2 g, 20 mmol) and potassium carbonate (1 g, 7 mmol) in chloroform (100 cm^3} was heated under reflux for 8 hours. The mixture was cooled, washed with water, dried (Na_2SO_4) and evaporated to give a residue. This was dissolved in dilute sulphuric acid (5M, 10 cm^3) and refluxed under nitrogen for 12 hours. The mixture was cooled, basified with solid sodium hydrogen carbonate and extracted with chloroform. Evaporation of the chloroform extract and column chromatographic separation of the residue gave noroxycodone (**131**), (0.10g, 16.6%).

The experiment was repeated by heating the mixture of acetyl oxycodone, ethyl chloroformate and potassium carbonate in chloroform under nitrogen for one week. The reaction mixture was found to contain N-ethoxycarbonyl-14-acetylnor-oxycodone in similar yield (15 - 20%).

4.5 O-Demethylation of Oxycodone

O-Demethylation of oxycodone with hydrogen bromide

Oxycodone (**104**), (0.60 g, 1.9 mmol) was introduced into concentrated hydrobromic acid (10 cm^3) at 90°C and the mixture was heated at 110 - 120°C for 1 hour. The mixture was cooled, basified with concentrated sodium hydroxide to pH 10-11 and extracted with chloroform to recover the unreacted oxycodone (0.1 g, 17%). The aqueous phase was chilled and made acidic with hydrochloric acid and then basic with concentrated ammonia to pH 8.5. The mixture was again extracted with chloroform, the chloroform extract was dried and evaporated to yield oxymorphone (**105**), (0.35 g, 61%, 73% based on the reacted oxycodone). It was crystalised from ethanol to give colourless crystals. M.p. 244 - 247°C darkening (lit.,[100] 248 - 249°C, darkening); R_f = 0.2 (CH_2Cl_2 : MeOH, 9 : 1); ν_{max} 3340 (br.), 1710, 1610 and 1300 cm^{-1}; δH ($CDCl_3$) 1.56 (1H, m, *J* = 13.9 Hz, 15-H_α), 1.68 (1H, dd, *J* = 14.3 and 3.3 Hz, 8-H_α), 1.9 (1H, m, 15-H_β), 2.1 - 2.34 (3H, m, 7-H_2 and 8-H_β), 2.42 (3H, s, NCH_3), 2.44 (1H, m, 16-H_α), 2.56 (1H, dd, *J* = 18.7 Hz and 5.5 Hz, 10-H_α), 2.9 (1H, d, *J* = 5.9 Hz, 9-H), 3.05 (1H, dd, *J* = 14.2 Hz and 5.1 Hz, 16-H_β), 3.16 (1H, d, *J* = 18.7 Hz, 10-H_β), 4.71 (1H, s, 5-H), 6.59 - 6.75 (2H, dd, *J* = 8.1 Hz, 1-H and 2-H); *m/z* (low E.V.E.I.) 301 (100%, M^+).

O-Demethylation with boron tribromide

A solution of oxycodone (**104**), (0.32 g, 1 mmol) dissolved in dichloromethane (30 cm^3) was treated with solution of BBr_3 (1 cm^3, 1M solution in dichloromethane, 10 mmol) in dichloromethane at -70°C under nitrogen. The mixture was allowed to warm to room temperature and continued stirring for one hour. Excess boron tribromide was destroyed by treating with methanol (2 cm^3), the mixture was

basified with 1% sodium hydroxide solution and extracted with chloroform to recover unreacted oxycodone. The aqueous phase was acidified with concentrated hydrochloric acid to pH 5 and then basified with concentrated ammonia to pH 9 and extracted with chloroform to yield oxymorphone **(50)**, (0.15 g, 49%).

Attempted O-demethylation with trimethylsilylchloride and sodium iodide

A mixture of oxycodone **(104)** (0.6 g, 1.9 mmol), in dry acetonitrile (10 cm^3), trimethylsilylchloride (0.4 cm^3; 0.38 g, 3.5 mmol) and sodium iodide (0.5 g, 3.3 mmol) was stirred under nitrogen at 45°C for 60 hours. The mixture was diluted with water (10 cm^3) and extracted with chloroform. The chloroform extract was analysed and found to contain only the starting material.

O-Demethylation with trimethylsilyliodide

Oxycodone (0.6 g, 1.9 mmol) dissolved in carbon tetrachloride (20 cm^3) was stirred with trimethylsilyliodide (0.6 g, 3 mmol) under nitrogen at 50°C for two days. The mixture was then cooled and then shaken with 1% NaOH solution (25 cm^3) and extracted with chloroform. The organic extract on evaporation yielded a mixture of oxycodone with some unidentified product (0.24 g, approximately 40%). The aqueous layer was acidified first with hydrochloric acid and then basified with concentrated NH_3 to pH 8.5 - 9.0 and extracted with chloroform to yield oxymorphone (0.1 g, 17%).

O-Demethylation with n-propanethiol

A solution of oxycodone **(104)**, (1.1 g, 3.5 mmol) in dry DMF was degassed under nitrogen by stirring under vacuum followed by inletting nitrogen. Potassium

tert-butoxide (1.10 g, 9.8 mmol) was added to the above solution and the degassing process was repeated and then *n*-propanethiol (1.2 cm^3, 13 mmol) was introduced by a syringe. The mixture was heated at 110°C under nitrogen for 3 hours cooled and quenched with acetic acid (1 cm^3). The solvent was removed under high vacuum and the residue was dissolved in dilute hydrochloric acid (1M, 20 cm^3). The solution was washed with ether, treated with 20% sodium bisulphite solution (2 cm^3) and basified with concentrated ammonia to pH 9.0. The precipitate was collected by filtration (0.88 g) and was found to be a mixture of oxycodone (R_f = 0.42, CH_2Cl_2 : CH_3OH = 9 : 1) and oxymorphone (R_f = 0.20, same solvent system). The mixture was separated by flash column chromatography to yield oxycodone (**104**), (0.5 g) and oxymorphone (**105**), (0.11 g, *ca* 10%).

Attempted O-demethylation of oxycodone with lithium diphenylphosphide

(i) Preparation of lithium diphenylphosphide

Lithium metal (0.14 g, 2 g atom) was added to dry THF (10 cm^3) and then chlorodiphenyl phosphine (1.1 cm^3, 5 mmol) was added dropwise under nitrogen. The mixture was stirred under nitrogen at room temperature for 2 hours. A red solution of the lithium diphenylphosphide resulted was used for demethylation as follows.

(ii) Demethylation

Oxycodone (**104**), (0.8 g, 2.5 mmol) was added to the above solution of lithium diphenylphosphide under nitrogen and the mixture was stirred for 2 hours. It was poured into 10% hydrochloric acid (100 cm^3) and extracted with ether (4 x 50 cm^3). The aqueous solution was then basified with concentrated ammonia and extracted

with chloroform (4 x 50 cm^3). The chloroform extract was washed with saturated sodium chloride solution and dried (Na_2SO_4) and evaporated to give a residue (0.7g) which on examination (TLC) was found to contain five or more compounds and none corresponding to oxymorphone (**105**).

4.6 Separation of noroxycodone from a mixture of it with oxycodone

1. *Attempted separation using polysiloxane film*

A glass cell which consists of two compartments separated by a polysiloxane film (12, Crown-4-polyorganosiloxane DD 300) was set up. A solution of a mixture of oxycodone and noroxycodone prepared by dissolving 0.1 g of the mixture in 10 cm^3 of 0.01M hydrochloric acid, was taken in one compartment while the other compartment was filled with a 0.01M solution of potassium hydroxide. The solution was left undisturbed for 2 days. It was noted that noroxycodone was not transported through the membrane to the KOH solution even after leaving for 2 days.

2. *Separation using 12-crown-4 functionalised polysiloxane*

An aqueous solution of a mixture of oxycodone and noroxycodone containing 1 mg mixture per 1 cm^3 of 0.01M hydrochloric acid was shaken vigorously with polysiloxane liquid (12-crown-4-polyorganosiloxane), (1 g). The mixture was allowed to separate overnight. The aqueous layer was analysed by HPLC. The solution of the mixture of oxycodone and noroxycodone before the treatment of the polymer was also analysed and it was found that there was a 6% decrease in the peak area of noroxycodone after polymer treatment while the oxycodone concentration was not affected.

4.7 Synthetic Routes to Normorphine, Hydromorphone and Noroxymorphone

*3,6-Bis (*tert*-butyldimethylsilyl)-morphine* (**154**)

A solution of morphine (**1**), (0.57 g, 2 mmol) in DMF (5 cm^3) was stirred with imidazole (0.75 g, 10 mmol, 2.5 equivalent per mole of OH) and TBDMS chloride (0.9 g, 6 mmol, 1.5 equivalent per mole of OH) under N_2 at room temperature for about 15 hours. When morphine reacted completely (followed by TLC) and a single spot on TLC plate corresponding to the title compound was resulted, the reaction mixture was partitioned between chloroform and water and extracted with chloroform (4 x 20 cm^3). The chloroform extract was washed with water, dried (Na_2SO_4) and evaporated under reduced pressure first and then under high vacuum to give the title compound (**154**), (1.01 g, 98% yield) as a white solid. It was crystallised from ethanol - water mixture (3:1). R_f = 0.58 ($CHCl_3$: CH_3OH = 9 : 1); m.p. 119 - 120° (lit.,[148] 119 - 119.5°); υ_{max}: 3140, 2880, 2834, 1618, 1570, 1432, 1370, 1340, 1320, 1250 - 1160 (br), 1115, 1090, 970, 940, 880 and 820 cm^{-1}; δ_H ($CDCl_3$) : 0.10, 0.125, 0.134 and 0.21 (4 × 3H, 4 × s, 4 × Si-CH_3), 0.93 and 0.97 (2 × 9H, 2 × s, 2 × Si-*t*Bu), 1.84 (1H, dm, J_{gem} = 12.5 Hz, 15-H_α), 2.01 (1H, td, J = 12.6 and 5.7 Hz, 15-H_β), 2.29 (1H, dd, J_{gem} = 18.5 Hz and $J_{10,9}$ = 6.2 Hz, 10-H_α), 2.42 (1H, td, J = 12.1 and 3.3 Hz, 16-H_α), 2.43 (3H, s, N-CH_3), 2.53 (1H, m, 16-H_β), 2.60 (1H, m, 14-H), 3.02 (1H, d, J_{gem} = 18.5 Hz, 10-H_β), 3.34 (1H, q, $J_{9,10}$ = 6.3, $J_{9,14}$ = 3.2 Hz, 9-H), 4.21 (1H, m, $J_{6,5}$ = 5.7 Hz, 6-H), 4.66 (1H, dd, $J_{5,6}$ = 5.7 Hz and $J_{5,7}$ = 1.3 Hz, 5-H), 5.23 (1H, dt, $J_{8,7}$ = 9.5 Hz, $J_{8,14}$ = 2.8 Hz, 8-H), 5.50 (1H, dm, $J_{7,8}$ = 9.7 Hz, $J_{7,6}$ = 3.3 Hz, 7-H), 6.40 - 6.80 (2H, dd, J = 8.1 Hz, 1-H and 2-H); *m/z* (%): (E.I.) 73 (100), 456 (42, [M - Bu]$^+$), 413 (40), 513 (12, M^+); (Low E.I.) 513 (100, M^+), 456 (80), 413 (20). Found: C = 67.5, H = 9.4 and N = 2.77%, calculated for : $C_{29}H_{47}Si_2NO_3$: C = 67.78; H = 9.2; N = 2.73%.

3-(tert-Butyldimethylsilyl)-morphine (**155**)

A solution of sodium ethoxide was prepared by dissolving dry sodium metal (0.13 g, 1.1 equivalent per mole of morphine) in absolute ethanol (40 cm^3). Morphine (**1**) (1.42 g, 5 mmol) was dissolved in this solution and the resulting solution was evaporated under reduced pressure. The residue was dissolved in benzene (20 cm^3) and evaporated again to give a white powder. This was dissolved in dry THF (40 cm^3) and to this solution TBDMSCl (1.10 g, 7.3 mmol) dissolved in dry THF (5 cm^3) was added slowly under nitrogen. The mixture was left stirring overnight under nitrogen at room temperature. The solvent was then evaporated, the residue was dissolved in chloroform, washed with water, dried (Na_2SO_4) and evaporated to give the title compound (**155**), (1.98 g, 99% yield). It was crystallised from ethyl acetate to give colourless needles. M.p. 201 - 203°C (decomp.); R_f = 0.35 ($CHCl_3$: MeOH = 9 : 1); υ_{max} 3540, 3360, 2905, 2840, 2280, 1595, 1440, 1380, 1320, 1270 - 1170 (br), 1108, 1055, 960, 875 and 825 cm^{-1}; δ_H($CDCl_3$) 0.16 and 0.19 (2 × 3H, 2 × s, 2 × Si-CH_3), 0.98 (9H, s, Si-*t*-Bu), 1.8 - 2.6 (4H, m, 15-H_2 and 16-H_2), 2.28 (1H, dd, J_{gem} = 18.7 Hz and $J_{10,9}$ = 6.2 Hz, 10-H_α), 2.44 (3H, s, N-CH_3), 2.60 (1H, m, 14-H), 2.81(1H, br.d, 6-OH), 3.02 (1H, d, J = 18.6 Hz, 10-H_β), 3.40 (1H, q, $J_{9,10}$ = 6.4 Hz, 9-H), 4.16 (1H, m, 6-H), 4.85(1H, dd, $J_{5,6}$ = 6.0 Hz and $J_{5,7}$ = 1.1 Hz, 5-H), 5.30 (1H, m, 8-H), 5.70 (1H, m, 7-H), 6.40-6.60 (2H, AB system, J = 8.2 Hz, 1-H and 2-H); *m/z* (E.I.) 399 (70%, M^+), 342 (100, M - *t*-Bu).

Normorphine (**94**)

3,6-Bis (tert-butyldimethylsilyl)-N-vinyloxycarbonylnormorphine (**157**)

A solution of 3,6-disilyl ether of morphine (**154**), (0.26 g, 0.51 mmol) in 1,2-dichloroethane (6 cm^3) and vinyl chloroformate (0.2 cm^3, 0.25 g, 5 equi.) were refluxed under nitrogen for 3 days. When the reaction was complete (followed by TLC), the solution was evaporated under reduced pressure to give a white solid. It was purified by column chromatography on silica eluting with chloroform to get the title compound (**157**), (0.28 g, 97% yield). R_f = 0.90 ($CHCl_3$: CH_3OH = 9 : 1); δ_H ($CDCl_3$) : 0.097, 0.12, 0.14 and 0.21 (4 x 3H, 4 x s, 4 x Si-CH_3), 0.93 and 0.97 (2 x 9H, 2 x s, 2 x Si-*t*-Bu), 1.90 - 2.00 (2H, m, 15-H_2), 2.52 (1H, m, 14-H), 2.75 (1H, m, 10-H_α), 2.89 (1H, d, *J* = 18 Hz, 10-H_β), 3.10 (1H, m, 16-H_α), 3.48 (1H, m, 16-H_β), 4.12 (1H, m, 9-H), 4.20 (1H, m, 6-H), 4.68 (1H, dm, *J* = 5.7 Hz, 5-H), 4.75 - 5.00 (2H, m, vinyl- CH=C$\underline{H}_2$), 5.26 (1H, m, 8-H), 5.65 (1H, m, 7-H), 6.42 - 6.62 (2H, q, AB system, *J* = 8.2 Hz, 1-H and 2-H), 7.20 - 7.30 (1H, m, vinyl- C$\underline{H}$=CH_2); *m/z* (%): (E.I.) 512 (50, M - *t*-Bu), 569 (8, M^+), 526 (5, M - C_2H_3CO); (C.I.) 570 (90, $[M+H]^+$), 512 (95)

Normorphine from 3,6-bis(tert-butyldimethylsilyl)-N-vinyloxycarbonylnormorphine (**157**)

Method 1.

The compound (**157**), (0.28 g, 0.49 mmol) was dissolved in dichloromethane (5 cm^3) and dry hydrogen chloride gas was passed for 1 hour. The solution was then evaporated and the residue was stirred with methanol (5 cm^3) at 45°C for 2 hours. The solution was evaporated to get the title compound (**94**). It was purified by dissolving in 1% sodium hydroxide solution, acidifying the solution with acetic acid

and then making basic with concentrated ammonia. The crystals of normorphine were collected by filtration washed with ice-cold water and dried in vacuum. (0.13 g, 97%) R_f = 0.05 ($CHCl_3$: MeOH = 9 : 1) R_f = 0.62 ($CHCl_3$: MeOH = 1 : 1) m.p. = 274 - 275° (*lit.*,[170] 276 - 277°) υ_{max} 3220, 3180, 1300 cm^{-1}: δ_H (CD_3OD) : 2.11 - 2.35 (2H, m, 15-H_2), 2.87 (1H, m, 14-H), 3.0 - 3.20 (2H, m, 16-H_2), 3.02 (1H, d, 10-H_α), 3.30 (1H, m, 9-H), 3.34 (1H, d, *J* = 18.0 Hz, 10-H_β), 4.26 (1H, m, 6-H), 4.92 (1H, dd, *J* = 5.1 Hz, 5-H), 5.32 (1H, dm, *J* = 9.9 Hz, 8-H), 5.76 (1H, dm, *J* = 10.1 Hz, 7-H), 6.57 (1H, d, *J* = 8.2 Hz, 1-H), 6.64 (1H, d, *J* = 8.1 Hz, 2-H); *m/z* (%): (E.I.) 271 (100, M^+), 201 (40), 150 (40), 148 (38); (C.I.) 254 (100, M - OH), 271 (82, M^+), 272 (40, M+H).

Method 2

A solution of 3,6-*bis* (TBDMS)-N-vinyloxycarbonyl normorphine (**157**), (0.2 g, 0.35 mmol) in 5cm^3 of methanol containing 3 drops of concentrated hydrochloric acid was heated under reflux for 2 hours (TLC examination showed the cleavage of silyl groups and carbamate group complete). The solution was evaporated and normorphine obtained was purified as explained above. (Yield = 0.092 g, 96%)

Normorphine using 1-chloroethyl chloroformate as a demethylating agent

A mixture of 3,6-*bis* (TBDMS)-morphine (**154**), (0.26 g, 0.51 mmol) in 1,2-dichloroethane (6 cm^3) and 1-chloroethyl chloroformate (0.5 cm^3, 0.66 g, *ca.* 9 equivalents) was heated under reflux in an atmosphere of nitrogen overnight. More 1-chloroethyl chloroformate (0.5 cm^3) was added and continued heating for 2 more days. The reaction was followed by TLC. R_f of 3,6-*bis* (TBDMS)-N-(1-chloroethoxycarbonyl normorphine = 0.89 ($CHCl_3$: CH_3OH = 9 : 1). When the reaction was complete, the reaction mixture was evaporated and the residue was heated under reflux with 10 cm^3 of methanol containing 3-4 drops of concentrated

hydrochloric acid for an hour. The solvent was evaporated off under reduced pressure and the residue of normorphine was purified as described above. (Yield = 0.11g, 80%)

*Preparation of N-bromoacetamide and its reaction with 3,6-*bis*(tert-butyl-dimethylsilyl)-morphine* **(154)**

(a) *N-Bromoacetamide*

To a solution of acetamide (2.0 g, 0.034 mol) in bromine (5.4 g, 0.034 mol) at 0 - 5°C, an ice cold aqueous solution of potassium hydroxide (50%) was added slowly, in small portions, stirring and cooling until the colour became light yellow. The mixture was allowed to stand at 0 - 5°C for 3 hours. It was then treated with solid sodium chloride (4g) and chloroform (20 cm^3) and warmed on a steam bath for 2-3 minutes. The clear red solution was decanted off and the residue was extracted with chloroform twice more (20 cm^3 and 10 cm^3). The combined extracts were dried (Na_2SO_4), filtered and mixed with hexane (50 cm^3) and chilled for 2 hours. The colourless crystals of N-bromoacetamide was collected with suction at the pump, washed with hexane and dried. (Yield = 1.8 g, 40%)

(b) *1-Bromo-3,6-bis(tert-butyldimethylsilyl)-morphine*

The compound (**154**), (0.26 g, 0.5 mmol) dissolved in methanol (5 cm^3) was kept cooled at 0 - 5°C while a solution of N-bromoacetamide (0.09 g, 0.65 mmol) in methanol (2 cm^3) was added very slowly (30 mins). The mixture was left stirring at 15°C for 3 hours. The reaction mixture was evaporated and the residue was column chromatographed on silica using chloroform - methanol solvent system to yield 1-bromo-3,6-*bis* (TBDMS)-morphine (**164**), (0.098 g, 33%) and the unreacted

compound (**154**), (0.05 g). R_f = 0.75 ($CHCl_3$: CH_3OH = 9 : 1); δ_H ($CDCl_3$) : 0.096, 0.12, 0.15 and 0.20 (4 x 3H, 4 x s, 4 x Si-CH_3), 0.91 and 0.96 (2 × 9H, 2 x s, 2 x Si-*t*-Bu), 1.98 (1H, m, 15-H_α), 2.60 (1H, m, 15-H_β), 2.80 (1H, m, 16-H_α), 2.81 (3H, s, N-CH_3), 2.83 (1H, dd, *J* = 18.6 Hz, 10-H_α), 2.92 (1H, d, *J* = 18.0 Hz, 10-H_β), 3.17 (1H, m, 16-H_β), 3.38 (1H, br.s, 14-H), 3.90 (1H, m, 9-H), 4.26 (1H, m, 6-H), 4.75 (1H, d, *J* = 5 Hz, 5-H), 5.17 (1H, dt, 8-H), 5.70 (1H, m, 7-H), 6.84 (1H, s, 2-H); *m/z* (Low E.V.E.I.) 536 (100%, M - *t*-Bu), 534 (90), 591 (25, M^+), 593 (25).

*Preparation of iodosobenzene and attempted oxidation of 3,6-bis(tert-butyl-dimethylsilyl)-morphine (**154**) with iodosobenzene.*

(1) *Preparation of iodosobenzene*

An aqueous solution of sodium hydroxide (3 M, 15 cm^3) was added slowly (5 mins) to finely ground iodosobenzene diacetate (3.2 g, 0.01 mol) with vigorous stirring. The lumps of solid were triturated with a glass rod and the mixture was stirred for 1 hour. Water (10 cm^3) was added to the mixture, stirred vigorously and filtered at the pump. The wet solid was triturated again with water (20 cm^3), filtered, washed with water (20 cm^3) and dried by maintaining suction. The dried solid was triturated with chloroform (10 cm^3), filtered and air-dried to give pure iodosobenzene (1.75 g, 80%).

(2) *Attempted oxidation of morphine disilyl ether* (**154**) *with iodosobenzene.*

Borontrifluoride-diethyl ether (0.3 g, 2 mmol) and then 3,6-*bis* (TBDMS)-morphine (**154**) (0.50 g, 1 mmol) were added to a stirred, ice cold (0 - 5°C) suspension of iodobenzene (0.24 g, 1.1 mmol) in a mixture of

dichloromethane (10 cm^3) and water (10 cm^3). The mixture was stirred at this temperature for 2 hours and then at room temperature for 2 hours. The mixture was neutralised with solid sodium hydrogen carbonate and extracted with chloroform. The chloroform extract on analysis was found to contain the starting material and no oxidation product of silyl morphine.

Oxidation of 3-(tert-butyldimethylsiliyl)- morphine (**155**) *to 3-(tert-butyl-dimethylsilyl)-morphinone* (**165**)

(1) *With manganese (IV) oxide.*

A solution of 3-(TBDMS)-morphine (**155**), (0.28 g, 0.7 mmol) in chloroform (50 cm^3) was stirred with activated manganese (IV) oxide (Aldrich) (2.8 g, 10 weight equivalents) at room temperature for 20 minutes. The mixture was filtered through a pad of silica gel (2-3 mm thick, taken in a sintered glass), washed with warm chloroform and the filtrate and washings were evaporated to give 3-(TBDMS)-morphinone (**165**), as an oil. It was purified further by flash column chromatography on silica with dichloromethane - methanol solvent mixture (98 : 2). Yield = 0.26 g, 91%; R_f = 0.43 ($CHCl_3$: CH_3OH = 9 : 1); υ_{max}: 3670, 3535, 3300 - 3000 (br), 2915, 2810, 1720, 1667, 1600, 1490, 1430, 1320, 1270 - 1170 (br), 980, 935 and 832 cm^{-1}; δ_H ($CDCl_3$) : 0.1 and 0.18 (2 x 3H, 2 x s, 2 x Si-CH_3), 0.97 (9H, s, Si-*t*-Bu), 2.40 (1H, dd, *J* = 18.6 and 5.1 Hz, 10-H_α), 2.46 (3H, s, N-CH_3), 2.57 (1H, m, 14-H), 3.09 (1H, d, *J* = 18.7 Hz, 10-H_β), 3.41 (1H, m, 9-H), 4.66 (1H, s, 5-H), 6.07 (1H, dd, $J_{8,7}$ = 10.3 and $J_{8,14}$ = 2.8, 8-H), 6.63 (1H, d, *J* = 10.4 Hz, 7-H), 6.52 - 6.64 (2H, dd, *J* = 8.2 Hz, 1-H and 2-H); *m/z* (%): (Low E.V. E.I.) 397 (100, M^+), 340 (90, [M - *t*-Bu]$^+$).

(2) *With selenium dioxide.*

Selenium dioxide (0.22 g, 0.2 mmol) was added to a mixture of dioxan (10 cm^3) and water (0.8 cm^3) and stirred at 40°C until dissolved. 3-(TBDMS)-morphine (**155**), (0.4 g, 0.1 mmol) was introduced to the above solution and the mixture was heated under reflux for 2 hours. The mixture was filtered, evaporated under reduced pressure and the residue was column chromatographed on silica with chloroform - methanol solvent mixture to yield 3-(TBDMS) morphinone (**165**), (0.06 g, 14.6% yield) and unchanged 3-(TBDMS)-morphine (**155**), (0.22 g).

(3) *With selenium oxide and tert-butyl hydroperoxide.*

A mixture of 3-(TBDMS)-morphine (**155**) (0.101 g, 0.25 mmol) in dichloromethane (12 cm^3), selenium dioxide (0.15 g, 1.4 mmol) and *tert*-butyl hydroperoxide (1 cm^3, 3 M solution in octane) was left stirring at room temperature for one day. TLC examination indicated no oxidation. So the mixture was heated under reflux for two days. The volatiles were removed under reduced pressure, the residue was extracted with chloroform, washed with sodium hydrogen carbonate solution, dried (Na_2SO_4) and evaporated. The product mixture was column chromatographed on silica with chloroform - methanol to yield 3-(TBDMS)-14-hydroxymorphinone (**166**), (*ca.* 0.01 g, <10% yield) and 3-(TBDMS)-morphinone (**165**), (0.045g, 43% yield). About 10% unreacted silyl morphine ether (**155**) was also recovered.

(4) *With tetrapropyl ammonium perruthenate and N-methylmorpholine N-oxide.*

To a stirred mixture of 3-(TBDMS)-morphine (**155**), (0.18 g, 0.45 mmol), N-methylmorpholine N-oxide (0.8 g, 0.7 mmol, 1.5 equivalents) and powdered 4 Å

molecular sieves (0.20 g) in dry dichloromethane (3 cm^3) was added solid TPAP (10 mg, 5 mol%) under nitrogen at room temperature. The mixture was then left stirring for 2 hours. The mixture was passed through a short column of silica (5 cm length, 1 cm diameter) and eluted with ethyl acetate. The solution was evaporated to give 3-(TBDMS)-morphinone (**165**), (0.16 g, 86% yield) which was chromatographically pure.

*3-(tert-Butyyldimethylsilyl)-dihydromorphinone (**175**, 3-tert-butyldimethylsilyl-hydromorphone)*

Hydrogen gas was passed through a mixture of 3-(TBDMS)-morphinone (**165**), (0.13 g, 0.33 mmol) in absolute ethanol (30 cm^3) and Pd/C catalyst (10%, 0.07 g) for 1 hour. The mixture was filtered, the residue was washed with ethanol and the filtrate was evaporated to give the title compound (0.12 g, 92%) as a glassy solid. R_f = 0.41 ($CHCl_3$: CH_3OH = 9 : 1). This product without further purification is converted to hydromorphone (**93**) as explained below.

Hydromorphone (**93**)

3-(TBDMS)-hydromorphone (**175**), (0.10 g, 0.25 mmol) dissolved in dry THF (2 cm^3) was stirred with tetrabutyl ammonium fluoride (0.5 cm^3, 1M solution in THF) under N_2 at room temperature for 30 minutes. When the reaction was complete (followed by TLC) the solution was evaporated, the residue was dissolved in minimum volume of dilute hydrochloric acid, cooled to 0°C and basified with concentrated ammonia. The white precipitate of hydromorphone formed was filtered, washed with cold water and dried. It was crystallised from ethanol. Yield = 0.064g, 90%. R_f = 0.21 ($CHCl_3$: MeOH = 9 : 1); m.p. = 265 - 266°C (lit.,[172] 266 -

267°C); υ_{max} 3380, 2660, 1710, 1615 cm^{-1}; δ_H (D_2O) (**93**.HCl) 1.16 (1H, m, 8-H_α), 1.98 (2H, m, 15-H_α and 15-H_β), 2.33 - 2.40 (2H, m, 7-H_α and 8-H_β), 2.65 (1H, td, *J* = 14.3, 4.8 Hz, 7-H_β), 2.77 - 2.89 (2H, m, 10-H_α, 16-H_α), 2.93 (3H, s, N-CH_3), 3.10 - 3.35 (3H, m, 14H, 16-H_β, 10-H_β), 4.01 (1H, br.s, 9-H), 5.08 (1H, s, 5-H), 6.75 - 6.82 (**AB** system, 2H, *J* = 8.2 Hz, 1-H and 2-H); *m/z* (%): (E.I.) 285 (90, M^+), 228 (25); (C.I.) 286 (100 $[M+H]^+$), 285 (60, M^+)

3-(tert-Butyldimethylsilyl)-14-hydroxymorphinone (**166**)

3-(TBDMS)-morphine (**155**), (0.62 g, 1.56 mmol) dissolved in chloroform (80 cm^3) was stirred with activated manganese (IV) oxide (6.0 g, 10 weight equivalent) at 38-40°C for 15 minutes. TLC on silica with chloroform - methanol (9:1) as solvent system showed the conversion of the compound (**155**), (R_f = 0.35) to 3-silyl morphinone (**165**), (R_f = 0.46) almost complete. Silica gel (1.8 g, 3 weight equi., Merck No 7736, Type 60H) was then added and continued stirring vigourously at the same temperature (38 - 40°C) for 3 hours. When the oxidation to 3-silyl-14-hydroxyl morphinone (**166**) was complete (followed by TLC, R_f = 0.55) the mixture was filtered through a sintered glass and the residue washed with warm chloroform (200 cm^3) containing 1% methanol. The filtrate on evaporation gave the title compound (**166**), (0.38 g, 59.2%) as an off-white solid. It was crystallised from ethyl acetate as colourless plates. R_f = 0.55 ($CHCl_3$: CH_3OH = 9:1); m.p. = 222-224°C (Ethyl acetate); υ_{max}: 3500, 3340 (br), 2905, 2840, 1740, 1700,1670, 1590, 1480, 1425, 1380, 1345, 1320, 1260-1180 (br), 1100, 1030, 990, 975, 940, 880 and 830 cm^{-1}; δ_H ($CDCl_3$): 0.10 and 0.16 (2 x 3H, 2 x s, 2 x Si-CH_3), 0.95 (9H, s, Si-*t*-Bu), 1.63 - 2.57(4H, m, 15-H_α, 15-H_β, 16-H_α, 16-H_β), 2.35 (1H, dd, *J* = 18.7, 6.0 Hz, 10-H_α), 2.44 (3H, s, N-CH_3), 3.03 (1H, d, *J* = 5.9 Hz, 9-H), 3.20 (1H, d, *J* = 18.7 Hz, 10-H_β), 4.67 (1H, s, 5-H), 6.16 (1H, d, *J* = 10.1 Hz, 8-H),

6.61 (1H, d, J = 10.1 Hz, 7-H), 6.53 - 6.64 (2H, AB system, J = 8.0 Hz, 1-H and 2-H); δ_H (DMSO): 5.4 (1H, br.s, 14-OH); δ_C ($CDCl_3$): 4.77 (Si-$\underline{C}H_3$), 4.64 (Si-$\underline{C}H_3$), 18.23 (Si-$\underline{C}Me_3$), 22.48 (C-15), 25.62 (Si-C($\underline{C}H_3$)$_3$), 29.55 (C-16), 42.55 (N-$\underline{C}H_3$), 45.12 (C-10), 46.71 (C-13), 64.16 (C-9), 67.79 (C-14), 86.86 (C-5), 119.46 (C-8), 122.54 (C-7), 125.46 (C-11), 130.55 (C-12), 134.67 (C-1), 137.85 (C-4), 146.35 (C-3), 147.45 (C-2), 194.03 ($\underline{C}$=O); *m/z* (%): (Low E.I.) 413 (100, M^+), 356 (90, [M - *t*-Bu]$^+$). [Found; C, 66.5; H, 7.5; N, 3.35. Required for $C_{23}H_{31}SiNO_4$; C, 66.8; H, 7.5; N, 3.4%].

Attempted oxidation of the morphinone (**165**), *to the 14-hydroxymorphinone* (**166**)

(1) *Oxidation with singlet oxygen*

Oxygen gas was bubbled through a mixture of 3-(TBDMS)-morphinone (**165**), (0.12 g, 0.3 mmol) dissolved in dichloromethane - methanol mixture (9 : 1; 50 cm^3) and Rose Bengal catalyst (10 mg, 0.01 mmol), maintained at a temperature of 10 - 12°C. The mixture was irradiated with a visible lamp (120V, 650W) for 1 hour. Thiourea was then added to the mixture and stirred for 12 hours. The solvents were evaporated off and the residue was extracted with chloroform. The chloroform extract was washed with water, dried (Na_2SO_4) and evaporated to give a residue which contained no 14-hydroxymorphinone (**166**).

(2) *Oxidation with selenium dioxide and tert-butyl hydroperoxide.*

A solution of 3-(TBDMS) morphinone (**165**), (0.10 g, 0.25 mmol) in dichloromethane (1 cm^3) was added slowly to a stirred solution of selenium dioxide (10 mg, 0.1 mmol) and *tert*-butyl hydroperoxide (1 cm^3, 3M solution in octane) in

dichloromethane (5 cm^3). The mixture was left stirring overnight at room temperature. TLC showed that no appreciable amount of the 14-hydroxymorphinone was formed.

3-(tert-Butyldimethylsilyl)-morphinone dienol acetate (**168**)

A mixture of 3-(TBDMS)-morphinone (**165**), (0.10 g, 0.25 mmol) , fused sodium acetate (20 mg) and acetic anhydride (3 cm^3) was heated under reflux under N_2 for 2 hours. The volatiles were removed under high vacuum and the residue was mixed with water and extracted with chloroform to give the title compound (**168**). It was purified by flash column chromatography on silica with chloroform - methanol (98 : 2) as solvent to yield the dienol acetate, (0.094 g, 84%). R_f = 0.73 ($CHCl_3$: CH_3OH = 9 : 1); δ_H ($CDCl_3$) 2.15 (3H, s, $COCH_3$), 2.51 (3H, s, N-CH_3), 5.4 (1H, s, 5-H), 5.52 (1H, d, *J* = 6.5 Hz, 8-H), 5.69 (1H, d, *J* = 6.5 Hz, 7-H), 6.5 - 6.6 (2H, dd, *J* = 8.5 Hz); *m/z* (%): (C.I.) 382 (100, M - *t*-Bu), 441 (42), 440 (40, M+H), 439 (12, M^+).

Attempted oxidation of the dienol acetate (**168**) *to 3-tert-butyldimethylsilyl)-14-hydroxymorphinone* (**166**)

The dienol acetate (**168**) (0.094 g, 0.21 mmol) was dissolved in a mixture of formic acid (98%, 0.5 cm^3) and sulphuric acid (1%, 2 cm^3) and to this mixture was added hydrogen peroxide (30%, 0.5 cm^3). The mixture was heated at 40°C for 6 hours, cooled, diluted with water and made basic with concentrated ammonia. The mixture was extracted with chloroform which on evaporation gave a residue (0.05 g). The residue on analysis was found to be some decomposition product of the substrate which contained no silyl group and aromatic ring.

3-(*tert-Butyldimethylsilyl*)-14-hydroxydihydromorphinone (**169**, 3-(*tert-butyl-dimethylsilyl*)-oxymorphone)

A mixture of the hydroxymorphinone (**166**), (0.20 g, 0.48 mmol) dissolved in absolute ethanol (50 cm^3) and Pd/C (10%, 0.1 g) was stirred under hydrogen for 2 hours. The mixture was filtered and the residue was washed with ethanol. The filtrate and the washings were evaporated to give the dihydromorphinone (**169**), (0.20 g, quantitative yield). It was crystallised from ethyl acetate. m.p. 133 - 135°C; R_f = 0.49 ($CHCl_3$: CH_3OH = 9 : 1); υ_{max}: 3650, 3380 (br), 2900, 2800, 1720, 1670, 1592, 1430, 1310, 1270-1180 (br), 1095, 1020, 985, 923, 880 and 825 cm^{-1}; δ_H ($CDCl_3$): 0.19 and 0.26 (2 x 3H, 2 x s, 2 x Si-CH_3), 0.98 (9H, s, Si-*t*-Bu), 1.52 (1H, m, 15-H_α), 1.67 (1H, m, 8-H_α), 1.97 (1H, m, 15-H_β), 2.20 - 2.60 (3H, m, 7-H_α, 7-H_β and 8-H_β), 2.53 (3H, s, N-CH_3), 2.67 (1H, m, 16-H_α), 2.68 (1H, dd, *J* = 18.5, 5.5 Hz, 10-H_α), 3.02 (1H, m, 16-H_β), 3.15 (1H, d, *J* = 18.5 Hz, 10-H_β), 3.20 (1H, m, 9-H), 4.63 (1H, s, 5-H), 6.55 - 6.66 (2H, q, AB system, *J* = 8.2 Hz, 1-H and 2-H); *m/z* (%): (E.I.) 358 (100, [M - *t*-Bu]$^+$), 315 (45), 415 (20, M^+).

Attempted 14-OH protection of the oxymorphone (169) as tert-butyldimethyl-silyl-ether

a) *With TBDMSCl*

A solution of 3-(TBDMS)-oxymorphone (**169**), (0.32 g, 0.77 mmol) in DMF (5 cm^3) was stirred with TBDMSCl (0.40 g, 2.6 mmol, 3 equivalents) and imidazole (0.14 g, 1.9 mmol, 2.5 equivalents) under nitrogen at room temperature. TLC taken after 4 hours indicated no silylation of the hydroxy group. So the mixture was left stirring overnight and found that no silylation had taken place. The starting material

was recovered from the reaction mixture.

b) *With TBDMS perchlorate*

A mixture of 3-TBDMS-oxymorphone (**169**), (0.42 g, 1 mmol), TBDMS perchlorate (0.22 g, 1 mmol) and pyridine (0.08 g, 1.1 mmol) in dry acetonitrile (5 cm^3) was stirred under nitrogen at room temperature for 2 hours. The reaction mixture was then poured into a mixture of saturated sodium bicarbonate solution and chloroform. The chloroform layer was washed, dried and evaporated under high vacuum to give a residue which was found to be the starting material.

c) *With TBDMS triflate*

A mixture of 3-TBDMS-oxymorphone (**169**), (0.4 g, 1 mmol), dry 2,6-lutidine (2 equi.) and TBDMS triflate (0.4 g, 1.5 equi.) in dichloromethane was stirred under nitrogen for 1 hour. TLC examination of the reaction mixture showed that no reaction had taken place.

3-(tert-Butyldimethylsilyl)-14-acetoxydihydromorphinone (**170**)

A mixture of 3-silyl-14-hydroxy dihydromorphinone (**169**), (0.62 g, 1.4 mmol) and acetic anhydride (10 cm^3) was heated under reflux for 1.5 hours. The volatiles were removed under high vacuum, the residue was dissolved in a mixture of water and chloroform, basified the mixture with ammonia to pH 9 and extracted with chloroform. The organic extract was dried (Na_2SO_4) and evaporated to give a brown residue which was column chromatographed on silica using chloroform to elute the title compound (**170**), (0.63 g, 92%). It was recrystallised from ethanol to give white shiny crystals. R_f = 0.60 ($CHCl_3$: CH_3OH = 9 : 1); m.p. 178 - 179°C;

υ_{max} .cm^{-1}: 2860, 2792, 2250, 1690, 1575, 1403, 1330, 1210 - 1160 (br), 1130, 1070, 960, 920 and 805; δ_H ($CDCl_3$): 0.18 and 0.26 (2 x 3H, 2 x s, 2 x $SiCH_3$), 0.99 (9H, s, Si-*t*-Bu), 1.47 (1H, dd, *J* = 11.7, 4.2 Hz, 15-H_α), 1.66 (1H, td, *J* = 14.3, 4.0 Hz, 8-H_α), 2.00 (1H, dd, *J* = 18.5 and 5.6 Hz, 10-H_α), 2.18 (3H, s, N-CH_3), 2.25 (1H, dd, *J* = 11.8 and 3.4 Hz, 15-H_β), 2.32 (3H, s, $COCH_3$), 2.40 - 2.55 (3H, m, 7-H_α, 7-H_β and 8-H_β), 2.58 (1H, dd, *J* = 14.8 and 5.5 Hz, 16-H_α), 2.79 (1H, m, *J* = 14.3 and 2.7 Hz, 16-H_β), 3.18 (1H, d, *J* = 18.5 Hz, 10-H_β), 4.16 (1H, d, *J* = 5.3 Hz, 9-H), 4.58 (1H, s, 5-H), 6.55 - 6.66 (2H, dd, *J* = 8.2 Hz, 1-H and 2-H); *m/z* (%): (Low E.V. E.I.) 400 (100, [M - *t*-Bu]$^+$), 457 (50, M^+).

N-Vinyloxycarbonyl-3-(tert-butyldimethylsilyl)-14-acetoxydihydronormorphinone **(171)**

A solution of 3-(TBDMS)-14-acetoxydihydromorphinone (**170**), (0.30 g, 0.66 mmol) in 1,2-dichloroethane (10 cm^3) was heated under reflux with vinyl chloroformate (0.3 cm^3, 0.38 g, 5 equi.) under nitrogen for 3 days. More vinyl chloroformate (0.2 cm^3 each) was added after 25 and 50 hours. When the reaction was complete (followed by TLC), the volatiles were removed under reduced pressure first and then at high vacuum to get the vinyl carbamate (**171**), (0.33 g, 98%) as an off-white solid. It was purified by flash column chromatography on silica with chloroform as eluant. R_f = 0.87 ($CHCl_3$: CH_3OH = 9 : 1); υ_{max} .cm^{-1} 3500 (br), 1698, 1640, 1600, 1415, 1360, 1312, 1180 - 1270 (br), 1140, 990, 940, 830; δ_H ($CDCl_3$): 0.20 and 0.27 (2 x 3H, 2 x s, 2 x Si-CH_3), 1.00 (9H, s, Si-*t*-Bu), 2.12 (3H, s, $COCH_3$), 4.50 (1H, m, 9-H), 4.62 (1H, s, 5-H), 4.81 (1H, m, CH=C$\underline{H}_2$), 5.61 (1H, m, CH=C$\underline{H}_2$), 6.59 - 6.72 (2H, dd, *J* = 8.1 Hz, 1-H and 2-H), 7.16 - 7.26 (1H, m, C$\underline{H}$=CH_2); *m/z* (%): (C.I.) 71 (100, $C_2H_3CO_2$), 456 (73, [M - *t*-Bu]$^+$), 514 (6, [M+H]$^+$), 513 (5, M^+).

Deprotection of tert-butyldimethylsilyl and vinyloxycarbonyl groups

14-Acetoxydihydronormorphinone hydrochloride (14-acetylnoroxymorphone hydrochloride) (**174**.HCl)

Method 1

Dry hydrogen chloride gas was passed through a solution of N-vinyloxycarbonyl-3-(TBDMS)-14-acetoxydihydronormorphinone (**171**), (0.30 g, 0.58 mmol) dissolved in dichloromethane (5 cm^3) for 1 hour. The solution was then evaporated and the residue was dissolved in methanol (10 cm^3) and heated under reflux for 2 hours. The resultant solution on evaporation gave 14-acetyl-noroxymorphone hydrochloride (**174**.HCl), (0.205 g, 95.9%). This was used without further purification to prepare noroxymorphone (**106**). R_f = 0.72 ($CHCl_3$:CH_3OH = 9:1); δ_H (CD_3OD): 2.31 (3H, s, $COCH_3$), 2.55 (1H, br.s, N-H), 3.26 (1H, m, 9-H), 4.93 (1H, s, 5-H), 6.69 - 6.78 (2H, dd, AB system, J = 8.2 Hz, 1-H and 2-H).

Method 2

A solution of N-vinyloxycarbonyl-3-(TBDMS)-14-acetylnoroxymorphone (**171**), (0.10 g, 0.2 mmol) in methanol (5 cm^3) containing 3 drops of concentrated hydrochloric acid was heated under reflux for 1 hour. The resultant solution on evaporation gave 14-acetyl noroxymorphone hydrochloride (**174**.HCl), (0.07 g, 98%).

Noroxymorphone (**106**)

A mixture of 14-acetylnoroxymorphone hydrochloride (**171**.HCl), (0.20 g, 0.55 mmol) and 25% dilute sulphuric acid (2 cm^3) was heated at 100 - 102°C under nitrogen for 5 hours. The mixture was cooled to 0°C and basified with concentrated ammonia. The precipitate was collected by centrifugation and dried. The crude product was dissolved in minimum amount of dilute hydrochloric acid, cooled to 0°C, basified with concentrated ammonia and the precipitate was collected, washed with cold water and dried to give noroxymorphone (0.138 g, 88%). υ_{max} (Nujol, 106.HCl) 3570, 3500 - 3280, 3160, 1710, 1620, 1540, 1055, 1020, 950, 910 and 885 cm^{-1}; δ_H (D_2O, 106.HCl) 1.65 (1H, dd, J_{gem} = 14.5 Hz and $J_{10,9}$ = 4.5 Hz, 10-H_α), 1.74 (1H, m, 15-H_α), 2.02 (1H, dm, J_{gem} = 14.1 Hz, 15-H_β), 2.28 (1H, dt, J_{gem} = 14.8 Hz, 8-H_α), 2.63 (1H, td, J_{gem} = 13.4 Hz and 4.9 Hz, 7-H_α), 2.85 (1H, td, J = 13.2 Hz and 4.2 Hz, 7-H_β), 2.99 (1H, td, J = 14.8 Hz and 5.1 Hz, 8-H_β), 3.19 - 3.32 (3H, m, 10-H_β and 16-H_2), 3.87 (1H, m, 9-H), 4.99 (1H, s, 5-H), 6.75 - 6.82 (2H, dd, AB system, J = 8.3 Hz, 1-H and 2-H); m/z (E.I.) 287 (100%, M^+). 202 (60); (C.I.) 288 (100, M + 1), 287 (70)

Noroxymorphone (**106**) *from 3-(tert-butyldimethylsilyl)-14-acetyloxymorphone* (**170**) *using 1-chloroethyl chloroformate*

A mixture of 3-(TBDMS)-14-acetyloxymorphone (**170**), (0.11 g, 0.24 mmol) in 1,2-dichloroethane and 1-chloroethyl chloroformate (0.5cm^3, 4.6 mmol) was heated under reflux under nitrogen for 2 days. (TLC showed the completion of the reaction). The volatiles were removed under reduced pressure and the residue was column chromatographed on silica with chloroform solvent to yield N-(1-chloroethoxycarbonyl)-3-(TBDMS)-14-acetylnoroxymorphone (**176**), (0.096 g, 72.6%). The carbamate (**176**) was refluxed with 5 cm^3 of methanol containing 3

drops of concentrated hydrochloric acid for 6 hours. When hydrolysis of N-carbamate group and TBDMS groups were completed (TLC) the solution was evaporated and the residue was heated under reflux with hydrochloric acid (6M, 5 cm^3) for 5 hours. The resultant solution was cooled, basified with concentrated ammonia and the precipitate of noroxymorphone was collected and purified as explained earlier (0.047 g, 68% overall yield).

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