STUDIES ON CYCLOADDUCTS OF THEBAINE AND THIOALDEHYDES

A thesis presented in part fulfillment of the requirements for the Degree of Doctor of Philosopy

by

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Dedication

This thesis is dedicated to my mum, Bridget, and John, my dearly departed dad.

"I DID IT"

(Rocky Balboa in 'Rocky')

Acknowledgements

I would like to thank my supervisor, Professor G.W. Kirby, for help and guidance throughout the course of this project. Thanks are also due to the technical staff of the Chemistry Department for their analytical work and helpful advice. I must mention the inhabitants, past and present, of the Loudon Lab and Lab 313 for their friendship and help during this period of work especially Guy Clarkson, Calum Henderson, Alistair Marr, Alison Peden, David Jaap, Neill Woods, Bill McGregor and Alistair Sclare. A special note of thanks to Miss Jean Hough for her time and patience in the excellent typing of this thesis.

A special thanks is due to my family; my sister Maureen, my brothers John and Paul but most especially my mum, for their continual love and support. And finally to Michelle McQuillan (nee McCusker) my best friend and wife, for proof reading this thesis and for her ever present love, support and encouragement.

CONTENTS PAGE

SUMMARY

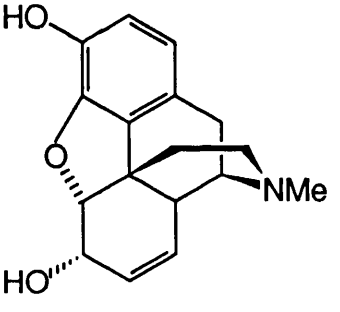
A new route to the synthesis of 14β-alkylmorphinans, of interest as potential analgesics, has been developed. Several such morphinans have been produced by desulphurisation of the Diels-Alder cycloadducts of thebaine and thioaldehydes, or of related, rearranged codeinones. Several methods of desulphurisation were explored. For example the 8α-ethoxycarbonyl-7-thia cycloadduct (49a) gave the 6,7-didehydro-14β-ethyl acetate derivative (114) on desulphurisation with Raney nickel, and also with tri-n-butyltin hydride; the (19S)-anilinoenone and thiobenzaldehyde codeinone derivatives (131) and (138), each gave 8β,14β-methano derivatives, i.e. (132) and (139), respectively, with Raney nickel; while the ethyl ester codeinone derivative (86) gave the 14β-alkylcodone (128) on treatment with aluminium amalgam. Raney nickel was found to be the best method for desulphurisation.

The Diels-Alder cycloadducts of thebaine and thioaldehydes were known to undergo molecular rearrangements under certain conditions. Several new rearrangements of these cycloadducts were encountered during this project. For example the 7-thia cycloadduct (49a) of thebaine and ethyl thioxoacetate gave a cyclopropane derivative (85) and a lactone (176) when treated with base under different conditions. As a necessary adjunct to studies on Raney nickel desulphurisation in ethanol, the chemistry of various codeinone acetals was investigated. For example, the cycloadduct (49b) of thebaine and p-nitrothiobenzaldehyde was converted in hot ethanolic ethoxide into a rearranged, 6,6-diethoxy derivative (99). Surprisingly, when this acetal was treated with methanolic methoxide, exchange of the hindered 6α-ethoxy group occurred, to give the corresponding 6β-ethyl-6α-methyl acetal (102).

1. INTRODUCTION

1.1 Natural Products

It is Man's ability to use his intellect to the full that has made him the most successful species to evolve on our planet. Nature has supplied all living creatures with essential food and water, but Man has used other natural substances for his benefit, for example, the extracts from plants, as medicines, perfumes, dyes, poisons etc. In recent history, morphine (1), a powerful analgesic, has been obtained from the opium poppy; menthol (2), a widely used flavouring and perfumery agent, from the peppermint plant; indigo, a blue dye, from plants bearing the same name; atropine (3), a muscle relaxant, from the leaves and roots of Atropa belladonna, the deadly nightshade.



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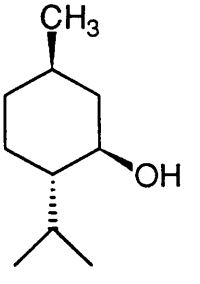

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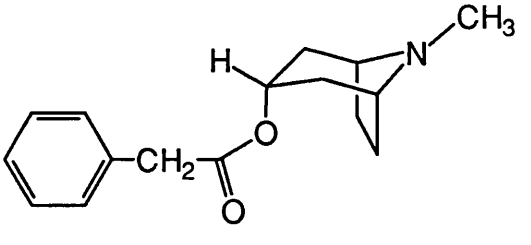

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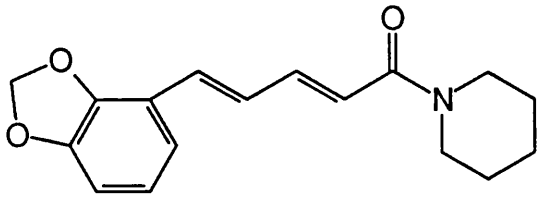
1.2 Alkaloids

Of the compounds mentioned above, two are alkaloids.[1] The term alkaloid applies to a very large group of compounds. These all contain at least one nitrogen atom but it need not cause "alkali-like" properties as the pharmacist W. Meissner implied by his term "alkaloid". Indeed, a satisfactory modern definition is extremely difficult to find, because chemists and pharmacognosists often differ in deciding what are and what are not alkaloids. Pelletier put forward this simple definition;[2]

> "An alkaloid is a cyclic organic compound containing nitrogen in a negative oxidation state which is of limited distribution among living organisms.

Nowadays, within the broader definitions are included amides, such as piperine (4); amino oxides, such as indicine N-oxide (5); and quaternary ammonium salts such as laurifoline chloride (6). However, nitro compounds such as aristolochic acid-II (7), from Aristolochia species are excluded. Traditionally, the widespread compounds such as amino acids, amino sugars, peptides, proteins, nucleic acids, nucleotides, porphyrins and vitamins are not classed as alkaloids.

The reasons why plants or animals produce such compounds having remarkable physiological activity is still to be fully understood, but one of the reasons must be the simplest facet of life; that is survival. The skin of the brightly coloured Columbian arrow-poison frog, Phyllobates aurotaenia, contains a highly lethal venom containing two steroidal alkaloids, one a cardiotoxin and the other a neurotoxin.[3] This helps to minimise attack by predators and thus enhances the survival of the frog. This principle can also be applied to the plant world. The often bitter taste and the biological activity of alkaloids may be part of the plant's defence system against grazing animals or insects.



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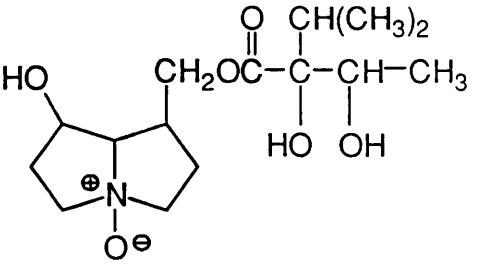

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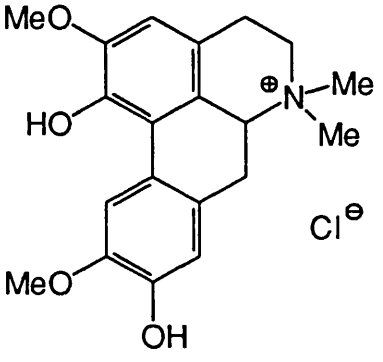

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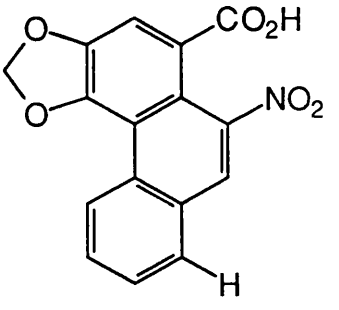


(7)

Other reasons for the presence of alkaloids may be their action as chelating agents, i.e. to help a plant in selecting one metal from the soil and rejecting others or as pheromones, as growth regulators etc.

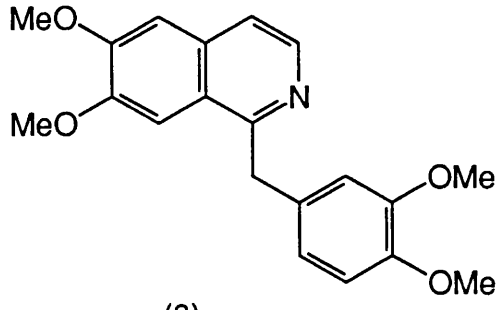
1.3 Opium Alkaloids[4,5]

The first alkaloid to be isolated in a pure state was morphine, extracted by Serturner in 1805 from the opium poppy, Papaver somniferum. When the ripe seed capsule of the poppy is cut, a viscous liquid is exuded which hardens and darkens on exposure to air. This hard sticky mass is known as opium. Opium contains over fifty alkaloids[6] (see Table 1), morphine being the major constituent, constituting 10-20% of its weight. These alkaloids fall into several classes. Examples are the papaverine alkaloids, e.g. papaverine (8) and laudanosine, and the protopines, e.g. protopine (9) and

Table 1 Major alkaloids from opium (with their discoverers and dates)

Morphine	Serturner	1805
Codeine	Robiquet	1832
Papaverine	G. Merck	1848
Noscapine	Derosne	1803
Thebaine	Thiboumery/Pelletier	1835
Narceine	Pelletier	1832
Cryptopine	T. & H. Smith	1867
Laudanosine	Hesse	1871

cryptopine. However, the best known are those alkaloids of the morphine series.[5] Examples of this group are morphine (1), codeine (10), and thebaine (11).



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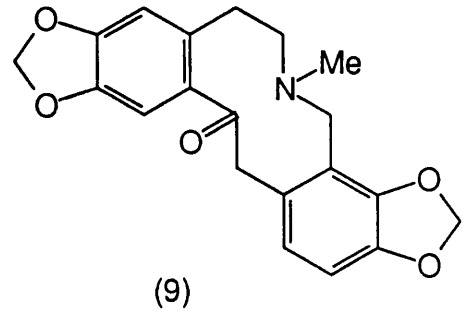

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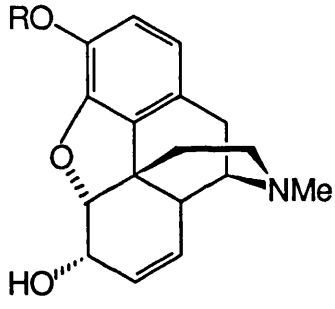
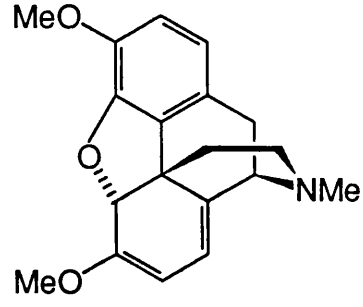


R = H (1)

R = Me (10)



(11)

Alkaloids of a particular class are not necessarily confined to one species or even genus of plant, e.g. alkaloids of the morphine group have been isolated from the following plant species:

Cocculus laurifolius, C. trilobus;

Papaver bracteatum, P. nudicaule, P. setigerum, P. somniferum;

Stephania epigae, S. gracilenta, S. suberosa.

Thebaine (11) is found in many Papaver species, but morphine (1) and codeine (10) are almost unique to Papaver somniferum, except for small amounts that are found in Papaver steigerum.

1.4 Analgesia

The pharmacologically active constituents of opium have been employed in medicine for many thousands of years. Authenticated samples of the extracts from the opium poppy have been found in the tomb of the Egyptian Cha (15th century BC). Even today, morphine is still the most commonly used analgesic for the control of severe pain even though there are more potent analgesics available. It is also used as an anti-diarrhoeal and sedative. Codeine (10) is about 10% as potent as morphine. Its ease of administration, due to its oral activity, has led to its use in combination with aspirin-like drugs, in a variety of pharmaceutical products. It is widely used for the treatment of mild to moderate pain, and is also an effective agent for the control of the cough reflex, i.e. as an antitussive. Although thebaine is highly toxic and of no therapeutic use itself, its chemical reactivity makes it a valuable starting material for the synthesis of useful analgesics. Sir Robert Robinson once described it as,

"the star performer in the field of molecular acrobats"

Analgesia[7] is defined as the absence of pain without loss of consciousness, while anaesthesia is similar except that consciousness is lost. The detailed reasons why drugs like morphine have such effects is beyond the scope of this Introduction; however, a simplified synopsis will be given here. Pain is a sensation that is common to all animals. It is a response from the body informing the brain of impairment. The sensation of pain is passed through a series of nerves to the spinal cord and the brain (the central nervous system, CNS). A biological response is then triggered off which releases natural pain killers, the enkephalins, which help to moderate this feeling of pain.

1.5 Opiate Receptors

The powerful analgesic effect of morphine long implied the existence of morphine receptors in the CNS, but only recently have they been identified, by radioactivity methods. The discovery of opiate (i.e. morphine-like) receptors in the brain and other nervous tissue, suggested that the organism must be producing its own morphine-like substances with the ability of relieving pain. Hughes, Kosterlitz[8] and co-workers discovered the first two endogenous ligands of the opiate receptor. They were found in pig brain and are pentapeptides. Structurally they are very alike. They were Met-enkephalin (12) and Leu-enkephalin (13).

Met-enkephalin H-Tyr-Gly-Gly-Phe-Met-OH (12)

Leu-enkephalin H-Tyr-Gly-Gly-Phe-Leu-OH (13)

Tyr ≡ L-tyrosine Gly ≡ glycine Phe ≡ L - phenylalanine

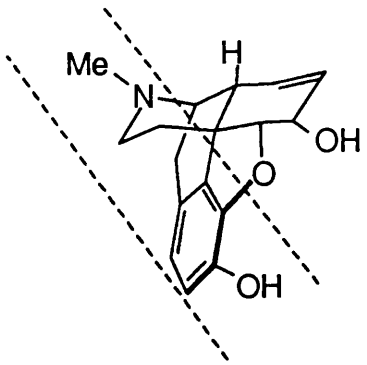
Met ≡ L-methionine Leu ≡ L-leucine

So far, four types of opiate receptor have been identified, namely the μ, κ, σ, and δ receptors. The structure and function of these receptors is not yet fully comprehended, but they are all macromolecules to which the molecules of morphine or an enkephalin can bind specifically. The binding sites probably have a flat lipophilic surface, which can accommodate the benzene ring of the tyrosine end of the enkephalins, or of morphine; a cavity, which can accommodate the hydrocarbon portions; and an ionic site with which the protonated amino groups can bind. However, each receptor is capable of binding several molecules having different shapes and sizes. This lack of selectivity is very important because the many "side-effects", i.e. effects other than analgesia, of morphine and other opiates have been attributed to its ability to bind to different

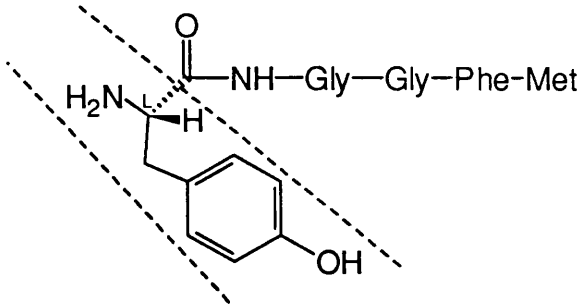
receptors. The undesirable effects such as respiratory depression, dysphoria, acquired tolerance and physical dependence may be mediated by the μ receptor which also seems to be the main receptor involved in the suppression of pain. The κ receptor may be responsible for sedation as well as analgesia. Hallucinations and dysphoria may be associated with the σ-receptor and as yet the role of the δ-receptor is not fully understood. There is, therefore justification to carry out research to produce yet more opiates and, one hopes, find some with greater selectivity.

1.6 Structural Features

The only structural similarity between morphine (1) and, for example, Met-enkephalin (12), is the phenolic ring and the basic nitrogen atom separated by a two-carbon chain. This phenylethylamine unit is apparently important in the structural-activity relationships of these and other opiate analgesics. It is not surprising that removal of the N-terminal tyrosine residue of the enkephalins results in complete loss of activity. In 1939, Eisleb and Schaumann[9], long before the enkephalins were discovered, recognised the structural similarity between meperidine (14) (drawn in the conformation that resembles that of morphine) and morphine (1A). It was found that meperidine (demerol) (14) has an analgesic potency in man of approximately one-eighth that of morphine. This discovery that a simple molecule, containing only a part of the morphine skeleton, was potent, stimulated further synthetic interest in this field of research.



(1A)



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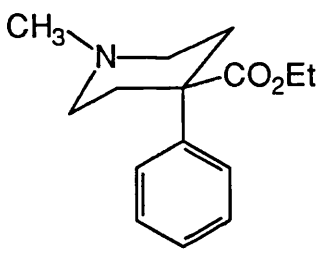
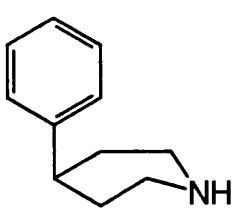


Meperidine (USA), or
pethidine (UK)

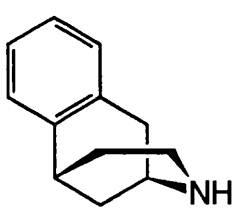
(14)

Meperidine (14) is a 4-phenylpiperidine (15). Benzomorphan (16) and morphinan (17) are other partial morphine skeletons which have been subjected to considerable synthetic manipulation in recent decades.



(15)

Phenylpiperidine



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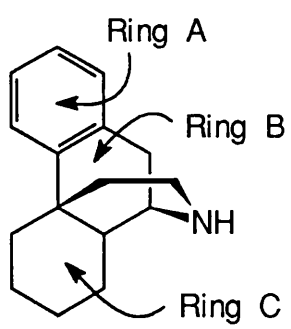
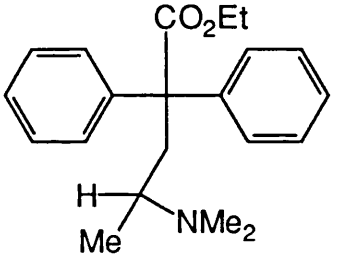
Benzomorphan



(17)

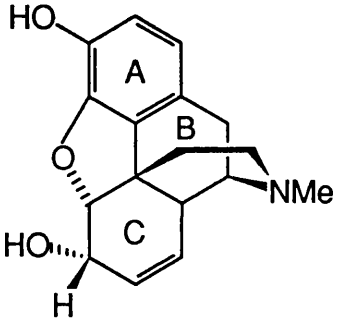
Morphinan

An analgesically active, acyclic compound (apart from phenyl groups), the simplest structural type related to morphine, was synthesised in the late 1940's. Methadone (18), and other "acyclic" compounds, have found use in medicine as "out-patient" medicines for the treatment of opioid physical dependence.



(18)

However, most research has been carried out on the morphinans [see (17)] basically because they contain a complex 4-ring system identical to that of morphine (1B). This molecule is essentially "T" shaped[10,11] since ring C and the ethanamine bridge unit are virtually perpendicular to rings A and B. This structural feature means that the molecule has an open face as well as a hindered face. This is important, as will be discussed later, since it determines greatly the outcome of many chemical reactions carried out on morphinans.



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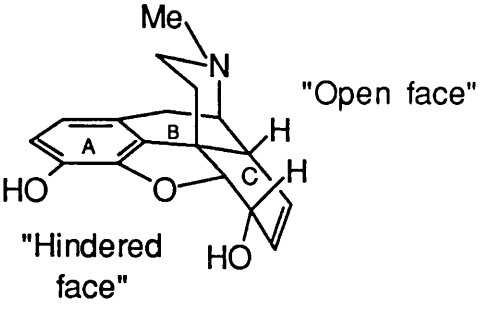


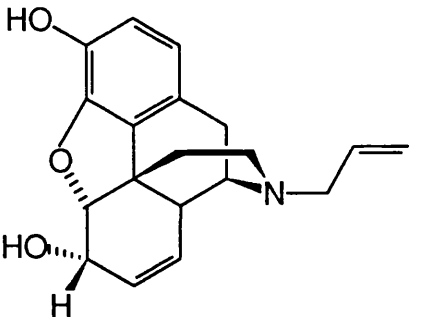
(1B)

1.7 Opiate Antagonists

Morphine is probably as well known for its illegal misuse as a drug inducing a state of euphoria and pleasant sedation as it is for its powerful painkilling properties. It is also addictive and regular users become tolerant of its effect thus requiring a larger dose and thus risking death by respiratory depression. Withdrawal of the drug, once tolerance has developed, produces an unpleasant physical reaction. An overdose of morphine, a powerful analgesic (an agonist), can be countered by a powerful antidote (an antagonist). These antagonist molecules can displace the agonist from the receptor and thus remove the effects of the agonist. Some antagonists can be analgesics as well and are then termed "partial agonists". These compounds are generally safer for use in medicine; one particular value being that the risk of overdosing is removed.

The first morphine antagonist to be discovered was nalorphine, N-allylnormorphine (19). Nalorphine not only displaces morphine from the receptor site but it is also an analgesic of substantial potency. However, it does have one major drawback; its clinical use is limited by often severe psychotomimetic side-effects at analgesic doses. In clinical use today for opiate overdose are naloxone (20) and naltrexone (21). Both are almost pure narcotic antagonists i.e. they have virtually no analgesic properties of their own.

Targets for current research are compounds which (a) are selective for particular receptors, (b) are potent but have no undesirable side-effects, and (c) are easy and cheap to produce in large quantities. It is not yet clear whether targets (a) and (b) are intimately connected. Of course, it is unlikely that a single compound will have all the desirable properties but world-wide research is in continual progress to achieve improved opiate analgesics.



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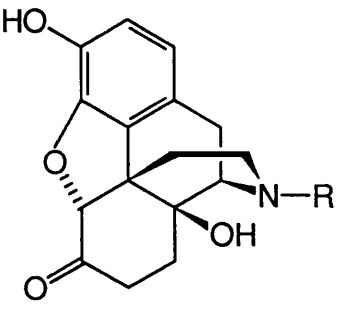
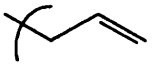
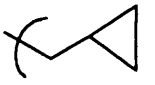
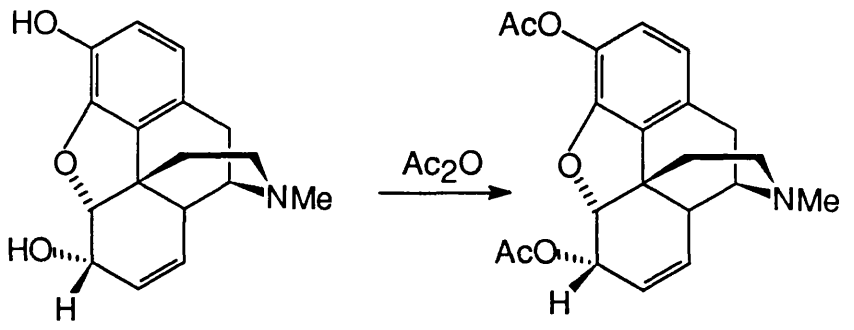


R =  Naloxone (20)

R =  Naltrexone (21)

1.8 Chemical Transformations of Morphine Alkaloids[12]

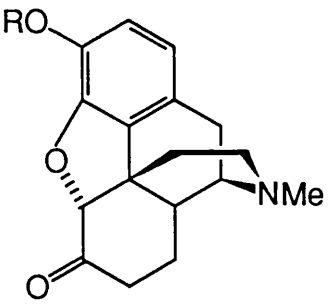
For over 100 years chemists have carried out chemical manipulations of morphine alkaloids and have synthesised simpler opiates. In this way, it has been possible to relate their pharmacological properties to structure and hence build up a set of structure-activity relationships. One of the early chemical transformations of morphine was acylation of its two hydroxyl groups with acetic anhydride to produce the diacetyl derivative, heroin (22) (Scheme 1). Heroin has approximately 2.5 times the potency of morphine and is still used as a powerful painkiller. However, despite original claims that it is non-addictive and causes less respiratory depression than morphine in animals, heroin does in fact have similar undesirable side-effects to morphine.



(1) (22)

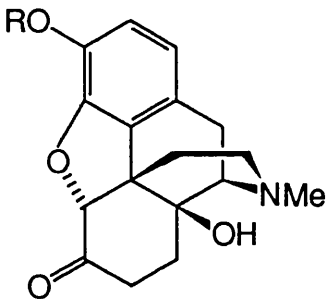
Scheme 1

Morphine itself finds only limited application as a starting material in opioid research. In fact, most of the morphine produced from opium is converted into codeine, because the natural supply of the latter is small. The useful analgesics (23)-(26) are formed by simple chemical transformations of existing morphinans. The derivatives (25) and (26) are prepared from thebaine rather than morphine or codeine.



Dihydromorphinone (hydromorphone) (23) ; R = H

Dihydrocodeinone (hydrocodone) (24) ; R = Me



14β-Hydroxydihydromorphinone (oxymorphone) (25) ; R = H

14β-Hydroxydihydrocodeinone (oxycodone) (26) ; R = Me

Many compounds have been derived from morphine, codeine, and especially thebaine and, from this extensive research, several generalisations can be made about the effects of modification of the morphinan nucleus on analgesic power. Some of these generalisations are as follows:

i) Methylation of the phenolic hydroxyl group decreases the potency. This modification and its effects is seen with morphine (1) and codeine (10); codeine is ca. 10% as potent as morphine.

ii) Methylation of the C-6 alcoholic hydroxyl group usually increases the potency somewhat.

iii) Reduction of the 7,8-double bond of, for example, morphine and codeine, results in an approximately three-fold increase in activity. Dihydromorphine and dihydro-codeine are easily produced by palladium catalysed hydrogenation of morphine and codeine, respectively. Dihydrocodeine, alone or in conjunction

with the non-steroidal anti-inflammatory analgesic, ibuprofen, is used as an analgesic in human medicine.

iv) Oxidation of the C-6 hydroxyl group to a carbonyl group increases the potency significantly. Although neither dihydromorphinone (23) nor dihydrocodeinone (24) is superior to morphine in freedom from side-effects, they are found in a variety of antitussive and analgesic preparations in use today.

v) Reductive removal of the 6-hydroxyl group increases the activity of morphine about three times.

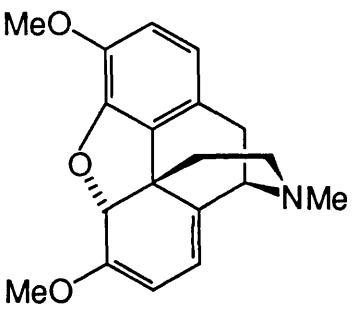
vi) Complete loss of activity is generally observed if the nitrogen-containing ring is cleaved.

vii) Replacement of the N-methyl group by various alkyl, aralkyl, alkenyl, or cycloalkyl groups can lead to significant changes in the molecule's physiological effect, i.e. its agonist or antagonist ability, as well as its potency. Opioid agonists generally have the N-methyl group present while antagonists have N-allyl, N-cyclopropylmethyl, or related groups. The N-β-phenylethyl derivative is the most potent, simple N-substituted derivative found so far. It can be ca. 14 times more potent than its N-methyl analogue. These generalisations are far from being comprehensive but show trends that can be utilised in the design of new compounds. These effects are not necessarily additive nor do they in any way help in dissecting analgesia from the side effects commonly associated with the opioids. As expected, the enantiomers of morphinan analgesics have little or no activity. The foregoing effects encompass only about a 10-fold change in potency. A structural change causing a vastly greater increase in potency will now be described.

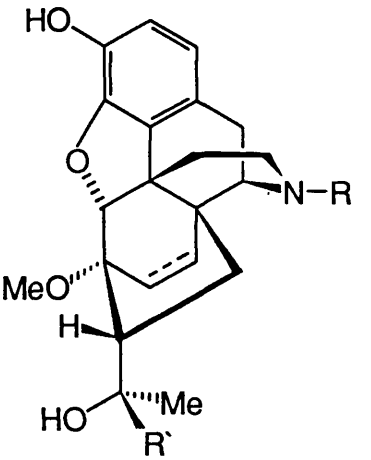
1.9 Highly Potent Morphinan Derivatives

The foregoing simplifications and modifications of the morphine nucleus were aimed at pharmacological selectivity, but Bentley and co-workers[13] employed the converse approach to the problem. They aimed to increase the rigidity and complexity of the morphine nucleus, as the means for achieving selectivity. Their idea was that a complex molecule would find only selective sites or specific orientations at the receptors, and thus be more selective in its effects. This idea again gave rise to an extensive area of opioid research. Their approach was to use the diene system of thebaine (11) in Diels-Alder reactions. The resultant cycloadducts would be rigid and more complex in structure. Indeed many new cycloadducts and especially their derivatives were more potent than their structurally similar morphinans. This work produced many useful, potent agonists and antagonists. Etorphine (27) is some 1000 times more potent than morphine and is used in veterinary medicine to sedate large animals. An antagonist such as diprenorphine (28) is ca. 100 times more potent than nalorphine (19). The partial agonist, buprenorphine[14] (29) is 10-20 times more potent as an analgesic than morphine and is used in human medicine. Many other complex derivatives have been synthesised, although few have proved to be clinically useful.

This work has produced many compounds with no better receptor selectivity, however the potency has greatly increased. The work carried out by, among others, Bentley and Rapoport suggests that this increase in potency is due to a rather remote, and unsuspected lipophilic site on the receptor. Rapoport has suggested that interaction of the C-20 alkyl group with this lipophilic site and of the C-20 hydroxyl group with a hydrophilic site are prerequisites for high agonist activity. He also suggested that this lipophilic site of the receptor might normally bind the phenyl residue of phenylalanine or perhaps the terminal methionine or leucine residues of the enkephalins (12) and (13).



Thebaine (11)



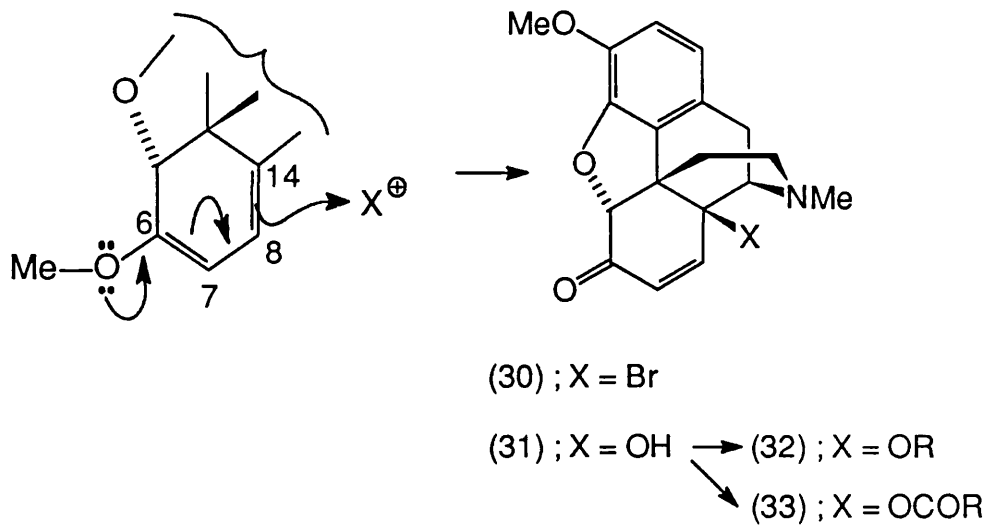
Etorphine (27); with double bond; R = CH_3, R` = n-C_3H_7

Buprenorphine (29); double bond reduced;
R = $-CH_2-$  ; R` = t-Bu

Diprenorphine (28); double bond reduced;
R = $-CH_2-$; R` = Me

1.10 14-Substituted Morphinans

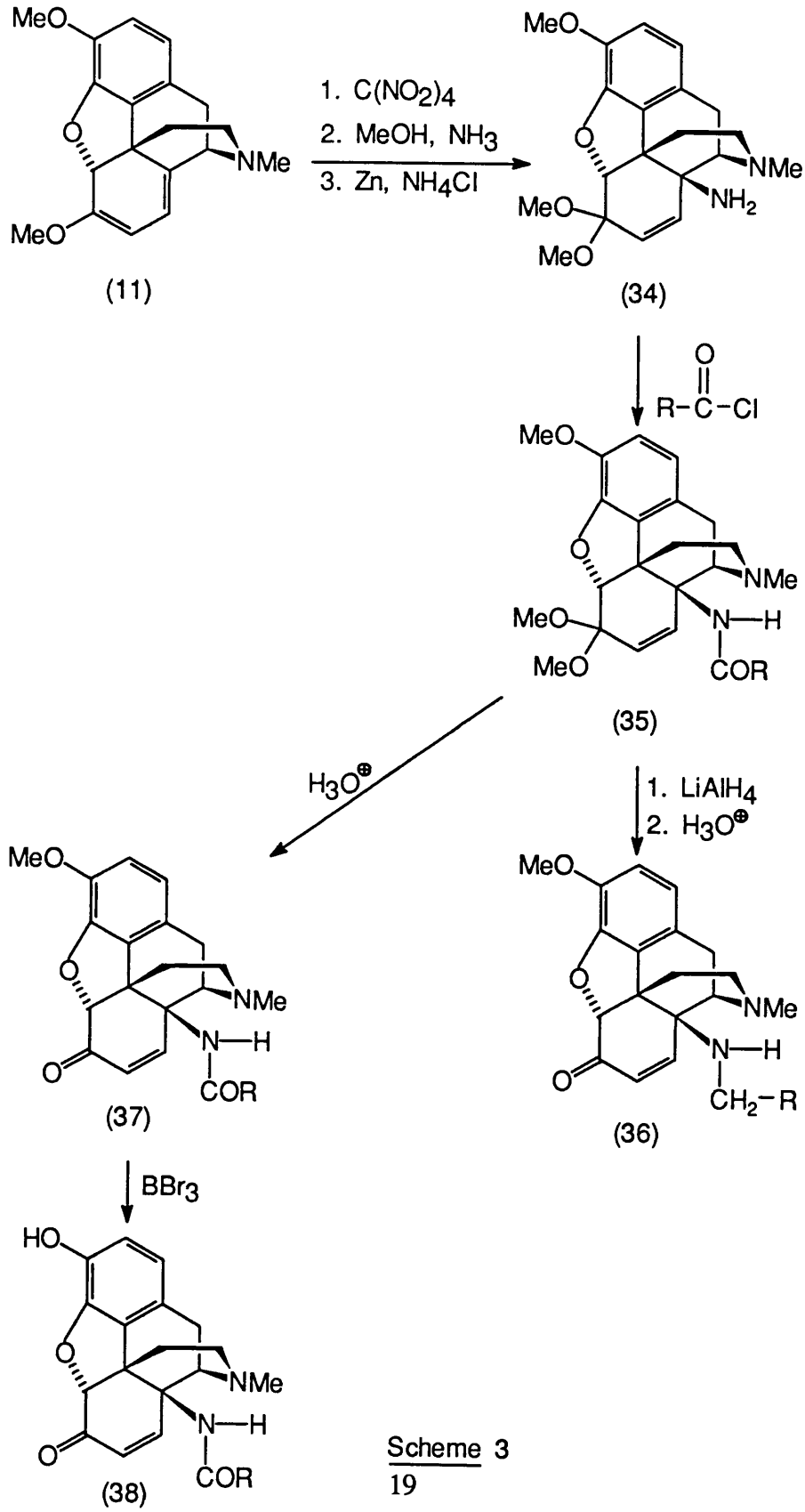
Much synthetic organic chemistry has been carried out to produce morphinans with various groups attached to various positions of the morphinan skeleton. However, for this project and this Introduction, only 14-substituted morphinans will be discussed. As mentioned earlier, thebaine is commonly used as a starting material in synthetic opiate research. It is available in large quantities as a by-product from the processing of opium to give morphine and codeine. Moreover, it serves as a versatile starting material for the synthesis of morphinans substituted in ring C. The methoxy diene system activates the 14-position towards electrophilic attack (Scheme 2). 14β-Bromocodeinone (30) and 14β-hydroxycodeinone (31) have been prepared by utilising this natural activating effect, using bromine and peracetic acid respectively. The alcohol (31) has



Scheme 2

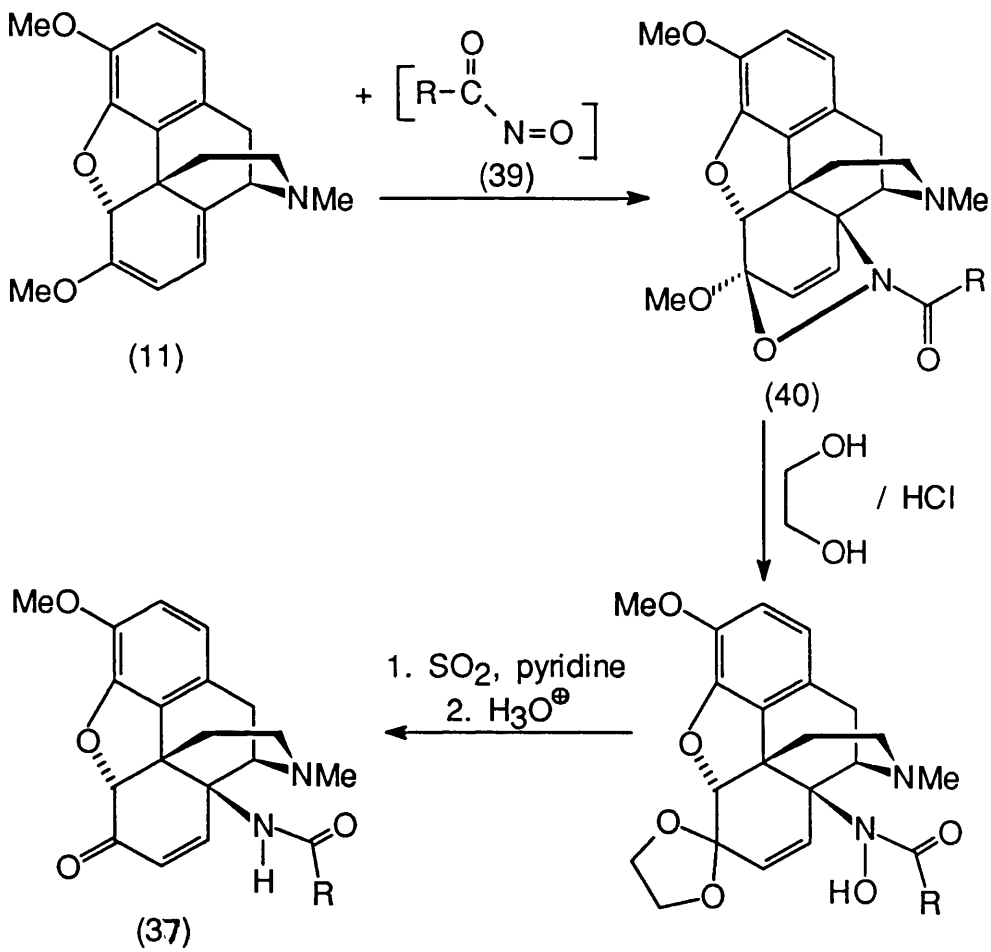
been converted into an extensive series of ethers (32) and esters (33), some having greatly increased analgesic potencies.

In some cases, selective or mild electrophilic reagents are required to attack the activated diene system rather than the activated aromatic ring. For example, nitration of thebaine using even dilute acid, causes nitration of the aromatic ring as well as acid-catalysed decomposition of the molecule. However, it has been found[15] that the mild nitrating agent, tetranitromethane, effects selective nitration at the 14-position. Reduction of this nitro compound to the corresponding amine (34), followed by formation of amides, of type (35), yielded several series of compounds, depending on the acid chloride used and further possible modifications. Lithium aluminium hydride reduction of the amide followed by acid hydrolysis yield the amines (36). Acid hydrolysis of the acetal (35) yielded the 14-acylaminocodeinones (37) and, if followed by boron tribromide demethylation of the 3-methoxy group, the corresponding morphines (38) (Scheme 3).


MeO
NMe
MeO
1. C(NO2)4
2. MeOH, NH3
3. Zn, NH4Cl
NH2
(11)
(34)
O
R–C–Cl
N—H
COR
(35)
H3O⊕
1. LiAlH4
2. H3O⊕
CH2–R
(36)
(37)
BBr3
HO
(38)

Scheme 3

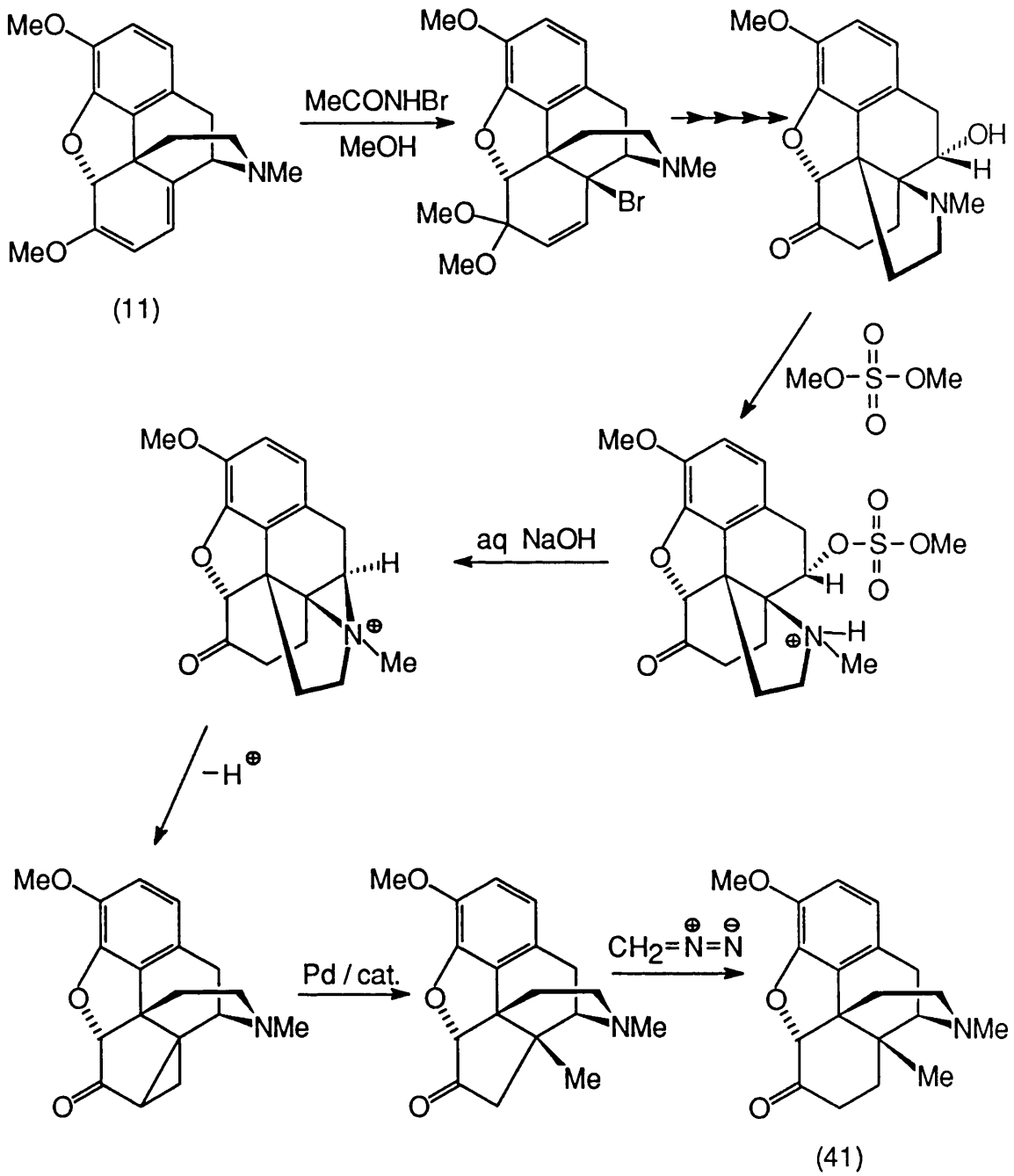
Another route[16] to the 14-acylaminocodeinones (37) exploited thebaine's diene system in a Diels-Alder reaction (Scheme 4). A transient acylnitroso compound (39) can be trapped with thebaine. The resultant cycloadduct (40), fortunately the desired stereoisomer, can undergo chemical transformations to give the codeinone derivative (35).



Scheme 4

1.11 14β-Alkylmorphinans

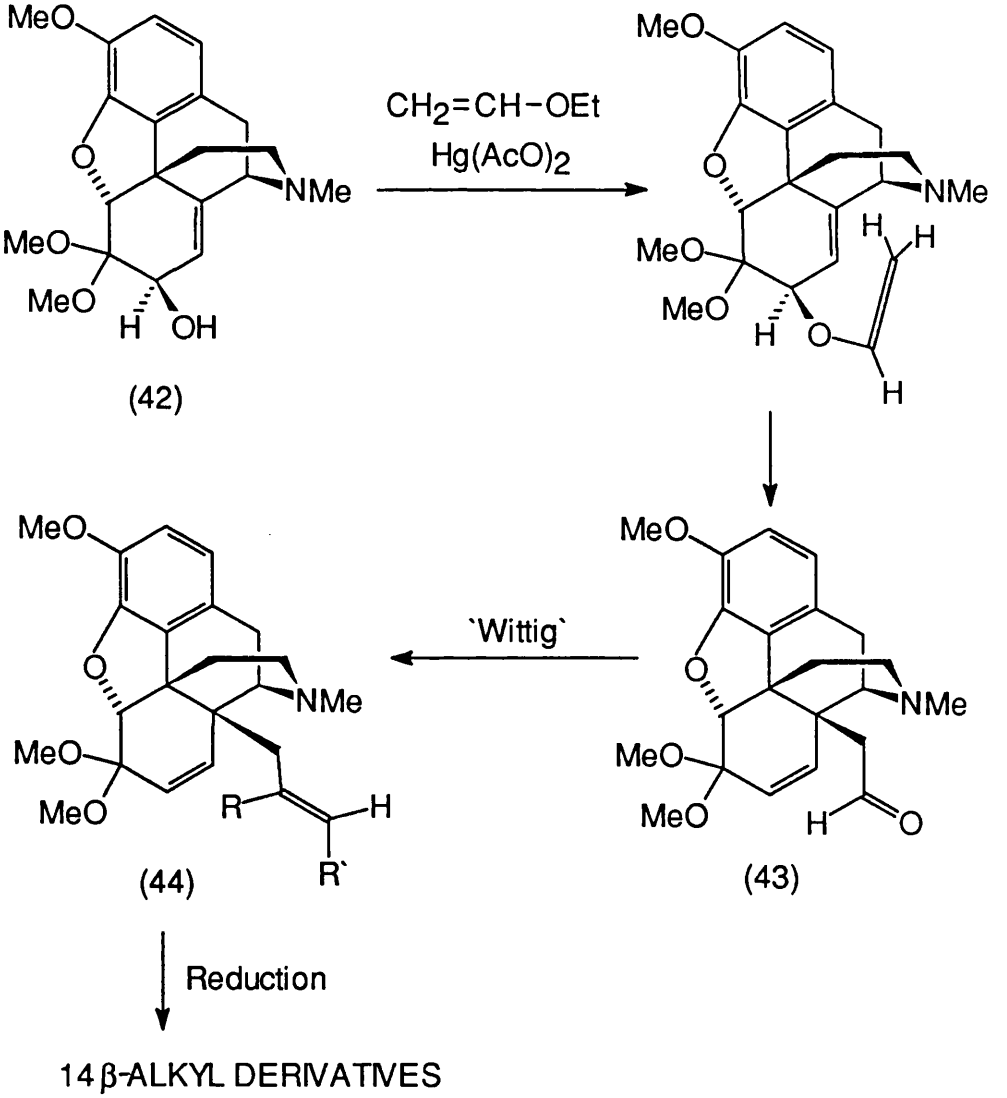
The aim of the present project was to develop a new route to 14β-alkylmorphinans. Relatively few derivatives of this type have been reported in the literature and there has been little systematic investigation of their pharmacology. There



Scheme 5

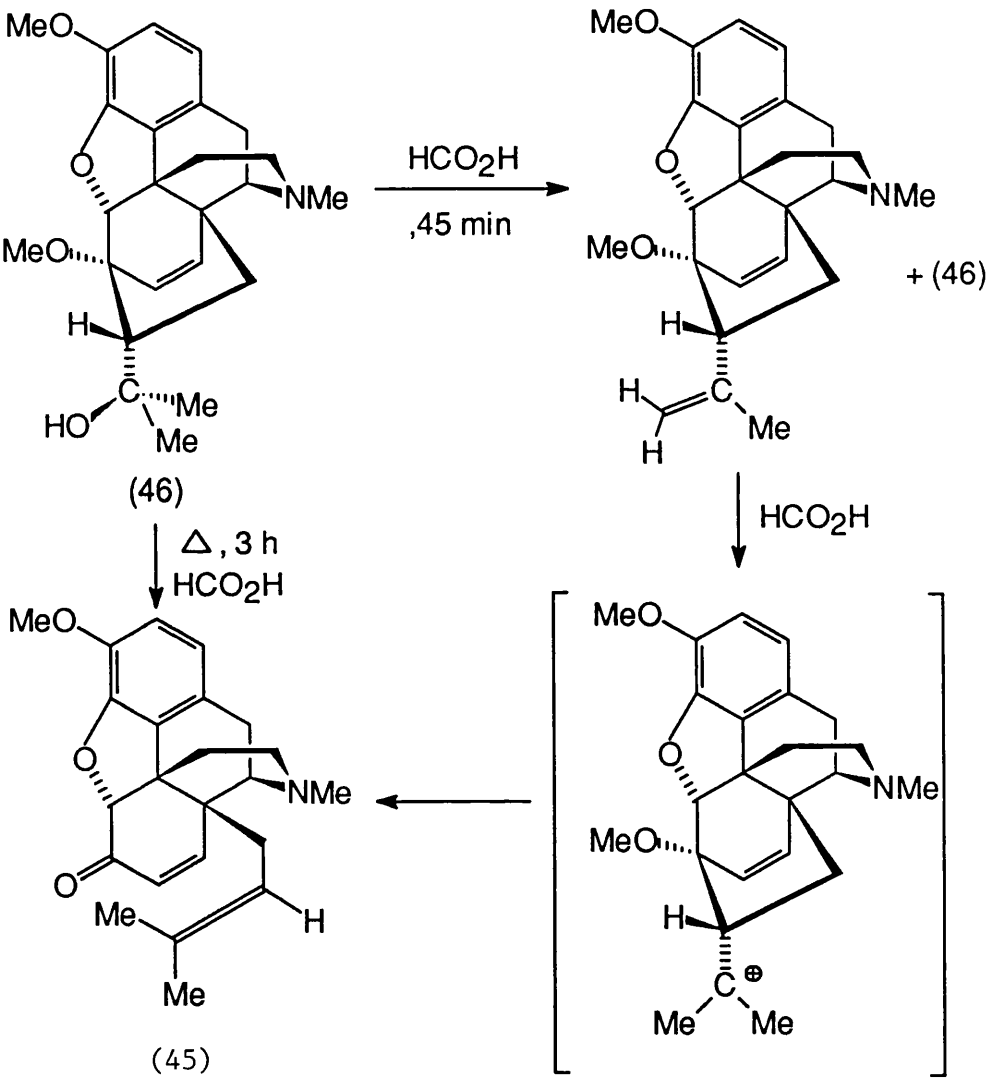
is, of course, no method of directly alkylating morphine or even the diene system of thebaine. There are, however, indirect methods of producing 14β-alkylated morphinan derivatives.

Fleischhacker and Klement[17,18] reported a route (Scheme 5) that led specifically to the 14β-methyl derivative (41). Fleischhaker and Richter[19] subsequently reported a general route to 14β-alkyl derivatives, making use of a suitable Claisen-Eschenmoser rearrangement (Scheme 6) on the neopine derivative (42). The aldehyde (43) thus produced could then be used in a Wittig reaction to give the olefin (44). Reduction of this olefin would give rise to 14β-alkyl derivatives of almost endless variety, depending on the Wittig reagent used.



Scheme 6

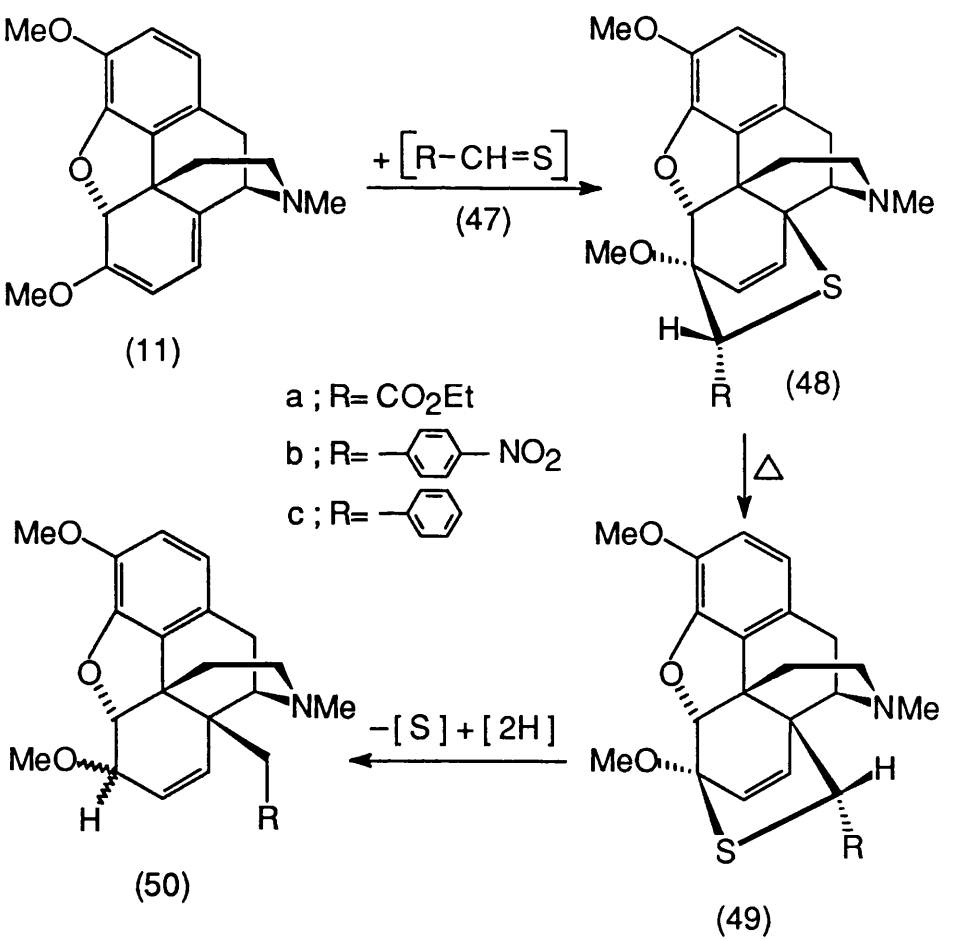
Bentley et al.[20i] discovered a route to 14β-alkenylcodeinones, for example 14β-(3-methylbut-2-enyl)codeinone (45), using acid-catalysed rearrangements of alcohols of the 6,14-endo-ethenotetrahydrothebaine series, for example compound (46) (Scheme 7).



Scheme 7

1.12 Desulphurisation Reactions

The approach adopted in this project employed the known Diels-Alder cycloadducts[21,22] of thebaine (11) and thioaldehydes. Transient thioaldehydes, RCHS (47), have been trapped by thebaine to give cycloadducts in good yield. Generally, when heated the 8-thia adducts (48) are converted into the more stable 7-thia isomers (49). The idea therefore was to remove sulphur reductively from the 7-thia cycloadducts (49) to produce 14β-alkyl derivatives (50) (Scheme 8). Several known methods of desulphurisation were investigated and these will be discussed in detail later.

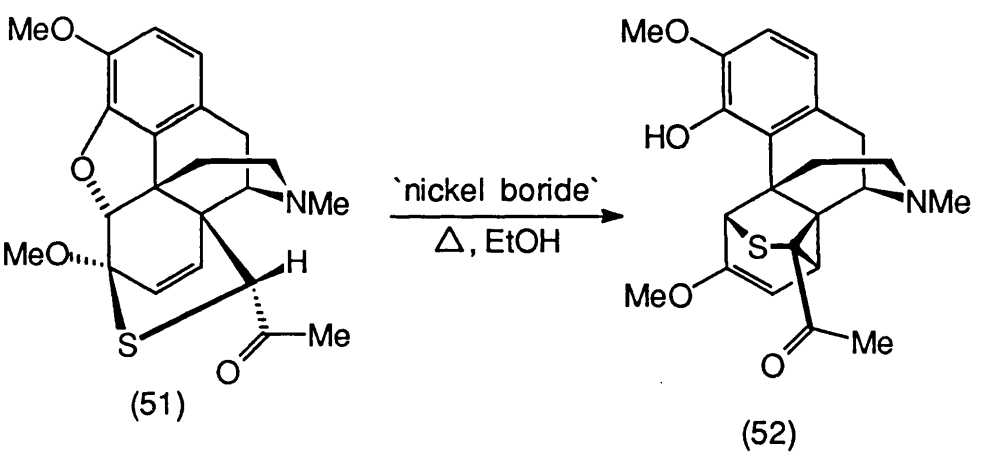


Scheme 8

While this study was in progress a preliminary paper[69] appeared (1989) describing a single compound made by the desulphurisation of a thioaldehyde adduct of a thebaine derivative. Recently (1990) the full paper has been published. The authors' major findings will be summarised after the account of the present author's investigations given in the next chapter.

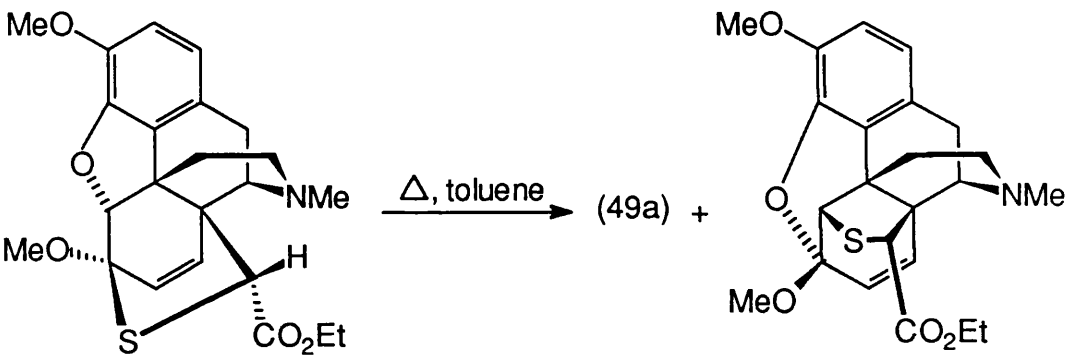
1.13 Earlier Studies on the Desulphurisation of Thebaine Cycloadducts

Sclare,[23] in an attempt to desulphurise the cycloadduct (51) of thebaine (11) and the thioaldehyde, MeCOCHS, with nickel boride,[24] obtained the unexpected cyclopropane compound (52) (Scheme 9). Also, when the compound (51) was treated with methylmagnesium iodide it also gave the product (52).



Scheme 9

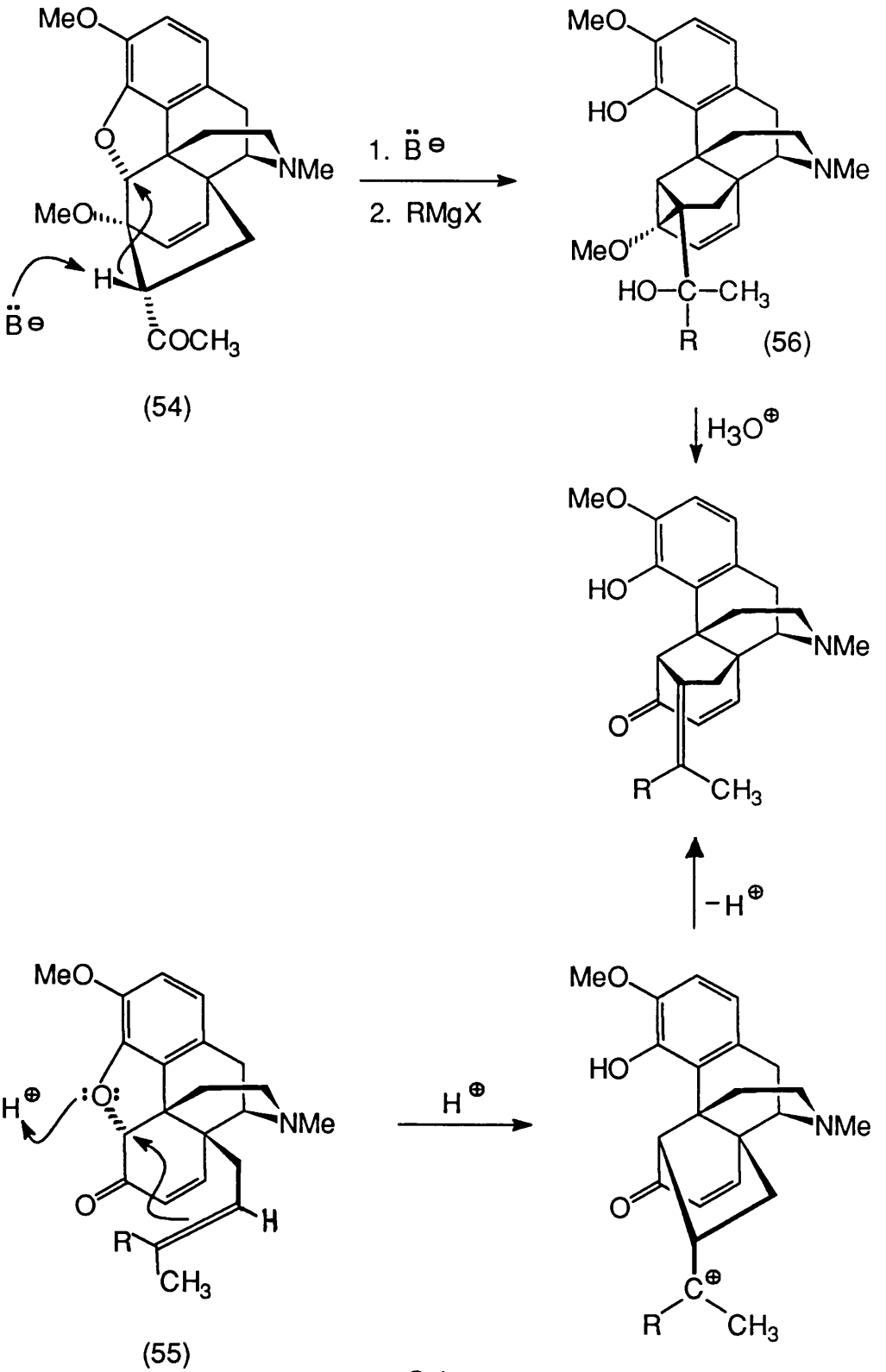
Apparently the proton at position 8, made acidic by the adjacent carbonyl group, was abstracted by some base during treatment of the adduct with nickel boride. This allowed a rearrangement to take place, yielding the cyclopropane compound (52). Sclare also found that heating the cycloadduct (49a) in toluene produced, eventually, an equilibrium mixture of (49a) and its isomeric, rearranged acetal (53) (Scheme 10).



(49a) (53)

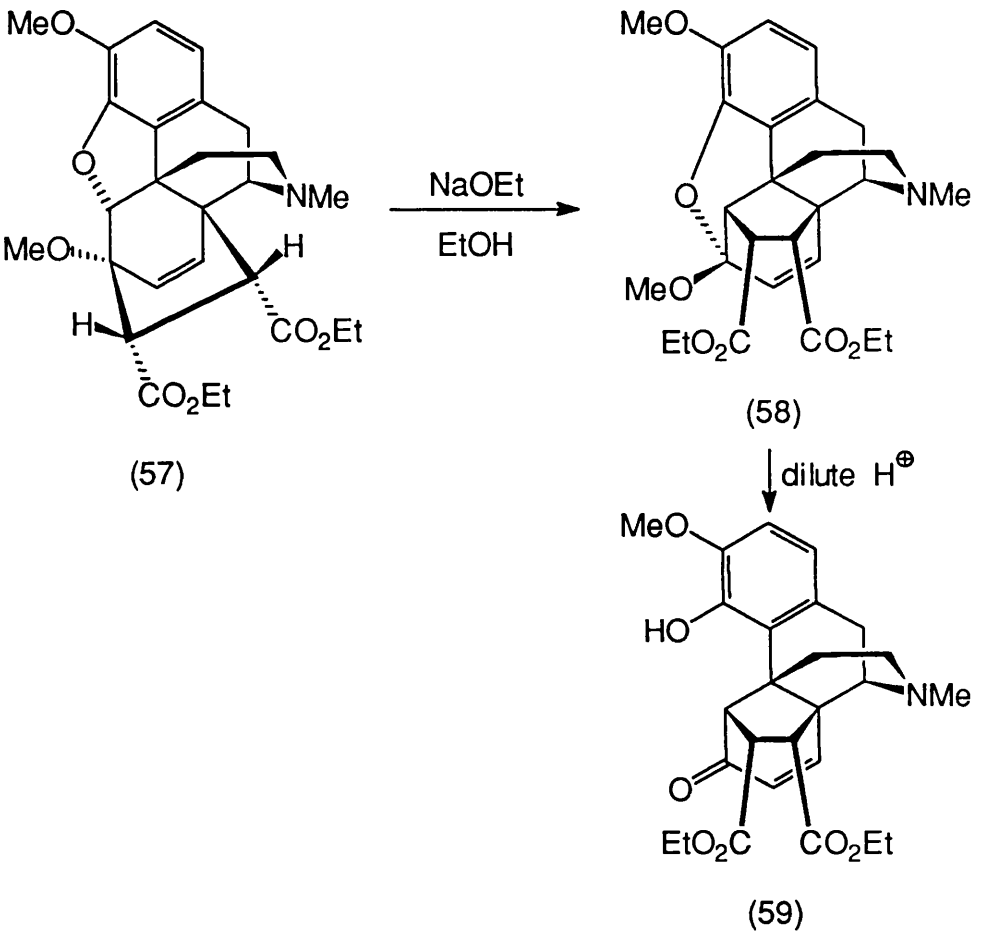
Scheme 10

Bentley et al.[20i-iii] have shown that carbocyclic cycloadducts, such as (54) and their derivatives, for example (55), can rearrange with acid[20i] or base[20ii] catalysis. An example is given in Scheme 11. Interestingly, the base-catalysed rearrangement leads to a 5β,6β-methanomorphinan (56). This reaction proceeds by abstraction of the acidic 7-H proton of the cycloadduct; the anion then opens the epoxide bridge resulting in the phenolic cyclopropane (56). This result closely resembles the rearrangement of 8-substituted cycloadducts under the same basic conditions (i.e. Scheme 9).



Scheme 11

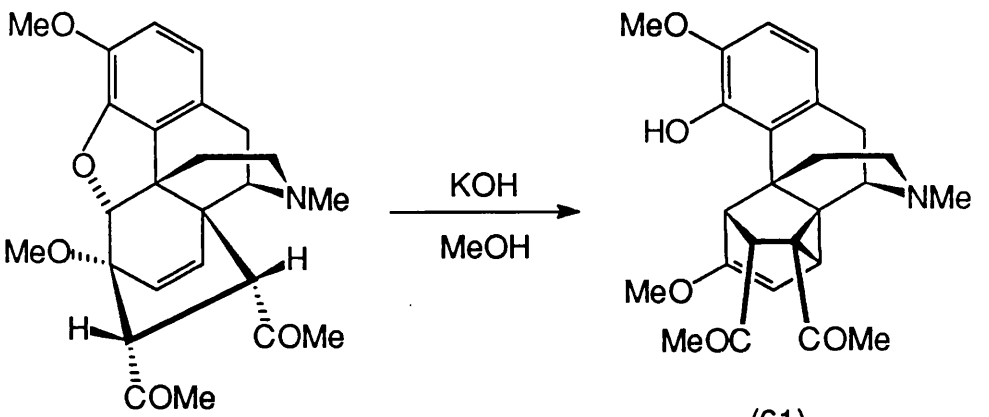
Lewis and Rushworth[25] have shown that 7,8-disubstituted carbocyclic cycloadducts can rearrange in base. For example, the diester cycloadduct (57), when treated with sodium ethoxide in ethanol rearranges to the 4,6α-epoxy diester (58). This product can then be hydrolysed with dilute aqueous acid to the enone (59) (Scheme 12).



(57) (58) (59)

Scheme 12

Ginsburg[26] has shown that the 7,8-diketo cycloadduct (60) can rearrange, when treated with potassium hydroxide in methanol, to give the cyclopropane derivative (61) (Scheme 13). This reaction is very similar to the result obtained by Sclare when he carried out reactions with the 8-acetyl-7-thia cycloadduct (51) in a basic medium (see Scheme 9).



(60) (61)

Scheme 13

1.14 Methods of Desulphurisation

As mentioned earlier, several methods of desulphurising the cycloadducts of thebaine and thioaldehydes, were investigated during this project. These methods will be briefly surveyed here. These employed: (1) W-2 Raney nickel, (2) tin hydrides, (3) aluminium amalgam, and (4) lithium or sodium in liquid ammonia or alkylamines.

There are numerous other methods that might be used but the foregoing were to various extents successful and therefore others were not investigated.

(1) Raney nickel. Raney nickel (usually W-2) is by far the most common reagent for desulphurisation. It is relatively inexpensive, easy to prepare,[27] and well documented in the literature.[28,29,30] The term, W-2, merely signifies the specific experimental conditions used to produce this grade (or activity) of the reagent. The overall reaction (see below) is cleavage of all sulphur to carbon bonds, with addition of hydrogen to the carbon atoms. This hydrogen is known to originate from the reagent itself, adsorbed on the nickel during its preparation. However, during preparation of the reagent (Scheme 14), from nickel-aluminium amalgam (62) and sodium hydroxide,

$$R-S-R' + Ni/H_2 \longrightarrow R-H + H-R' + NiS$$

potentially explosive hydrogen gas is also produced. Raney nickel is highly pyrophoric when dry and due care must be exercised when handling the reagent.

$$NiAl_2 + 6\ NaOH \longrightarrow Ni + 2\ Na_3AlO_3 + 3\ H_2$$

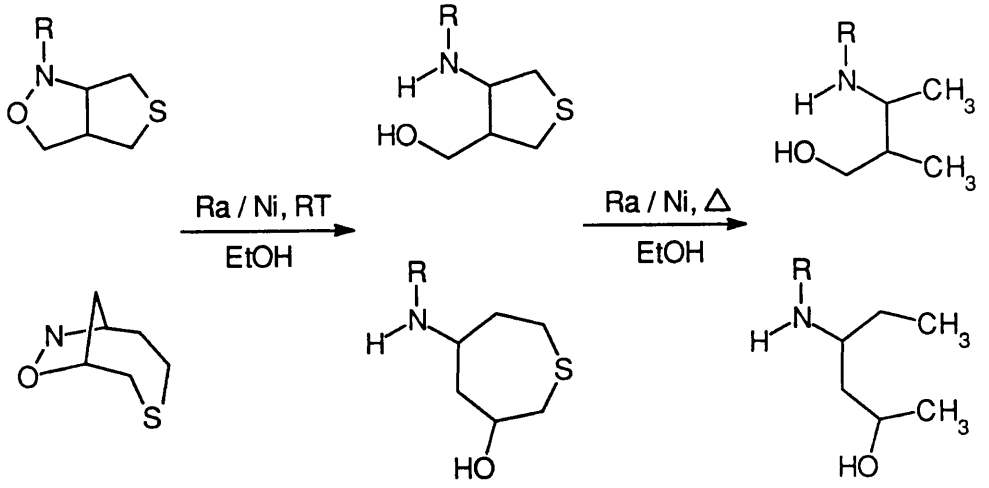
(62)

Scheme 14

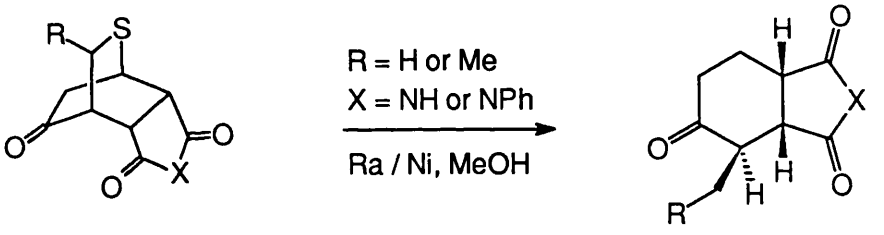
The yields of desulphurised products can often be quite low, and desulphurisation is often accompanied by undesirable side reactions. For example, reduction of carbonyl groups, olefinic double bonds and nitro groups often occur, as well as rearrangements of the carbon skeleton. These side reactions can sometimes be avoided by deactivating the Raney nickel. This is achieved by stirring or refluxing the pre-formed reagent in acetone. Apparently, this treatment with acetone, a hydrogen acceptor, destroys most of the active centres on the nickel surface, producing a reagent more selective in its action. This deactivated form, however, is still pyrophoric. Several examples of Raney nickel desulphurisations of complex molecules are shown in Schemes 15,[31] 16,[32] 17[33] and 18.[34]

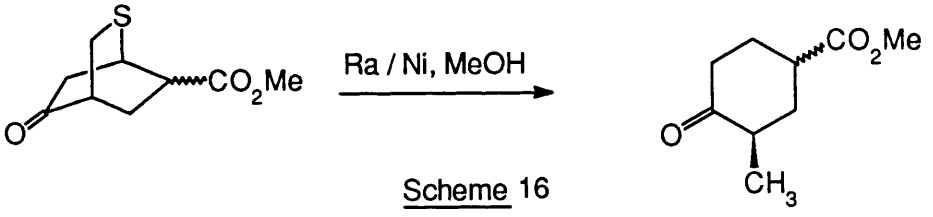
In Scheme 17, the product (63) is the one expected, but the formation of almost equal proportions of the cyclopropane derivative (64), suggests that the reaction may proceed via a radical mechanism. The involvement of radicals in the Raney nickel desulphurisation reactions carried out in the present project, may account for the formation of some unexpected products, as will be described later.

(2) Tin hydrides.[35-39] Baldwin et al.[40] have shown that penicillins (65) can be desulphurised using triphenylstannane (66) (a tin hydride) and a radical initiator, azoisobutyronitrile (AIBN) (Scheme 19). This approach was favoured over the use of Raney nickel since consistently low yields and mixtures of saturated and unsaturated products were obtained with the latter reagent. However, tin hydrides can also be used to

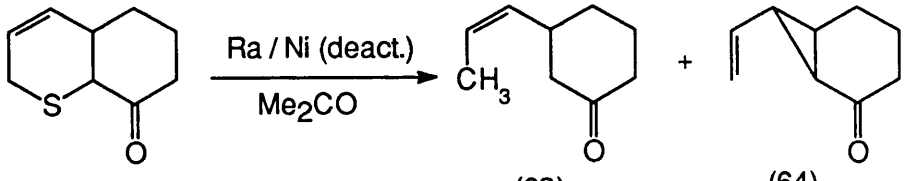


Scheme 15



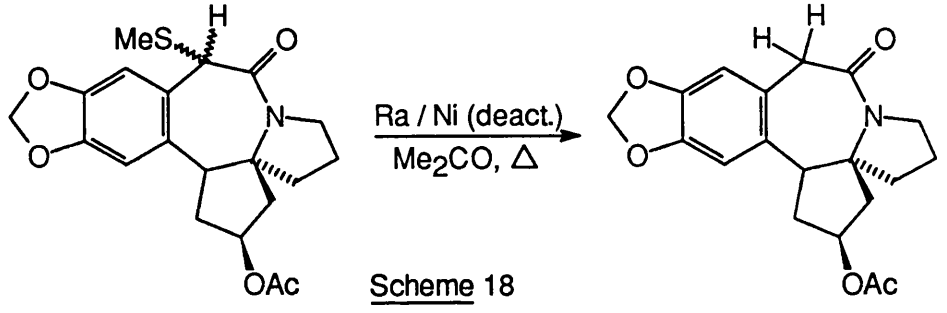


Scheme 16

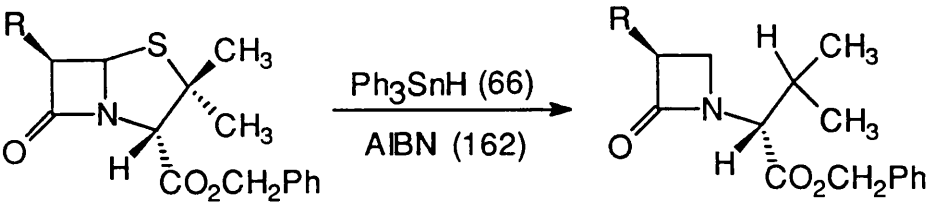


(63) (64)

Scheme 17



Scheme 18

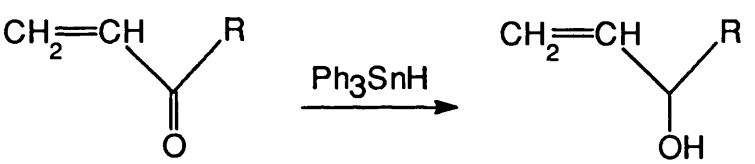


(65)

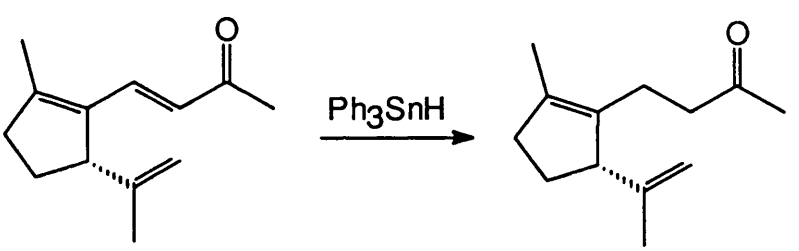
For example R = $PhOCH_2CONH$ or t-BuOCONH

Scheme 19

reduce a carbonyl group to an alcohol (Scheme 20) and also to reduce double bonds (Scheme 21). Again, these alternative reactions often dictated the final products formed



Scheme 20



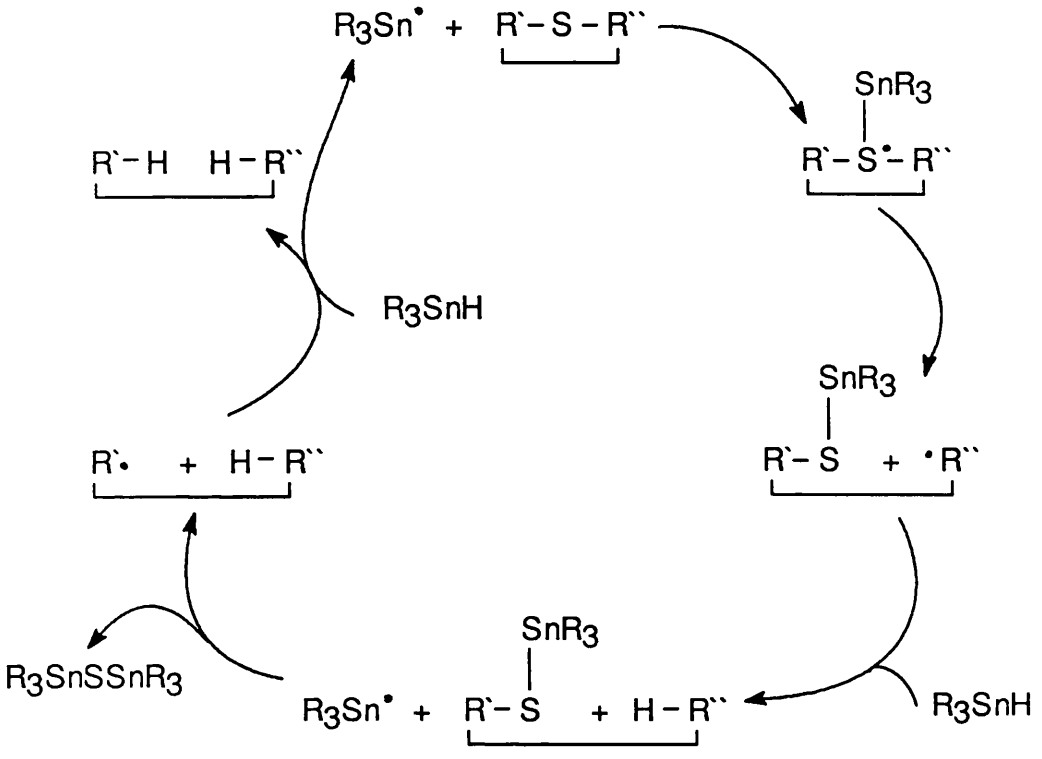
Scheme 21

in the several desulphurisation experiments carried out in the present project. The overall reaction for trialkylstannane desulphurisation is shown in Scheme 22.

$$R\text{-}S\text{-}R' + 2\ R''_3SnH \longrightarrow R\text{-}H + H\text{-}R' + R''_3Sn\text{-}S\text{-}SnR''_3$$

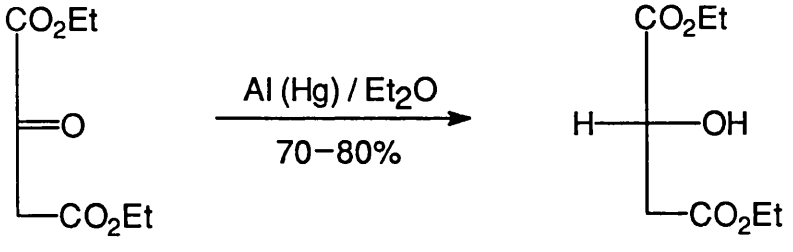
Scheme 22

However, Baldwin et al. have found that a thiostannane, R'-S-SnR_3, a proposed intermediate in the desulphurising reaction, can sometimes be isolated, despite the use of more than the required 2 mol equivalents of tin hydride. It has been proved that tin hydride reactions follow a radical mechanism.[41] The mechanism put forward by Baldwin for desulphurisation is outlined in Scheme 23. The initial R-S bond broken in the sulphide, to give the thiostannane, depends on the stability of the two possible carbon radical intermediates, R·. The more stabilised radical, ·R"; is reduced by hydrogen from the tin hydride while the thiostanne is formed from the less stabilised R' group. Complete desulphurisation can be achieved by adding more tin hydride to the preformed thiostannane or by using 3-5 equivalents initially. Gutierrez et al.[42] have shown that thiostannanes can undergo destannylation to the corresponding thiol when they are absorbed on silica gel columns and then eluted, or when treated with aqueous hydrochloric acid.



Scheme 23

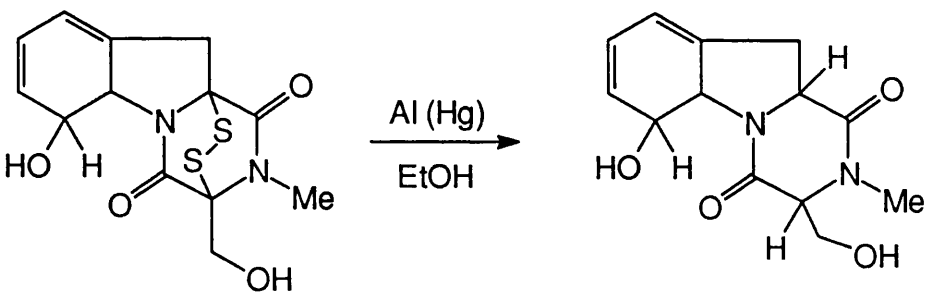
(3) Aluminium amalgam. Aluminium amalgam can be used for a variety of reductions. An important feature of its usefulness is that the reagent and products are essentially neutral. This allows alkali-sensitive molecules, such as diethyl oxaloacetate (67), to be reduced, to diethyl malate (68) (Scheme 24).



(67) (68)

Scheme 24

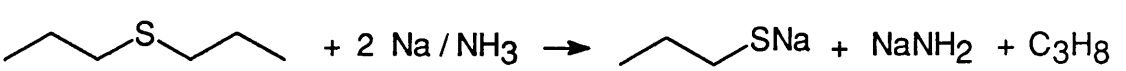
The ability of aluminium amalgam to desulphurise the antibiotic, gliotoxin (69), to give desthiogliotoxin (70), under neutral conditions (Scheme 25)[43,44] is important because this could indicate an advantage for the present studies, since the cycloadducts (49), of thebaine and thioaldehydes, are susceptible to acid or base catalysed rearrangements.



(69) (70)

Scheme 25

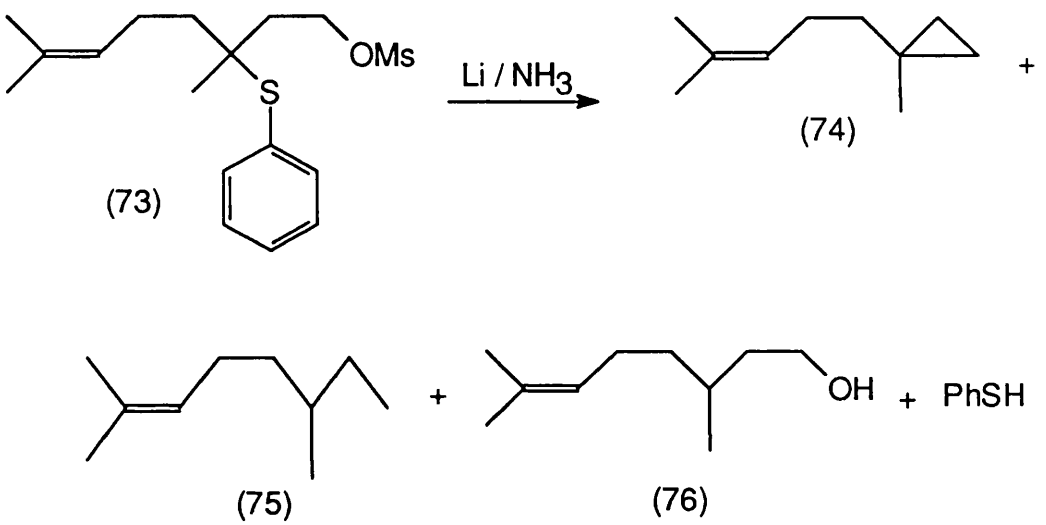
(4) Lithium or sodium in liquid ammonia or alkylamines. The cleavage of carbon-sulphur bonds using an alkali metal dissolved in liquid ammonia or an alkylamine has been known for a long time.[45-47] Diphenyl sulphide was desulphurised to give 2 moles of benzene using sodium in liquid ammonia. However, complete removal of sulphur is not the normal outcome of these reactions. Di-n-propyl sulphide (71), for example, and sodium in liquid ammonia gave n-propyl sodium mercaptide (72), sodamide and propane (Scheme 26). However, the products of this type of reaction are



(71) (72)

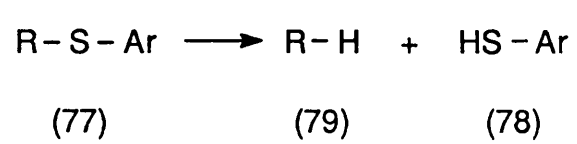
Scheme 26

not always entirely predictable. In the reduction of the sulphide (73) (Scheme 27), thiophenol is formed but the hydrocarbon product is a mixture of the terpenes (74), (75), and (76).[48] The direction of the cleavage has been established for a number of unsymmetrical sulphides.[49-51]



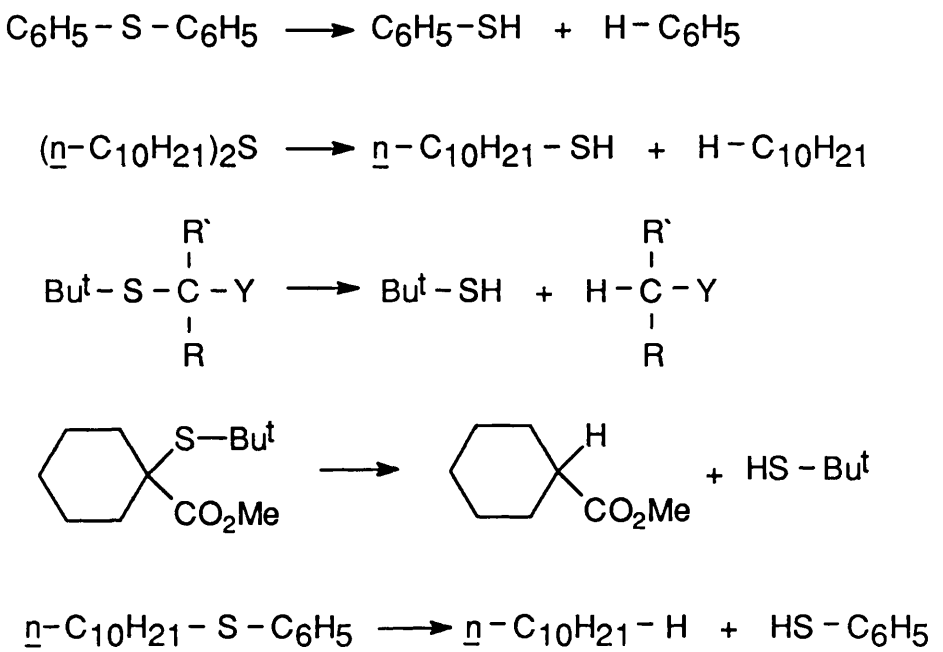
Scheme 27

In the case of an alkyl aryl sulphide (77), the carbon-sulphur bond cleavage gives rise to the less basic of the two possible thiolate anions. Thus, a thiophenol (78) and an alkyl derivative (79) are the products (Scheme 28).



Scheme 28

Examples of the cleavage of symmetrical and unsymmetrical sulphides by lithium in methylamine are shown in Scheme 29.

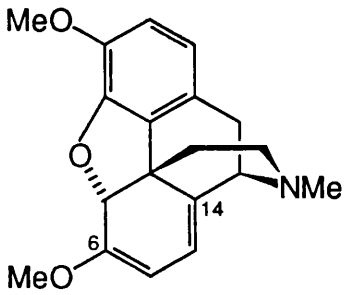


Scheme 29

2. RESULTS AND DISCUSSION

2.1 Introduction

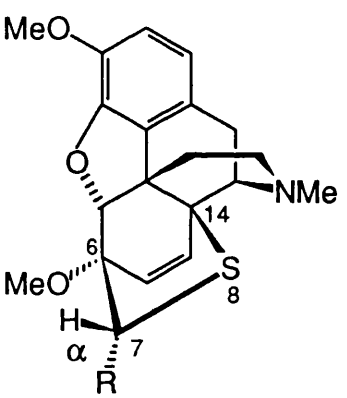
The object of this project was to investigate a possible route to 14β-alkyl derivatives of thebaine. The aim was to prepare known Diels-Alder cycloadducts (49) of the diene thebaine (11) and transient thioaldehydes, RCHS[52,53] (47) (Scheme 30), and then to remove sulphur reductively from the 7-thia cycloadducts (49), leaving a carbon residue, RCH_2, attached β to the 14-position of the morphinan skeleton (see Scheme 8). Many cycloadducts of thebaine and thioaldehydes have been prepared but, for this project, the thioaldehydes (47) chosen had R=ethoxycarbonyl, p-nitrophenyl and phenyl. The thioaldehydes can be prepared in a number of ways,[54] however, the following procedures were used in this project. Ethyl thioxoacetate, $EtO_2C.CHS$ (47a) was prepared from either the Bunte salt[55] (80a) (Scheme 31) or the sulphenyl chloride[56] (81) (Scheme 32); p-nitrothiobenzaldehyde (47b) from the corresponding Bunte salt (80b) (Scheme 31); and thiobenzaldehyde (47c) from the corresponding alkyl thiosulphinate[58] (82) (Scheme 33).



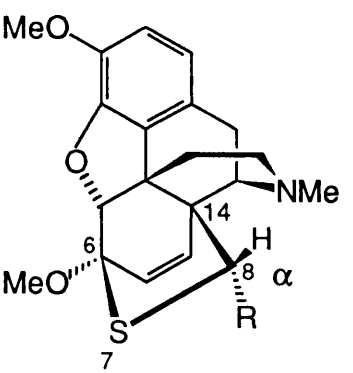
(11)

[R–CHS]

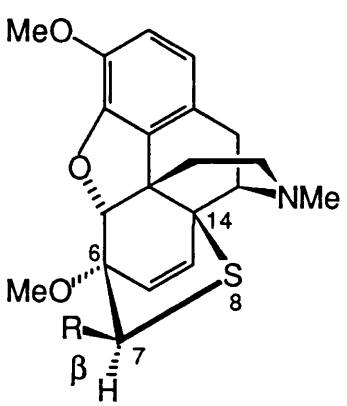
(47)



(48)



(49)



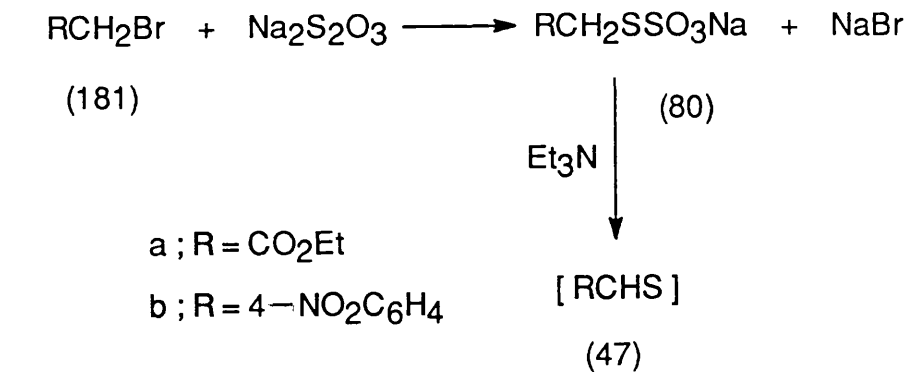
(84)

a ; R = CO_2Et

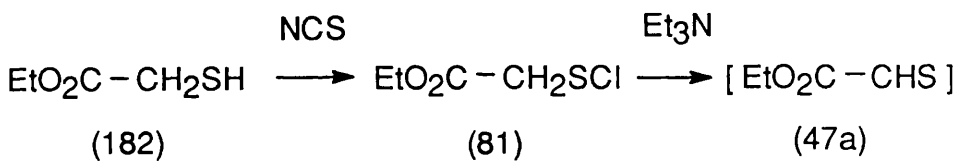
b ; R = 4–$NO_2C_6H_4$

c ; R = Ph

Scheme 30

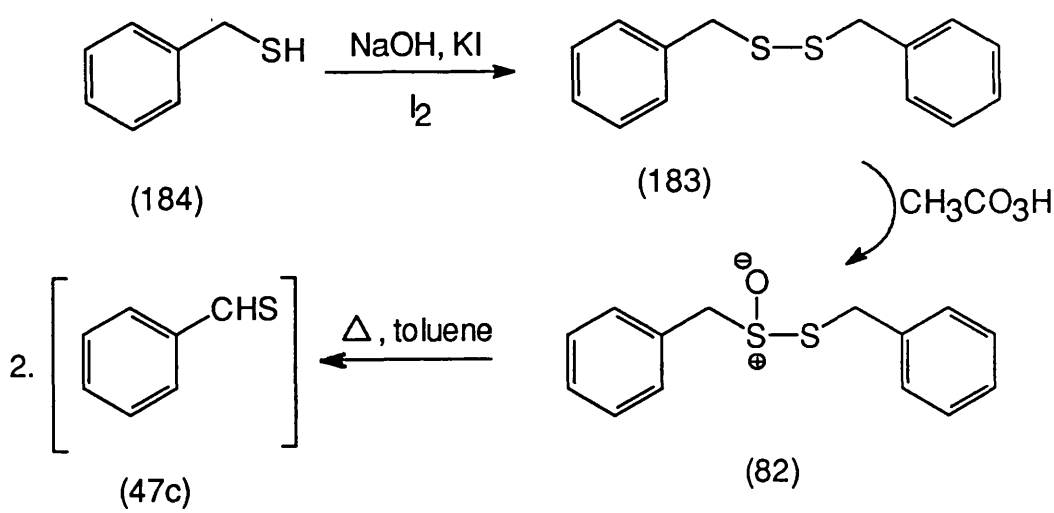


Scheme 31

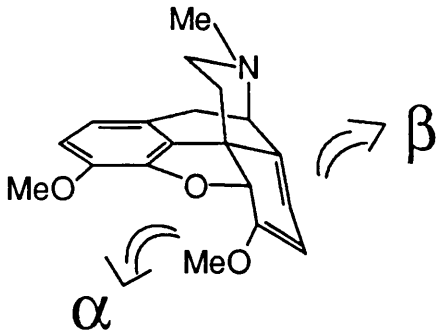


NCS ≡ N−Chlorosuccinimde

Scheme 32



Scheme 33



(83)

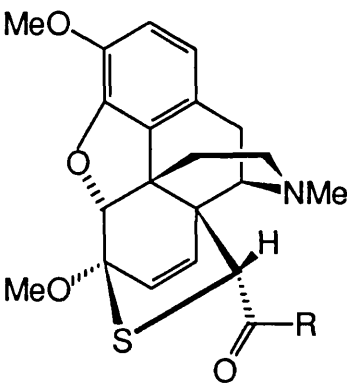
The shape (83) of the diene, thebaine, is such that underside (α) approach of the dienophile, the thioaldehyde, is unfavourable. To date, all dienophiles have been found to add exclusively from the exposed, β face. Therefore the maximum number of possible regio- and stereo-isomeric cycloadducts is reduced from eight to four. That is, for an unsymmetrical dienophile there are two possible regioisomers and each may exist as endo or exo stereoisomers. Under conditions of kinetic control, ethyl thioxoacetate (47a) produced[59] only three isomers, namely the 8-thia (48a) and 7-thia (49a) endo isomers, and the 8-thia exo isomer (84a), in the approximate ratio 75:4:5, respectively. p-Nitrothiobenzaldehyde (47b), perhaps due to its steric bulk, produced only two cycloadducts,[60] namely the 7-thia (49b) and 8-thia (48b), endo isomers in the ratio of 1:1, although small amounts of the isomer (84b) might easily have been overlooked. Thiobenzaldehyde (47c) is produced from the thiosulphinate (82) (Scheme 33) by heating and gives exclusively the 8α-phenyl-7-thia cycloadduct (49c). However, it has been found[61] that the thiobenzaldehyde cycloadduct (49c) can also be formed exclusively at room temperature. In order for desulphurisation to give 14-substituted morphinans, the cycloadducts require to have the sulphur atom at position 7, as explained in the Review. Fortunately it has been found that the desired 7-thia cycloadducts of both the ethoxycarbonyl and p-nitrophenyl series are formed almost exclusively under 'thermodynamic' conditions, i.e. when the 8-thia adducts are heated at 111°C and 80°C,

respectively. This isomerisation is known to occur by retro-Diels-Alder dissociation of the cycloadduct and recombination of the components. These results suggest that under kinetic conditions, the regio-chemistry of the cycloaddition is determined by electronic effects. Electron-withdrawing groups favour the 8-thia products and thus the ester group induces predominately formation of the 8-thia product. With the p-nitrothio-benzaldehyde dienophile (47b), the electronic effect is lessened, thus giving the 1:1 quantities of the regio-isomers (48b) and (49b). With thiobenzaldehyde, the electronic effect is reduced even more such that the only cycloadduct encountered is the 7-thia isomer (49c). Isomerisation of the 8-thia to the 7-thia derivatives requires heating at 111°C for the ester but only at 80°C for the p-nitrothiobenzaldehyde adduct, and so it is possible that isomerisation of the thiobenzaldehyde adduct occurs even at room temperature. This possibly explains why no 8-thiabenzaldehyde cycloadduct (48c) has yet been detected.

2.2 Rearrangements of the 8α-ethoxycarbonyl-7-thia cycloadduct (49a).

2.2.1 Base-catalysed reactions

During an attempt to desulphurise the cycloadduct (51) of thebaine and the thioaldehyde, MeCOCHS, with nickel boride,[62] Sclare[63] obtained the unexpected product (52). Also, when the same cycloadduct was treated with methylmagnesium iodide, again the rearranged cyclopropane compound was produced. Apparently, during the course of these reactions some base had abstracted the proton at C-8, adjacent to the carbonyl group, giving ultimately the rearranged cyclopropane compound (52) (Scheme 34).

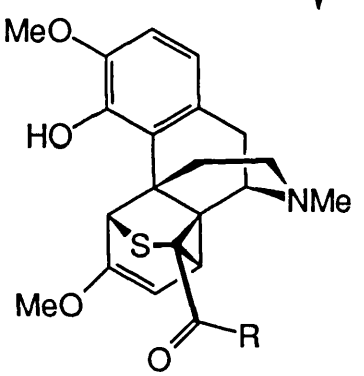


(51) ; R = Me

(49a) ; R = OEt

R = Me ; `Nickel boride` or MeMg I

R = OEt ; NaOEt



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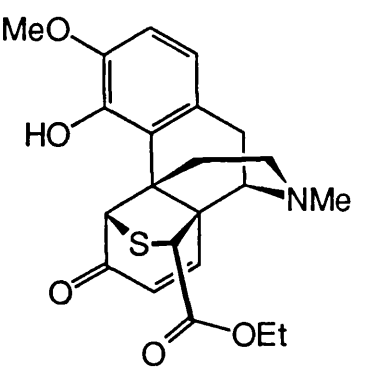
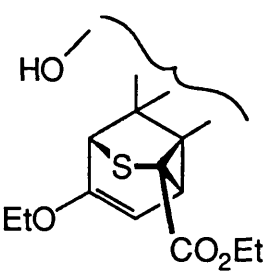


(52) ; R = Me

(85) ; R = OEt

(86)



(87)

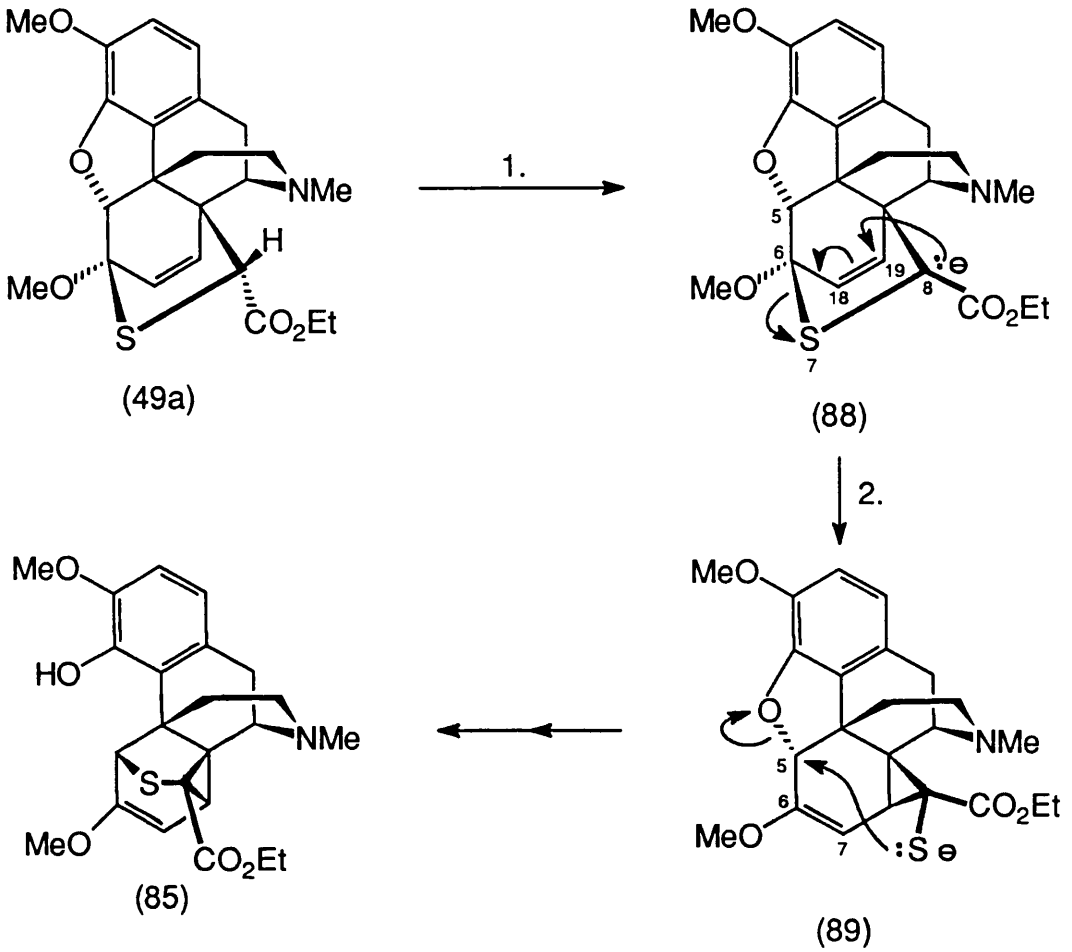
Scheme 34

The 8α-ethoxycarbonyl-7-thia cycloadduct (49a), being similar to the ketone (51), could possibly suffer a similar fate under basic conditions. For example, the Raney nickel used for desulphurisation may contain residual sodium hydroxide from its preparation. Therefore it was necessary to investigate the stability of the 7-thia ester under basic conditions. Thus this adduct (49a) was treated with a catalytic amount (ca. 25% mol equiv.) of sodium ethoxide in refluxing ethanol for 26 h. Indeed, if the reaction mixture was kept dry, the rearranged, cyclopropane derivative (85) was obtained in ca. 65% yield. When the ethanol contained water, the cyclopropane derivative (85) was accompanied by the enone (86). The structure of the cyclopropane ester (85) was confirmed by comparison of its spectroscopic data with those derived from the corresponding methyl ketone (52). The ^1H n.m.r. spectrum of the ester (85) showed signals at δ 4.38 (d, J 2.4 Hz, 5-H), 4.61 (dd, J 6.9 and 2.5 Hz, 7-H) and 2.56 (d, J 6.9 Hz, 8-H), which corresponded well with the signals at δ 4.49 (d, J 2.3 Hz), 4.61 (dd, J 6.9 and 2.3 Hz) and ca. 2.50 (partly obscured) of the methyl ketone (52). Also, a singlet at δ 5.82 disappeared upon exchange with D_2O and the i.r. spectrum had a band at 3 420 cm^{-1}, these data signifying the presence of a phenolic proton and thus indicating that a molecular rearrangement had occurred. Microanalysis and accurate mass spectral data were consistent with the molecular formula $C_{23}H_{27}NO_5S$, confirming the product to be isomeric with the cycloadduct (49a).

In a subsequent reaction under similar conditions, but with heating for 2 d, two products were formed. The main product, presumably arising because moisture entering the reaction mixture, was the enone (86), and the other product appeared to be a rearranged cyclopropane derivative. However, the ^1H n.m.r. spectrum (90 MHz) of the latter showed no 6-OMe signal at ca. δ 3.33, which is present in the spectrum of the cyclopropane (85). Instead a multiplet was present at δ 1.25, possibly arising from

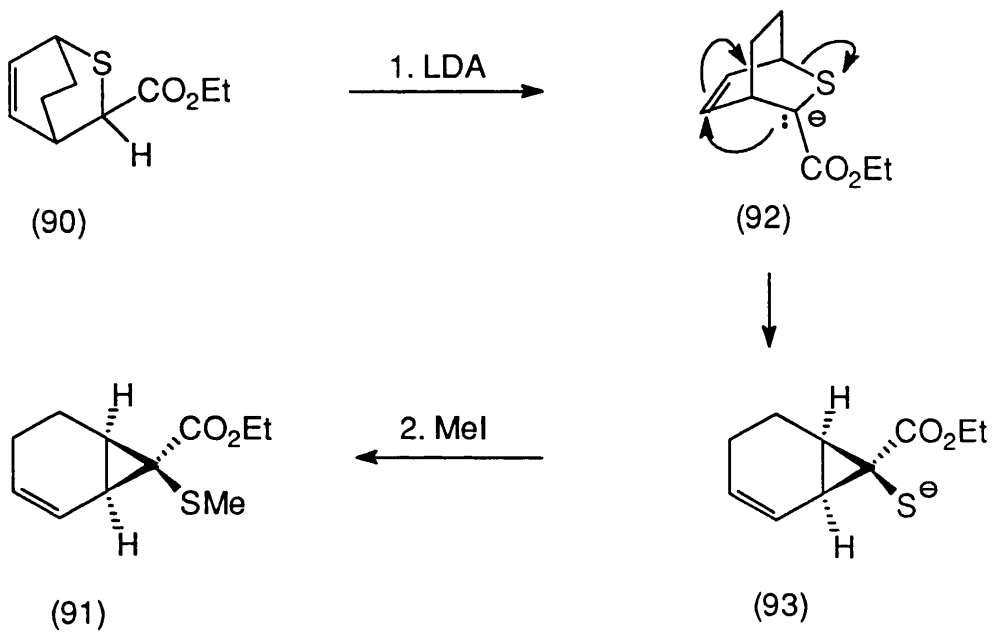
overlap of two methyl triplets from ethoxy groups. This new cyclopropane derivative was tentatively assigned the structure (87). Clearly, exchange of the 6-methoxy group with an ethoxy group from the ethoxide ions or the ethanol solvent had occurred at some time during the reaction or work-up. Although this last observation was not important for the project, an experiment was carried out to investigate whether exchange of the 6-methoxy group had occurred before or after the rearrangement had taken place. Thus, the methyl enol ether (85) was treated with a catalytic amount of sodium ethoxide in refluxing ethanol. After 25 h, the ^{1}H n.m.r. spectrum of the product clearly showed that no change had occurred, thus signifying that the earlier exchange process must have occurred before rearrangement to the cyclopropane. A possible mechanism for this exchange process will be discussed later.

The rearrangements just described were presumably caused by base abstraction of the acidic proton at C-8 as the preliminary step. The resultant anion (88) attacks the double bond at C-19 giving the cyclopropane ring, while movement of the double bond causes expulsion of the thiolate anion. The thiolate (89) displaces the oxygen atom from the C-5 position leading to the phenolic cyclopropane derivative (85) (Scheme 35).



Scheme 35

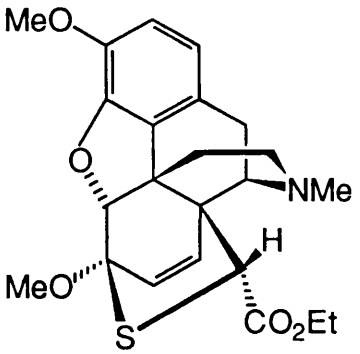
This proposed mechanism was in good agreement with work carried out by Kirby et al.[64] They showed that the cycloadduct (90), prepared from cyclohexadiene and ethyl thioxoacetate, reacted with lithium diisopropylamide (LDA) and methyl iodide to give the cyclopropane ester (91) stereospecifically in good yield. Presumably, the carbanion (92) rearranged to give the thiolate (93), which was then methylated (Scheme 36). This shows that steps 1 and 2 in Scheme 35 are at least feasible. Although reactions of the thebaine cycloadduct (49a) are complicated by opening of the 4,5-epoxide ring, the formation of a cyclopropane derivative from the simpler cyclohexadiene adduct (90) appeared to provide an informative model. The cycloadduct (49a) [c.f. (90)] was thus



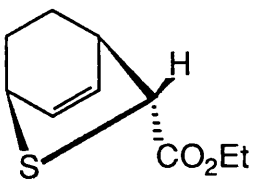
(90) (92) (91) (93)

Scheme 36

treated with two equivalents of LDA for 1 h. After mild acidic workup, the reaction mixture was found to contain, as judged by ^{1}H n.m.r. spectroscopy, the starting cycloadduct and the ketocyclopropane (94) in the ratio of 1:4, respectively. Accurate mass spectral data of this mixture gave the molecular ion m/z 415.1450, which is consistent with the molecular formula $C_{22}H_{25}NO_5S$ for the ketone (94). ^{13}C N.m.r. spectroscopy confirmed the presence of a ketone with a signal at δ 196.9, as well as giving the correct number of carbons and their multiplicities. In the ^{1}H n.m.r. spectrum, the broad signal for the phenolic hydroxyl group was shown to disappear after exchange with D_2O. In this reaction, it was likely that the keto group of the ketocyclopropane (94) was formed by hydrolysis of an intermediate enol ether (85), during the acid workup.

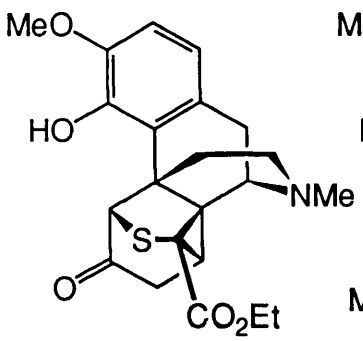


cf.

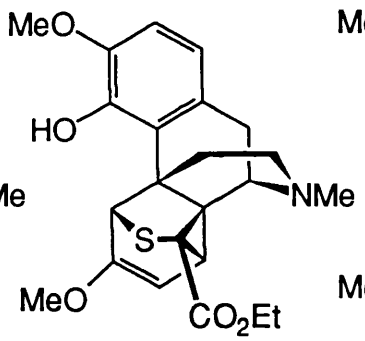


(49a)

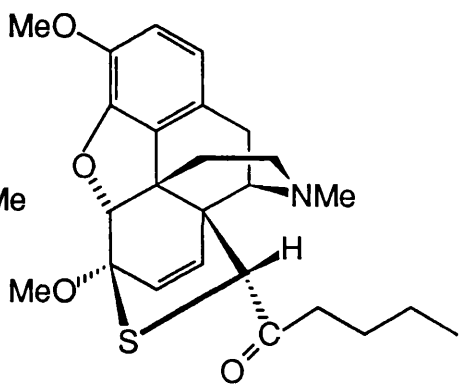
(90) N.B. (49a)≡(90)



(94)



(85)



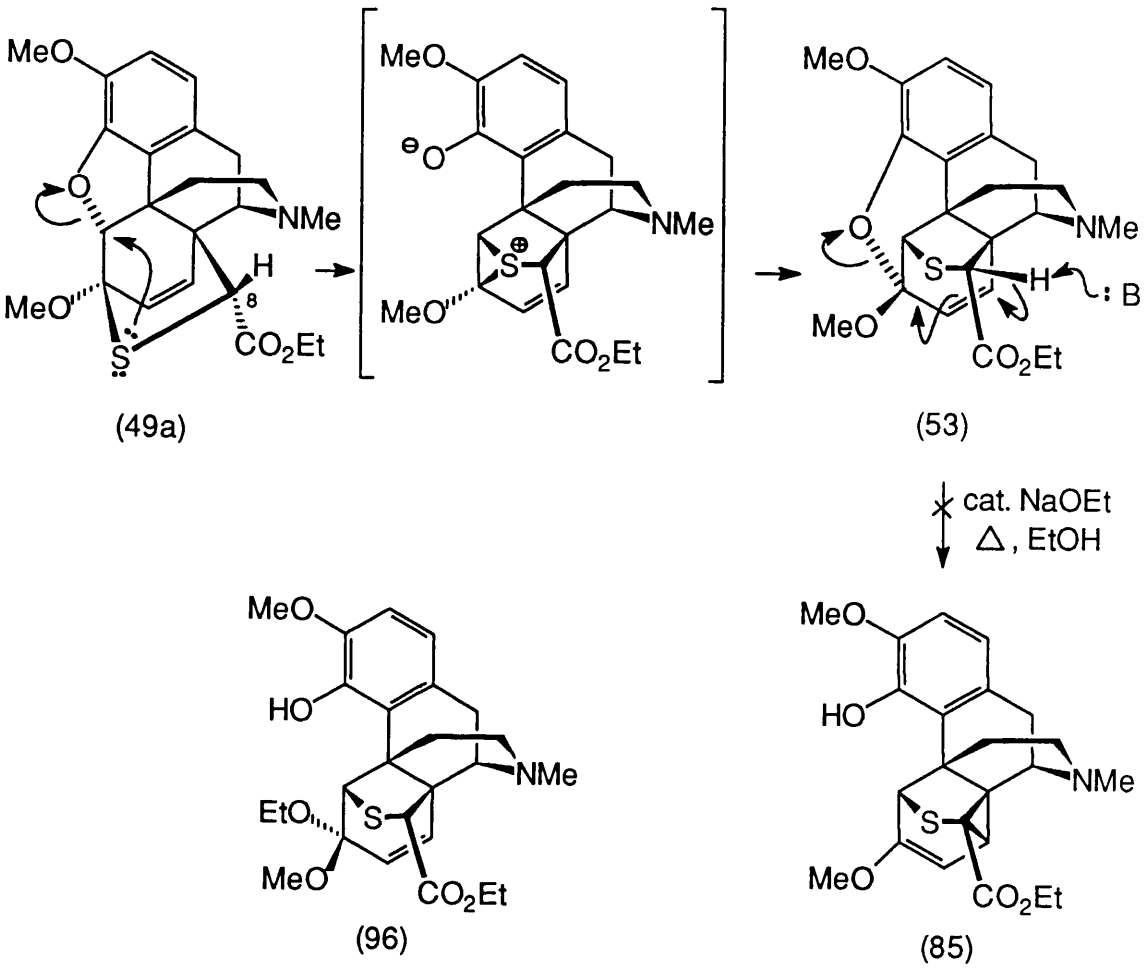
(95)

Therefore the cycloadduct (49a) was again treated with an excess of LDA and then a non-acidic workup. As expected the cyclopropane enol ether (85) was produced in ca. 40% yield. However, due to an experimental error, an excess of butyllithium must have been present which gave the butyl ketone (95) as a minor product, in 15% yield. This cyclopropane enol ether (85) was hydrolysed to the ketone (94) when stirred at room temperature in dilute hydrochloric acid for 25 min. The ^{1}H n.m.r. spectrum of the product was identical to that obtained by the LDA/H^{+} reaction. The LDA-mediated rearrangement of the cycloadduct (49a) to give the cyclopropane(s) is a quicker method, although less convenient, when compared with the sodium ethoxide induced rearrangement as previously described.

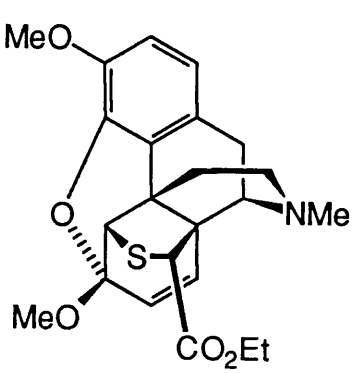
Another possible mechanism for the base-catalysed rearrangement of the 8α-ethoxycarbonyl-7-thia cycloadduct (49a) to the cyclopropane derivative (85) might proceed via the 4,6α-epoxy acetal (53) as shown in Scheme 37. This acetal, prepared from the 7-thia cycloadduct by refluxing in toluene (see following section), was tested as a possible intermediate in the base-catalysed rearrangement. Thus the acetal (53) was heated in ethanol under reflux for 20 h with a catalytic amount of sodium ethoxide. However, the cyclopropane (85) was not the observed product. The product was found to be the 6α-ethyl-6β-methyl acetal (96). The interesting feature of this acetal is that the ethoxy group had approached from the hindered α-face [see Section 2.3, "The p-nitrophenyl compounds", p. 54 for further discussions on this observation].

2.2.2 Rearrangements without added base

Under neutral reaction conditions, i.e. in ethanol alone, abstraction of the acidic proton at C-8 should not occur. However, Sclare[59] found that refluxing the 7-thia adduct (49a) in neutral, but non-polar, toluene produced an equilibrium mixture of the cycloadduct as well as the rearranaged acetal (53) in the ratio of 19:81, respectively. Indeed, when the cycloadduct (49a) was heated in refluxing ethanol for several hours it was clear from t.l.c. and ^{1}H n.m.r. analyses that the adduct had reacted to give several compounds. This experiment was repeated and the whole reaction mixture was evaporated to dryness and a 90 MHz ^{1}H n.m.r. spectrum taken of the residue. The deuteriochloroform solution was then evaporated and the residue was redissolved in the same volume of dry ethanol and then further heated under reflux. This procedure was carried out at 2 h, 5 h, 20 h, and 45 h and thus a comparison of products and ratios could be determined throughout the course of the reaction. The ratio of products were determined by their relative integrations of certain distinctive proton signals. A table of the results will be given later.


MeO
O
NMe
H
MeO
S
CO2Et
(49a)
MeO
⊖O
S⊕
NMe
MeO
CO2Et
MeO
O
NMe
S
H
: B
MeO
CO2Et
(53)
cat. NaOEt
△, EtOH
MeO
HO
NMe
EtO
S
MeO
CO2Et
(96)
MeO
HO
NMe
S
MeO
CO2Et
(85)

Scheme 37


MeO
O
NMe
S
MeO
CO2Et

(53)

After 2 h

The starting material, the 8α-ethoxycarbonyl-7-thia adduct (49a) was characterised by the signals for the olefinic protons, 18- and 19-H, and for 5- and 8-H. These signals were at δ 6.20 (dd, J 9 and 2 Hz, 18-H), 5.70 (d, J 9 Hz, 19-H), 4.90 (s, 5-H) and 5.20 (s, 8-H). After heating for 2 h, there appeared to be three major compounds present. Integration showed 62% starting material. The ^{1}H n.m.r. spectrum of the 4,6α-epoxy acetal (53), obtained when the cycloadduct was heated in toluene, matched several signals in the spectrum of the 2 h reaction mixture, and since both reactions were under neutral conditions it was logical to assume that the acetal (53) was present. The characteristic signals for this acetal were at δ 3.55 (s, 6β-OMe), 5.25 (dd, J 9 and 3 Hz, 7-H), 5.55 (s, 19-H) and 6.05 (d, J 9 Hz, 8-H). Integration showed this acetal to be present in 25% yield. The remaining compound (ca. 12%) was found to be the mixed acetal (96) (see Table 1). For this product, the characteristic signals are those from the 6α-ethoxy and the 6β-methoxy groups and also the signal at ca. δ 4.4 (s, 5-H). The methyl protons in the ethoxy group give an abnormally high field triplet at δ 0.70, due to the shielding effect of the morphinan's aromatic ring. The 6β-methoxy group gives a singlet at ca. δ 3.2. These signals were confirmed by comparison of signals of the equivalent mixed acetal compound, with a p-nitrophenyl group in place of the ethoxycarbonyl group. The p-nitrophenyl series of acetals will be discussed later.

After 5 h

The ^{1}H n.m.r. spectrum of the reaction mixture was quite complex in the region δ 4.4-6.3 and so interpretation of the integration is open to error. The amount of starting material was estimated as 54%, the 4,6α-epoxy acetal (53) as 19%, the mixed acetal (96) as 19%, with the remainder being the 6,6-diethyl acetal (97). The presence of this compound was determined by analysis of the integral for the high field 6α-ethoxy signal.

This integral was greater than the integral for the 6β-methoxy signal at δ 3.2 hence another acetal, with a 6α-ethoxy group, must have been present. This presumed 6,6-diethyl acetal (97) was present in ca. 8% overall yield (see Table 1). Further evidence came from the multiplet at δ 4.45. Its appearance suggested the overlap of two similar higher-field methylene signals arising from the two 6α-ethoxy groups of the acetals (96) and (97). Also the integration suggested that more than one similar 5-H proton was present.

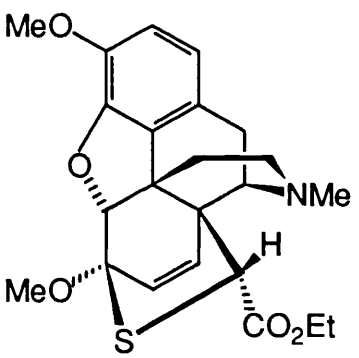
In the p-nitrophenyl series (described later), formation of a diethyl acetal from the corresponding 6α-ethyl-6β-methyl acetal was observed by heating in ethanol alone, and so a similar reaction could possibly occur with the mixed acetal (96) in the 5 h reaction. This information, along with the spectroscopic data supports the formation of the diethyl acetal (97).

After 20 h

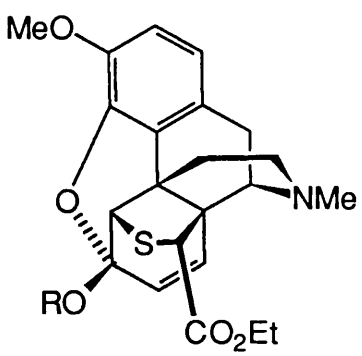
At this stage no starting material was detectable. The 4,6α-epoxy acetal (53) (29%) and the diethyl acetal (97) (54%) were the major products. The remaining material (17%) appeared to be the 6β-ethoxy analogue (98) of the methoxy acetal (53). This product was characterised by signals identical with those of the acetal (53), except that the 6β-methoxy singlet was absent.

Table 1 Yields (%) of products obtained when refluxing an ethanolic solution of the 8α-ethoxycarbonyl-7-thia cycloadduct (49a); for various total times at reflux.

After total time at reflux		2 h	5 h	20 h	45 h
Starting cycloadduct	(49a)	62	54	-	-
4,6α-Epoxy acetal	(53)	25	19	29	-
Mixed acetal	(96)	12	19	-	-
Diethyl acetal	(97)	-	8	54	50
4,6α-Epoxy-6β-ethyl acetal	(98)	-	-	17	50

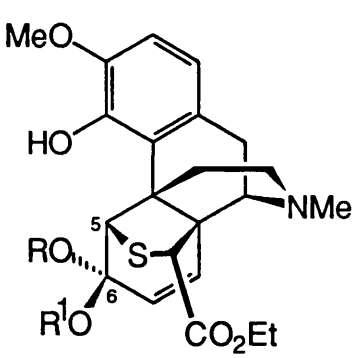


(49a)



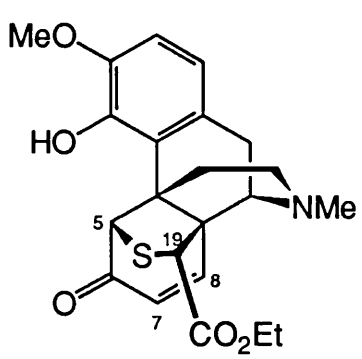
R = Me (53)

R = Et (98)



R = Et, R^1 = Me (96)

R = R^1 = Et (97)



(86)

After 45 h

Only two products were now clearly identifiable. They were the diethyl acetal (97), and the 4,6α-epoxy-6β-ethyl acetal (98) in the ratio of ca. 1:1. This reaction mixture was chromatographed on silica plates eluted with diethyl ether-light petroleum (65:35). The fraction of higher R_f gave the diethyl acetal (97), identified by ^1H n.m.r. spectroscopy. However, the fraction of lower R_f did not give the epoxy acetal (98). Instead the product was the phenolic enone (86), presumably obtained during the preparative chromatography. The enone (86) was characterised by the following distinctive ^1H n.m.r. signals; δ 4.66 (d, J 2 Hz, 5-H), 5.38 (s, 19-H), 5.92 (dd, J 9 and 2 Hz, 7-H), and 6.76 (d, J 9 Hz, 8-H), which are in agreement with Sclare's data.[63]

Several attempts were made to produce the diethyl acetal (97) from the cycloadduct (49a) in the presence of dry ethanolic hydrogen chloride. However, the sole product on most occasions was found to be the enone (86), even in the presence of triethyl orthoformate as a water scavenger. In one attempt, however, a weak high-field triplet, possibly belonging to a 6α-ethoxy acetal, was detected in the ^1H n.m.r spectrum of the reaction mixture.

Before any discussion of the likely reaction mechanisms is given, the series of experiments carried out on the p-nitrophenyl cycloadduct (49b) and related compounds will be described. These results help to formulate a logical, if not complete, layout of the several mechanistic pathways occurring during these reactions.

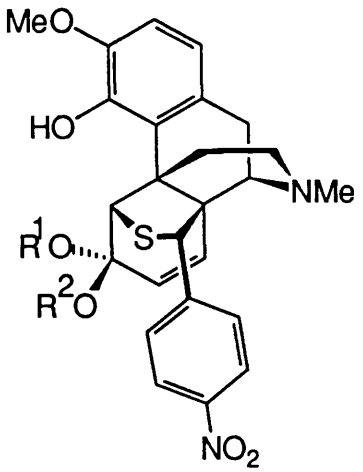
2.3 Rearrangement of the p-nitrophenyl compounds

The 8α-p-nitrophenyl-7-thia cycloadduct (49b) can be prepared regio- and stereo-selectively from thebaine and the corresponding Bunte salt in high yield (see Chapter 2, Scheme 28). The electronic and steric environments of the proton at position 8, adjacent to the nitrophenyl ring, will differ from those of the corresponding proton of the 8α-

ethoxycarbonyl-7-thia cycloadduct (49a). First, 8-H will be more acidic in the ester than in the p-nitrophenyl compound. That is, a stronger base will be required to abstract this benzylic proton (8-H) of the p-nitrophenyl cycloadduct (49b) [see also the lithium diisopropylamide (LDA) reactions on both the ester (49a) and the p-nitrophenyl (49b) compounds]. Secondly, the steric bulk of the p-nitrophenyl group, in conjunction with that of the ethanamine bridge of the morphinan, may physically hinder abstraction of the 8-proton.

2.3.1 Rearrangements with added base

The same experimental conditions were employed as for the ester cycloadducts. Thus, a catalytic amount of sodium ethoxide was added to a solution of the p-nitrophenyl cycloadduct (49b) in dry ethanol. This mixture was heated under reflux for 51 h. A crystalline solid formed, when the mixture was cooled, and was collected and washed with ethanol. This product was found to be the rearranged, 6,6-diethyl acetal (99) and not a cyclopropane derivative as encountered with the ester. The ethanolic washings were found to contain the enone (100), presumably arising from hydrolysis of the starting cycloadduct or of the diethyl acetal (99). The diethyl acetal was identified by a high-field, ^{1}H n.m.r. triplet at δ 0.8, due to the methyl protons of the 6α-ethoxy group, shielded by the morphinan's aromatic ring [see (111A), Scheme 41], a triplet at δ 1.27 due to the 6β-ethoxy group and the lack of a 6-methoxy signal. Other data from ^{13}C n.m.r. and i.r. spectra and microanalysis confirmed the identity of this acetal. However, the mass spectrum failed to give a molecular ion (m/z 538), but some useful data on fragment ions were obtained. This information will be discussed later in this sub-chapter.



(99) ; $R^1 = R^2 = Et$

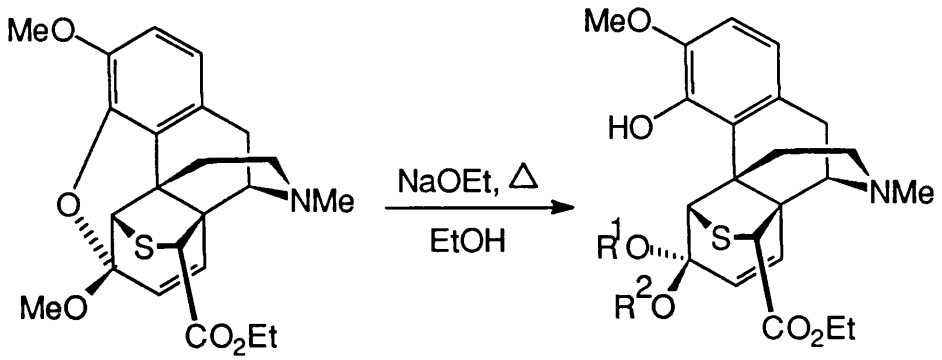
(101) ; $R^1 = Et$, $R^2 = Me$

(102) ; $R^1 = Me$, $R^2 = Et$

(103) ; $R^1 = R^2 = Me$

Due to the low solubility of the cycloadduct (49b) and the diethyl acetal (99) in ethanol, further reactions with the p-nitrophenyl compounds were carried out in a 1:1 mixture of benzene and alcohol (ethanol or methanol). The azeotropic boiling point will be higher for the benzene and ethanol mixture than the benzene and methanol mixture. These differing temperatures will slightly alter the rates of the reactions, but the interesting chemical transformations should not be affected. The transformation from the cycloadduct (49b) into the 6,6-diethyl acetal (99) must have proceeded via at least one intermediate, probably a mixed, methoxy-ethoxy acetal. In an attempt to detect this intermediate, the cycloadduct (49b) containing a catalytic amount of sodium ethoxide was heated in ethanol-benzene under reflux for ca. 20 h rather than 51 h. As explained before, benzene was used to aid solubility of both reactants and products. The reaction mixture, as judged by ^1H n.m.r. (90 MHz) spectroscopy, contained the starting cycloadduct (49b), the diethyl acetal (99) and, most importantly, the 6α-ethyl-6β-methyl acetal (101). The 6α-ethoxy methyl protons resonated at a high field, δ 0.74, due to the shielding effect of the aromatic ring, while the 6β-methoxy group gave a singlet at δ 3.30, the expected chemical shift for an unshielded methoxy group. This showed that the first ethoxy group was introduced from the hindered α-face. However, on this evidence alone, it was not clear whether the second ethoxy group was introduced α or β.

Therefore, the diethyl acetal (99) was treated with a catalytic amount of sodium methoxide in refluxing methanol-benzene for 47 h. The only product observed, apart from starting material (99), was the 6β-ethyl-6α-methyl acetal (102), although a trace amount of the epimeric 6α-ethyl-6β-methyl acetal (101), may have been present. This mixed acetal (102) was characterised by the following signals, δ 2.80 (s, 6α-OMe) and ca. 1.28 (t, J 7.0 Hz, 6β-$OCH_2\underline{CH_3}$). This result clearly signified that the methoxy group had approached from the hindered underside of the molecule, i.e. the α-face, giving rise to the abnormally high field 6α-methoxy signal. This underside attack of alkoxy groups was further verified by treating a pure sample of the mixed acetal, 6α-ethyl-6β-methyl acetal (101) (prepared from the dimethyl acetal; see below), with a catalytic amount of sodium methoxide in methanol-benzene. After 17 h at reflux, this mixture contained the mixed acetal (101) as well as the 6,6-dimethyl acetal (103). This dimethyl acetal was prepared in a manner similar to that for the corresponding diethyl acetal, i.e. by heating under reflux a solution of the cycloadduct (49b) in methanol-benzene in the presence of a catalytic amount of sodium methoxide. The 6α-methoxy signal resonated at δ 2.78 and the 6β-methoxy signal at δ 3.32. This dimethyl acetal was treated with ethanolic sodium ethoxide in the same manner as previously described. After 8 d at reflux, the only compound obtained was the product of underside attack of an ethoxy group, i.e. the mixed 6α-ethyl-6β-methyl acetal (101). This clearly signifies that attack of alkoxy groups on 6,6-dialkyl acetals is exclusively from the α-face. A similar observation was encountered, as previously mentioned, when the ethyl ester, 4,6α-acetal (53) was heated in ethanol under reflux in the presence of a catalytic amount of sodium ethoxide. The only product was the 6α-ethyl-6β-methyl acetal (96), signifying approach of the incoming ethoxy group from the hindered α-face (Scheme 38).



(53)

(96) ; R^1 = Et, R^2 = Me

(97) ; R^1 = R^2 = Et

(109) ; R^1 = Me, R^2 = Et

Scheme 38

The foregoing experiments show that the p-nitrophenyl cycloadduct (49b) when heated in ethanol in the presence of a catalytic amount of ethoxide for a limited period, unexpectedly forms the 6α-ethyl-6β-methyl acetal (101), together with the diethyl acetal (99). However, when the 6,6-dimethyl acetal (103) was heated under reflux for 8 days in ethanol with a catalytic amount of sodium ethoxide, the sole product was the 6α-ethyl-6β-methyl acetal (101). Significantly, no diethyl acetal was observed. This implies that different conditions must apply when the cycloadduct rather than a phenolic acetal is the starting material.

The proposed mechanisms for these observed reactions will be discussed in detail shortly, however briefly, exchange from the hindered α-face is believed to depend upon assistance from the phenolic hydroxy group. The undissociated phenolic group assists loss of an α-alkoxy group from the acetal. Thereafter, the phenoxide anion directs introduction of an alkoxy group from the same side. Hence, if the undissociated phenolic group is not present then the acetal should not exchange. To test this idea, an excess of 1 mol equivalent of sodium ethoxide was added to the phenolic dimethyl acetal (103), to

form the corresponding phenoxide. As expected, only starting material was observed when this mixture was heated. Therefore, in theory, there should be no need for any base at all since the phenol acts as a general acid catalyst for acetal exchange.

Finally, when the cycloadduct (49b) was treated with LDA, only starting material was recovered. This would suggest that the steric bulk of the p-nitrophenyl group prevents abstraction of the proton at position 8. This of course, assumes that LDA is a strong enough base to remove this proton.

2.3.2 Rearrangements without added base

When the ethyl ester cycloadduct (49a) was heated in ethanolic sodium ethoxide, the alkoxide ions removed the acidic 8-H proton giving rise to cyclopropane formation (see Scheme 35). However, rearrangements of this same cycloadduct also occurred with heating in ethanol alone (see Section 2.2.2). These products, e.g. 6α-ethyl-6β-methyl acetal (96) and 6,6-diethyl acetal (97), obtained under neutral conditions, are similar to the ones encountered so far in the p-nitrophenyl series. Since cyclopropane formation did not occur in the p-nitrophenyl series with base added, then it is possible that the rearrangements which did take place in the p-nitrophenyl series were due to the solvent alone. This is quite possible since acetals do not normally require catalysis with base to undergo exchange reactions with alcohols. Thus, the p-nitrophenyl cycloadduct (49b) was heated under reflux for ca. 50 h in ethanol. The only product, apart from some enone (100), was the diethyl acetal (99). Again, a shorter time at reflux was employed to identify the mixed acetal through which the solvolysis must have proceeded. Thus, after 25 h at reflux, the mixed acetal, 6β-ethyl-6α-methyl (102), appeared, from the ^{1}H n.m.r. spectrum, to be present along with the diethyl acetal. It is possible that the epimeric, mixed 6α-ethyl-6β-methyl acetal (101) may also have been present as a minor component. This experiment suggests that the ethoxy group had approached from the

sterically accessible face of the morphinan, i.e. the β-face. This observation was further verified by the following reactions. The diethyl acetal in methanol-benzene was heated under reflux for 20 h. Assuming that no starting diethyl acetal is now present, the ^1H n.m.r. (90 MHz) spectrum of the reaction mixture showed the 6α-ethyl-6β-methyl acetal (101), the dimethyl acetal (103) and apparently the 6β-ethyl-6α-methyl acetal (102) to be present. This reaction mixture was then heated under reflux in methanol-benzene, and ^1H n.m.r. spectra were recorded at several intervals. A gradual increase in the yield of dimethyl acetal (103) and a decrease in the amount of the 6α-ethyl-6β-methyl acetal (101) was observed from these spectra. In the early stages, the 6β-ethyl-6α-methyl acetal (102) appeared to remain at ca. 20% of the reaction mixture. However, after ca. 10 days at reflux, only the dimethyl acetal was shown to be present along with some of the corresponding enone. The diethyl acetal (99) was also the eventual product, after ca. 4 days at reflux, of refluxing a pure sample of the dimethyl acetal (103) in ethanol-benzene. Also the mixed, 6α-ethyl-6β-methyl acetal (101), in ethanol-benzene was heated under reflux for 18 h. An ca. 1:1 mixture of this mixed acetal and the diethyl acetal was observed, as judged by ^1H n.m.r. spectroscopy, but again possible signals arising from the other mixed acetal, the 6β-ethyl-6α-methyl isomer, may have been present and difficult to distinguish from other signals. A list of the ^1H chemical shifts of the 6,6-alkoxy groups of the morphinans just described is given in Table 2.

2.3.3 Mechanisms

The proposed mechanisms for the rearrangements of the p-nitrophenyl series under alkaline and neutral conditions will now be discussed. These mechanisms are also relevant for rearrangements of the ethyl ester compounds.

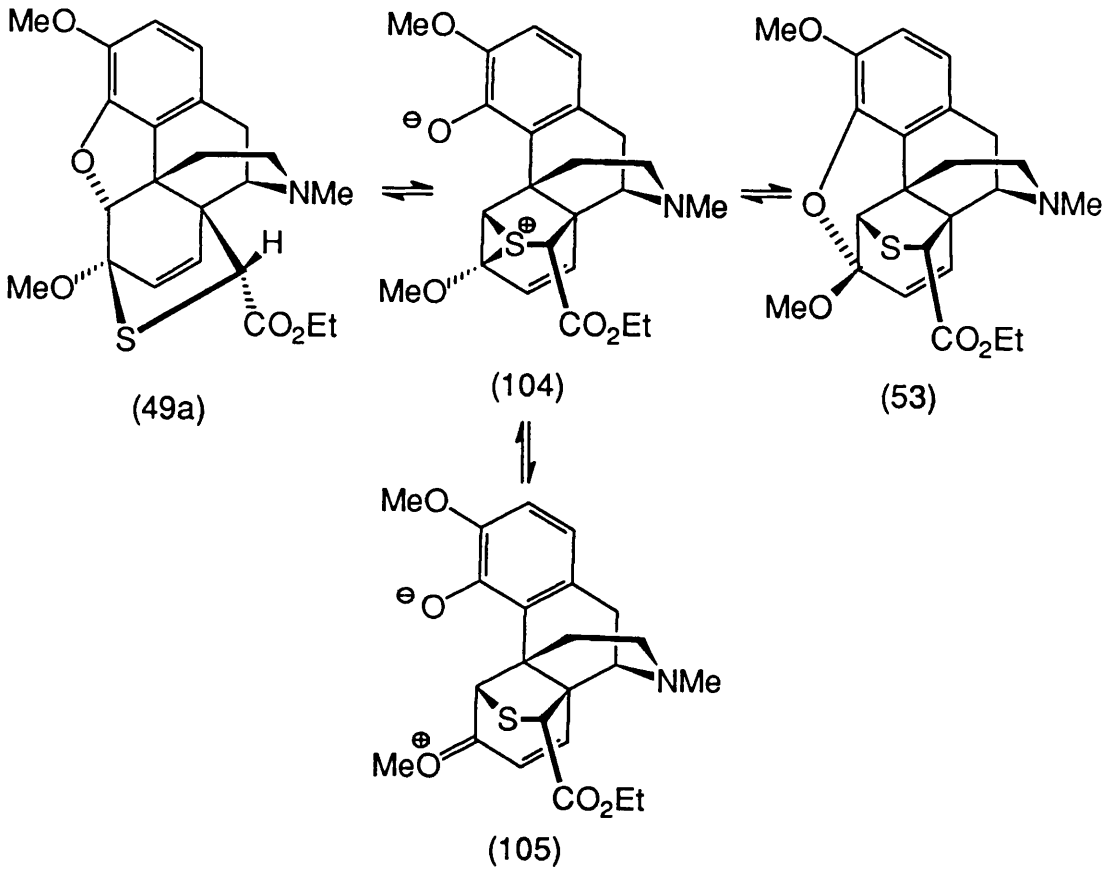
The cycloadducts, (49a) and (49b), are likely to be in equilibrium with transient intermediates, through which these cycloadducts react. However, these ethyl ester (49a)

Table 2 A list of the ^{1}H n.m.r. signals (δ) of the 6,6-dialkoxy groups of the following p-nitrophenyl derivatives (99), (101), (102) and (103).

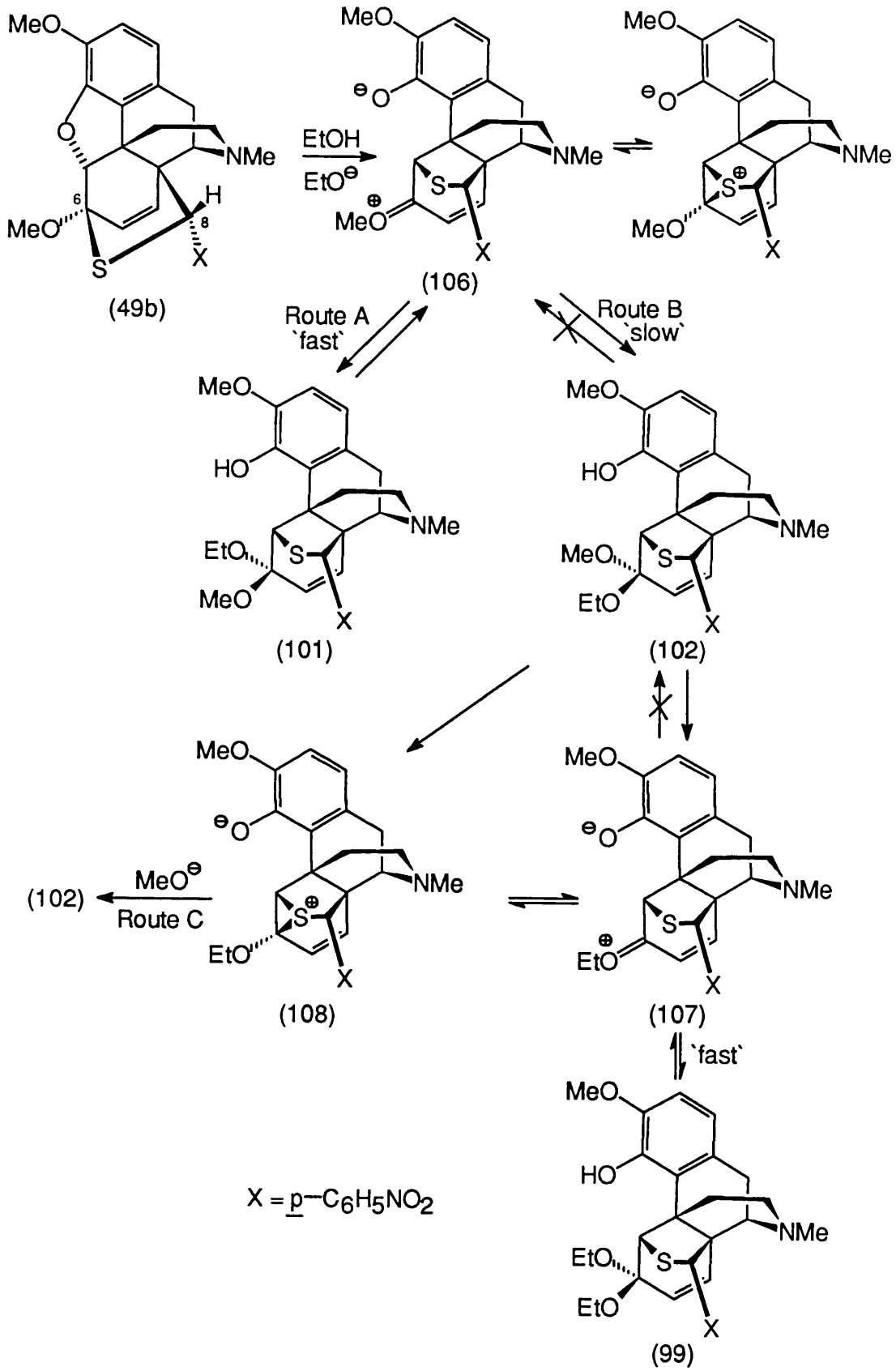
	(99)	(101)	(102)	(103)
6α-OMe	-	-	2.80	2.78
6β-OMe	-	3.30	-	3.32
6α-$OCH_2C\underline{H}_3$	0.74	0.73	-	-
6β-$OCH_2C\underline{H}_3$	1.25	-	1.28	-

and p-nitrophenyl (49b) cycloadducts may behave differently under similar conditions, although similar transient intermediates may participate. For example, the ethyl ester cycloadduct rearranges to the cyclopropane (85) (see Section 2.2.1, Scheme 35) with the aid of sodium ethoxide, while the p-nitrophenyl cycloadduct as has just been described, gives 6,6-dialkyl acetals under the same conditions. Sclare[59] suggested that the episulphonium ion (104) may be an intermediate in the rearrangement of the cycloadduct (49a), in refluxing toluene, to give the 4,6α-epoxy-6β-methyl acetal (53) (Scheme 39). The oxonium ion (105) may also be an intermediate in reactions involving these cycloadducts, and indeed the oxonium (105) and episulphonium (104) ions may be in equilibrium with each other (see Scheme 39).

When the p-nitrophenyl cycloadduct (49b) is heated in ethanol (or methanol) the methoxonium ion (106) is believed to form. Ethanol, or an ethoxide anion, can approach from the α-face (Scheme 40, route A) or the β-face (Scheme 40, route B). In route A the phenoxide ion can assist α-addition of an ethoxy group from an ethanol molecule (see Scheme 42). Thus, in the experiment with the shorter reflux time, the mixed 6α-ethyl-6β-methyl acetal (101), was observed as the major product. In contrast, although route B involves approach of the ethoxy group from the exposed β-face, the mixed 6β-ethyl-6α-methyl acetal (102) was a minor product, if indeed it was present at all. Now, either of the mixed acetals (101) and (102) could in principle lose the 6α-alkoxy group (see Scheme 41) to give the corresponding oxonium intermediate. Route A, giving the 6α-ethyl-6β-methyl acetal (101), is reversible, regenerating the methoxonium ion (106). However, route B gives the 6β-ethyl-6α-methyl acetal (102) which, on loss of the 6α-alkoxy group, gives a different oxonium ion, the ethyloxonium ion (107). Therefore, route B can lead only to the diethyl acetal (99) (Scheme 40). Therefore, with a sufficient reaction time, all of the 6α-ethyl-6β-methyl acetal will undergo the route B pathway.


MeO
NMe
H
MeO
S
CO2Et
(49a)
MeO
NMe
MeO
S
CO2Et
(104)
MeO
NMe
O
S
MeO
CO2Et
(53)
MeO
NMe
S
MeO
CO2Et
(105)

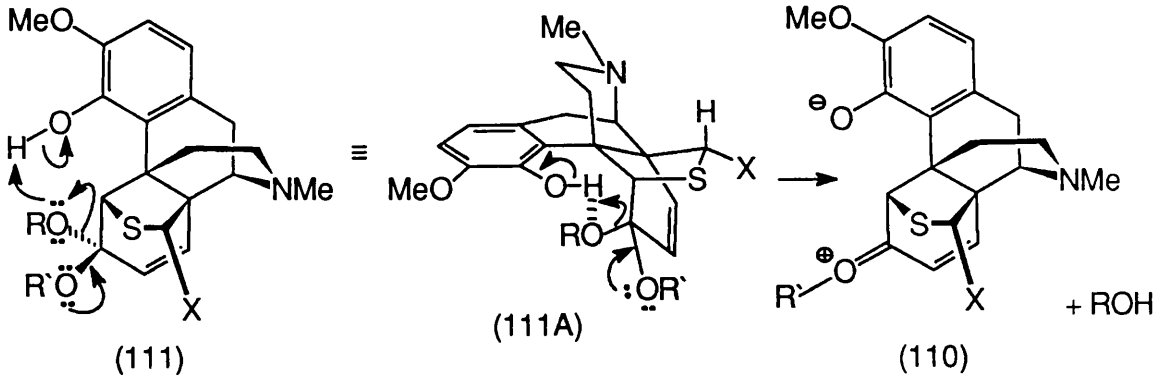
Scheme 39


MeO
NMe
EtOH
EtO⊖
(49b)
(106)
Route A
`fast`
Route B
`slow`
HO
EtO
(101)
(102)
(108)
(107)
(99)
`fast`
(102)
MeO⊖
Route C
X = p−C6H5NO2

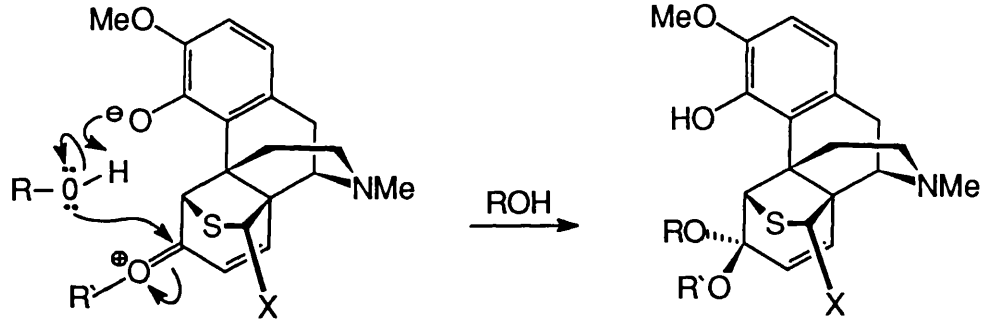
Scheme 40

In the sodium methoxide catalysed reaction involving the phenolic diethyl acetal (99) in methanol, the only product, even after 8 days with heating at reflux, was the 6β-ethyl-6α-methyl acetal (102). The dimethyl acetal (103) would have been the expected product, considering the facts previously just discussed. The observed product is significant because it suggests that the sequence or rate of reactions involved, is different from those with the cycloadduct (49b). An explanation for this is that the starting material, i.e. the diethyl acetal (99), is a phenol, which would be partly converted into phenoxide in the presence of a catalytic amount of methoxide ions. This highly polar species in a polar solution could affect the relative rates of formation of the oxonium (107) and episulphonium (108) intermediates (Scheme 40). Therefore it is suggested that the o-ethylepisulphonium ion (108) is favoured over the corresponding oxonium ion (107) and hence only α-face approach of the incoming methanol group is allowed (Scheme 40, Route C). A similar observation was encountered when the ethyl ester, 4,6α-epoxy acetal (53) (Scheme 38) in ethanol, was treated with a catalytic amount of ethoxide ions. The observed product was the 6α-ethyl-6β-methyl acetal (96). Neither the diethyl acetal (97) nor the other mixed acetal isomer (109) was observed and so it is possible that ethanolysis of the epoxy acetal (53), also favours the episulphonium ion intermediate.

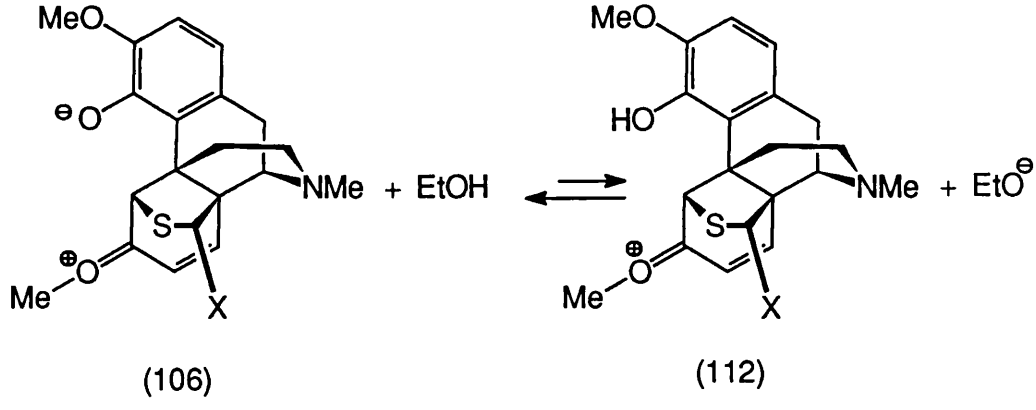
Many of the experimental results involve the stereoselective loss of a 6α-alkoxy group. The requirement for this loss is the close proximity of the phenolic hydroxy group to the 6α-alkoxy group. This allows the elimination of the alkoxy group as the alcohol and hence the formation of the oxonium-phenolate intermediate (110) (Scheme 41). The reverse process (Scheme 42) must follow the same mechanism in detail. Thus a molecule of alcohol can now hydrogen-bond to the phenolate (110), and hence be delivered to the oxonium ion from the hindered α-face, to give the acetal (111). The



Scheme 41



Scheme 42



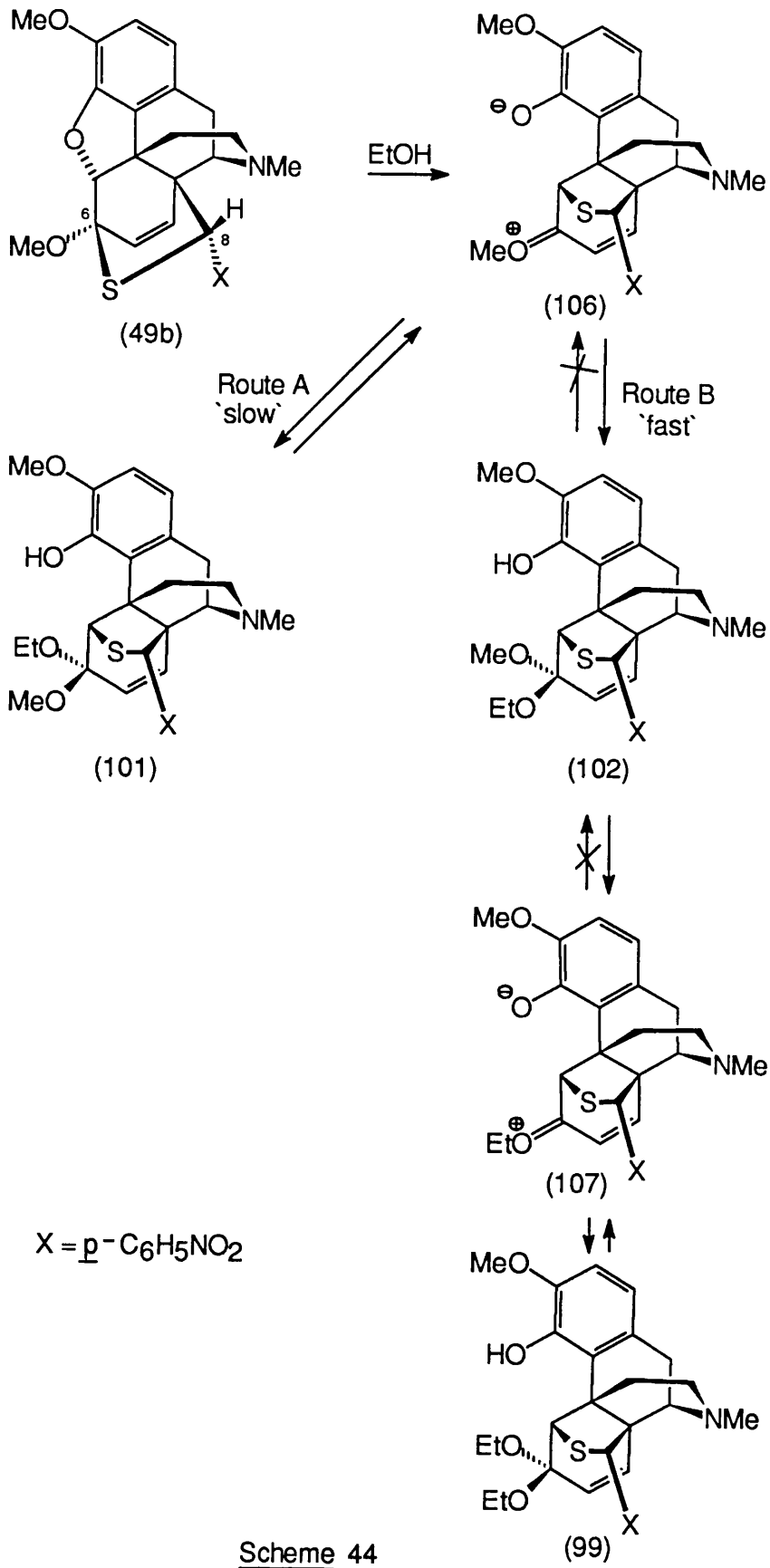
Scheme 43

X = p-$C_6H_5NO_2$

close proximity of the phenolic hydroxy group to the 6α-alkoxy group was experimentally observed by recording the i.r. spectrum of the mixed acetal (101) at one concentration and then re-recording the spectrum after a dilution of this sample had been carried out.

Retention of all absorbancies and relative intensities was observed in the 'diluted' spectrum signifying the internal hydrogen bonding of the hydroxy group to the nearby 6α-alkoxy group was occurring. (N.B. Molecular models of this acetal clearly show the close proximity of these groups and so are undoubtedly the groups responsible for the above i.r. data.)

When the reactions are carried out in ethanol or methanol without alkoxide, only the oxonium ion, and not the episulphonium ion is proposed to be involved in the reaction mechanism. When the p-nitrophenyl cycloadduct (49b) is heated in ethanol alone, the methoxonium ion (106) is believed to be formed. This intermediate has an electrophilic centre at position 6 as part of a flat oxonium ion. Also, in the presence of ethanol this phenolate intermediate could be protonated to give the phenol (112) (Scheme 43). An incoming molecule of ethanol can approach from either face. However the α-face is sterically hindered by the phenol/phenolate whereas the β-face is unobscured. Approach from the hindered α-face gives the 6α-ethyl-6β-methyl acetal (101) (Scheme 44, route A). As described previously, this acetal can lose the 6α-alkoxy group as the alcohol (see Scheme 41). This acetal (101) would regenerate the methoxonium ion (106) and hence route A is reversible. Approach from the β-face would give the 6β-ethyl-6α-methyl acetal (102) (Scheme 44, route B). This was indeed the observed major intermediate. However, loss of the 6α-alkoxy group would give the ethyl- and not the methyl-oxonium ion; hence route B is essentially non-reversible. An incoming

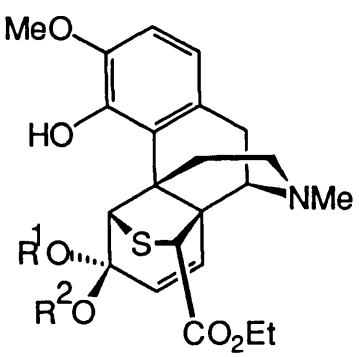


$X = \underline{p}\text{-}C_6H_5NO_2$

Scheme 44

molecule of ethanol can approach from either the α- or β-face, of this ethyloxonium ion and hence the product would be the same in both cases i.e. the 6,6-diethyl acetal (99).

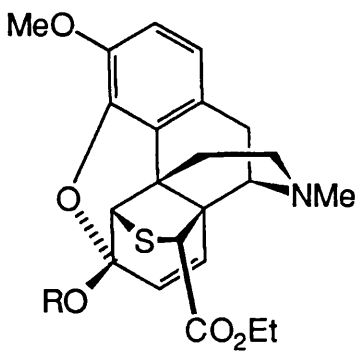
When the 8α-ethoxycarbonyl-7-thia cycloadduct (49a) was heated in ethanol without base, a mixture of the acetals (53), (96), (97) and (98) was formed. The observed product ratios at various reaction times cannot be easily explained, but methyl- and ethyl-oxonium and episulphonium intermediates are almost certainly involved in this complex reaction. However, the mixed, 6β-ethyl-6α-methyl acetal (109) could have been present as a minor intermediate and would help explain why only ethoxy acetals are eventually present, since a 6α-methoxy group can be replaced (see Schemes 41 and 42) by an ethoxy group from the ethanol solvent.



(96) ; R^1 = Et, R^2 = Me

(97) ; R^1 = R^2 = Et

(109) ; R^1 = Me, R^2 = Et



(53) ; R = Me

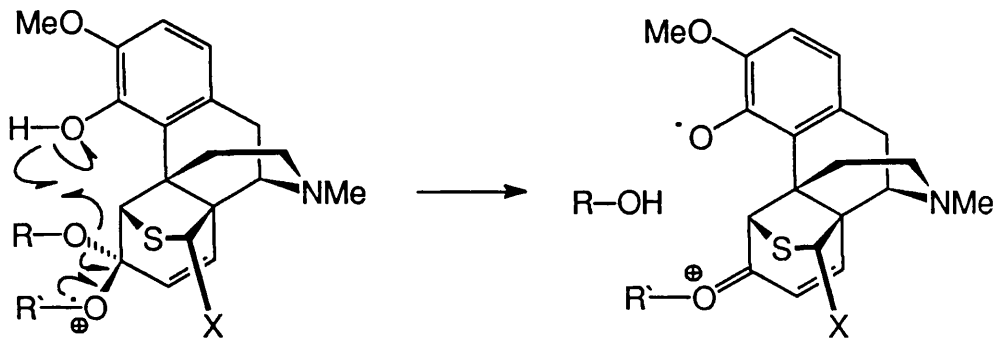
(98) ; R = Et

2.3.4 Mass spectral data

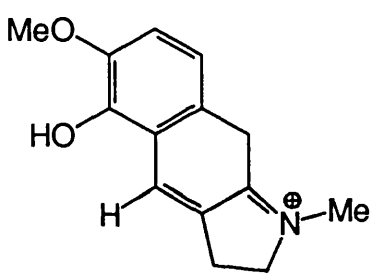
None of the 6,6-dialkoxy morphinans of the p-nitrophenyl series gave stable molecular ions upon electron impact, owing to the ready cleavage of the acetals. However, a diagnostically useful effect was observed in the mass spectra of these compounds. The 6,6-dialkoxy morphinans lost the 6α-alkoxy in preference to the 6β-alkoxy group. The groups are actually lost as the protonated alkoxy group i.e. as ethanol or methanol. For example, the 6α-ethyl-6β-methyl acetal (101) (M, 524) gave the following peaks, m/z 492 (19%, M-MeOH) and 478 (50%, M-EtOH), whereas the 6β-ethyl-6α-methyl acetal (102) gave the same peaks but with reverse intensity, i.e. m/z 492 (31%) and 478 (8%). Also the diethyl acetal (99) gave a peak at m/z 492 (26%, M-EtOH), and the dimethyl acetal (103) gave a similar peak at m/z 478 (70%, M-MeOH). These peaks from the symmetrical acetals can arise from cleavage from either the favourable α-face or from the β-face, and hence, in most cases, the high percentage of the solitary peaks. Loss of ethanol or methanol, rather than an ethoxy or methoxy group, together with the favoured loss of an α-alkoxy group can be explained by the mechanism shown in Scheme 45, which resembles that proposed for solvolytic exchange (see Scheme 41).

Another important feature in the mass spectra of these and other phenolic morphinans, is the common mass spectral peak at m/z 230 (accurate mass measurement of this peak gave the molecular formula, $C_{14}H_{16}NO_2$). This peak is sometimes the most intense in the spectra of phenols and is possibly due to the fragment ion (113). Migration of carbon and hydrogen atoms are common in mass spectroscopy and hence this conjugated, rearranged structure might plausibly account for the preference for this fragmentation. Although observation of this peak is not conclusive structural evidence, it

provides a useful indication that the 4,5α-epoxy bridge in a morphinan has opened to give a phenol.



Scheme 45



(113)

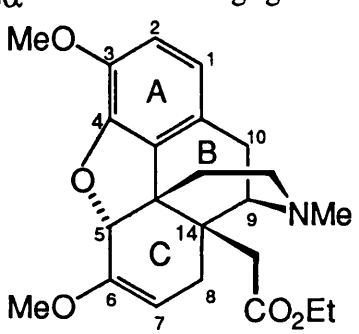
2.4 Desulphurisation with Raney nickel

As described earlier, cycloadducts such as (49a) and (49b), have been shown to rearrange in ethanol, with or without the presence of added base, and also these cycloadducts can be quite easily hydrolysed to the corresponding enones. Therefore, in the Raney nickel desulphurisation experiments that follow, care was taken to try to avoid inadvertently mediating possible rearrangements. The solvent, whether ethanol or methanol, was dried with magnesium turnings followed by distillation and usually the experiment was carried out under nitrogen. The Raney nickel was always freshly prepared[27] and during this preparation the washing procedures were repeated many times, firstly to remove any residual sodium hydroxide used in the preparation and

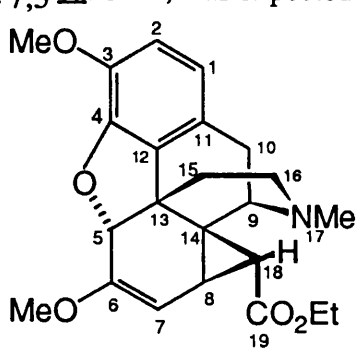
secondly, with ethanol, to remove any water present. The Raney nickel was always prepared as the W-2 reagent.

2.4.1 The 8α-ethoxycarbonyl-7-thia cycloadduct (49a).

On a relatively small scale the cycloadduct (49a) was treated with an excess of Raney nickel in ethanol for 3 h. In this reaction only two products were observed and were subsequently identified. They were the 14β-ethoxycarbonylmethyl derivative (114) and the 8β,14β-methanomorphinan (115) in the ratio 45:55, respectively. This ratio was approximate and was based on the relative heights of the 6-0Me signals in the ^{1}H n.m.r. spectrum (90 MHz) of the reaction mixture. The 200 MHz ^{1}H n.m.r. spectrum of the 14β-alkyl derivative (114) gave the following signals, δ 3.45 (s, 6-OMe) and 3.80 (s, 3-OMe), while the corresponding signals for the cyclopropane (115) were δ 3.44 and 3.83, respectively. This separation between the 3-OMe and 6-OMe signals for each compound was more distinct in the 90 MHz spectrum and was the basis for the identification of the products in the mixture. Once the mixture had been chromatographed, the separated desulphurised products were identified by the signals for the ring C protons at positions 5, 7 and 8. Ring C of the 14β-alkyl derivative (114) would probably have a chair conformation (114A). A model of this conformation helps to confirm the proton couplings observed. The 7-H signal at δ 4.61 was a double-doublet, $J_{7,8\beta}$ 6.7 and $J_{7,8\alpha}$ 2.0 Hz. The negligible allylic coupling, $J_{7,5}$ ca. 0 Hz, was expected since the

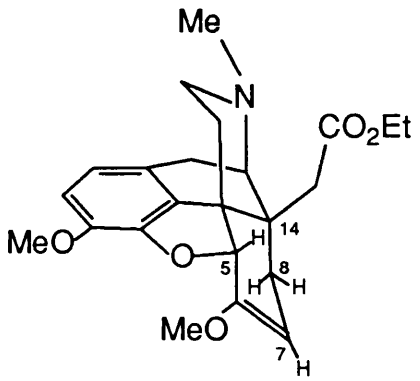


(114)



(115)

dihedral angle is ca. 90° in the model, although 5-H gave a homoallylic doublet δ 4.74, $J_{5,8\alpha}$ 1.3 Hz. Accordingly, signals for the 8α and 8β protons, with a geminal coupling of 16.5 Hz were observed at δ 1.85 (dd, J 16.5 and 1.4 Hz, 8β-H) and 2.07 (dd, J 16.5 and 6.8 Hz, 8α-H). Accurate mass spectral data confirmed the composition of $C_{23}H_{29}NO_5$



(114A)

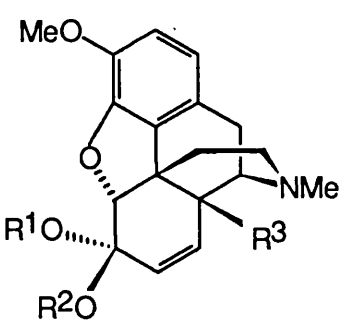
for the molecular ion and ^{13}C n.m.r. gave data consistant with the proposed structure (114). The cyclopropane (115), with ring C in a distorted chair conformation, was identified by the signals at δ 4.57 (s, 5-H), 5.03 (d, $J_{7,8}$ 5.9 Hz, 7-H) and 2.05 (dd, J 5.8 and 3.8 Hz, 8-H). Coupling between the protons at positions 8 and 18 accounted for the splitting of 3.8 Hz, however, the reciprocal coupling of 18-H was not identified because the ^1H n.m.r. spectrum (200 MHz) was poorly resolved for the signals of some protons, including that of 18-H. This may have been due to complexing of the morphinan, probably through nitrogen, and nickel (from the Raney nickel reduction) thus causing broadening of the signals for the protons in close vicinity to the nickel. However, other spectroscopic data confirmed the identity of this product. For example, the ^{13}C n.m.r. spectrum confirmed 7 methine protons, attached to C-1, -2, -5, -7, -8, -9, and -18.

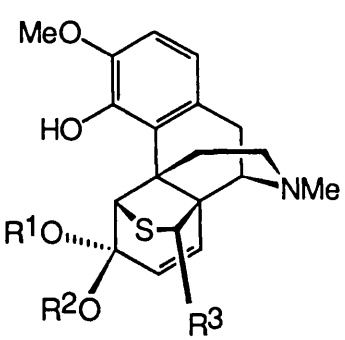
When this experiment was repeated but on a larger scale, a much more complex mixture of products was obtained. The crude reaction mixture was chromatographed on a silica column. The first few fractions, containing morphinan material, were combined

and further chromatographed to partially separate 4 products. Each of the two major products were accompanied by minor components, these being apparently analogues of the main products. The first major product was believed to be the 6β-ethyl-6α-methyl acetal (116), accompanied with its analogue the 6,6-diethyl acetal (117). The ratio of these products, based on the relative heights of the olefinic proton doublets, centred at δ 5.60 (7-H) and δ 5.89 (8-H) was 82:18, respectively. The mass spectrum of the mixture gave the ratio of the molecular ions as 85:15. These 6,6-dialkoxy acetals, (116) and (117), are different to the acetals [for example (96), (99) and (103)] obtained in the solvolysis reactions of the ethyl ester and p-nitrophenyl cycloadducts. Those solvolysis acetals, (96), (99) and (103), are phenolic acetals and thus the 6α-alkoxy groups are shielded by the morphinan's aromatic ring and so the protons of this alkoxy group resonate at higher fields than normally expected. For example, the 6α-ethoxy group of (99) has the methyl protons at δ 0.74; cf. 6β-$OCH_2\underline{CH_3}$ at δ 1.25: and the 6α-methoxy group of (103) at δ 2.78; cf. 6β-OMe at δ 3.32. The acetals produced in the desulphurisation experiment have the 4,5α-epoxy bridge intact and therefore the chemical shifts of their alkoxy groups are as would be predicted when compared to other known codeinone acetals (Table 3) (see also Table 2).

Table 3 ^{1}H Chemical shifts (δ values for ($CDCl_3$ solutions) for various acetals of 6-oxomorphinans

Compound	6α-OCH_2CH_3	6β-OCH_2CH_3	6α-OMe	6β-OMe
(116)	/	ca. 1.21	3.42	/
(117)	ca. 1.21	ca. 1.21	/	/
I[65]	/	/	3.34	3.00
II[66]	/	/	3.44	3.16
III[15]	/	/	3.45	3.05
(96)	0.74	/	/	3.25
(99)	0.74	1.25	/	/
(103)	/	/	2.78	3.32





(116) ; R^1 = Me, R^2 = Et, R^3 = CH_2CO_2Et

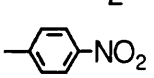
(117) ; R^1 = R^2 = Et, R^3 = CH_2CO_2Et

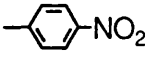
I ; R^1 = R^2 = Me, R^3 = H

II ; R^1 = R^2 = Me, R^3 = Br

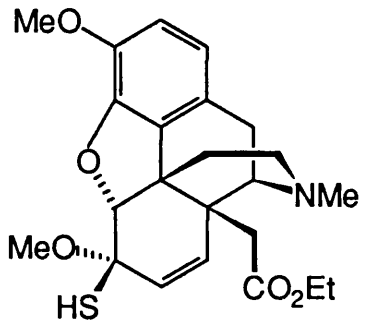
III ; R^1 = R^2 = Me, R^3 = NO_2

(96) ; R^1 = Et, R^2 = Me, R^3 = CO_2Et

(99) ; R^1 = R^2 = Et, R^3 = 

(103) ; R^1 = R^2 = Me, R^3 = 

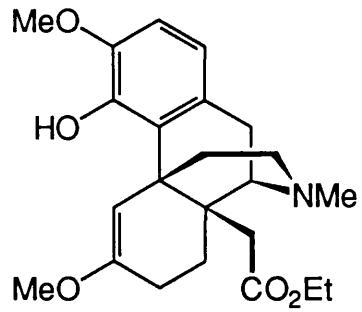
In the desulphurisation reaction, it is likely that the Raney nickel reduced the S-C(CO_2Et) bond first, the resultant intermediate (118) could then give the acetals (116) and (117) and hydrogen sulphide solvolytically.



(118)

The other major product (119), and its minor relative (120), from these early fractions could not be identified despite ^1H, ^{13}C and mass spectral data. The products gave mass spectral peaks at m/z 415 and 429, in the ratio 86:14 respectively, that might arise from molecular ions. The low resolution mass spectral data suggests that the products were both 14β-ethoxycarbonylmethyl derivatives since both gave distinctive peaks corresponding to the fragments M-$C_4H_7O_2$. The ^1H n.m.r. (200 MHz) spectrum suggested that the 4,5α-epoxy bridge was intact and that the 3-OMe and 6-OMe groups were also present. Also, signals at δ 4.33 (1H, d, J 9.7 Hz), 4.69 (1H, d, J 9.7 Hz), 5.70 (1H, d, J 13.4 Hz) and 6.15 (1H, d, J 13.4 Hz) suggested that at least one double bond was present. However, the doublets at δ 4.33 and 4.69 are at unusually high field for olefinic protons. The lower field doublets have a very large coupling constant which effectively rules out the possibility of an endocyclic double bond. The identity of these products is obscure and hence no structures have been assigned.

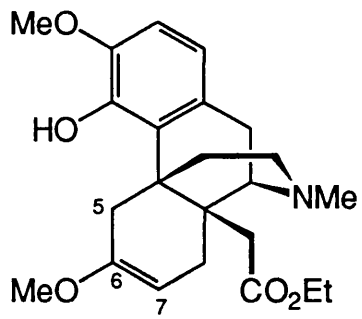
The next several fractions contained three compounds. The major product in these fractions was tentatively assigned the structure (121). This 5,6-didehydro-4-hydroxymorphinan structure was proposed since a singlet at δ 5.40 was attributable to



(121)

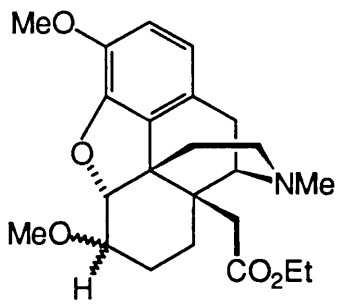
the olefinic 5-H, at unusually low field due to its lying in the deshielding zone of the aromatic ring [c.f. δ 4.35 (7-H) in the 6,7-didehydro phenol (122)]. A broad singlet at ca. δ 5.95, strongly suggested that this product was a phenol. The other two products in these fractions were identical with those from the small scale reaction, namely the 6,7-didehydro-4,5-epoxymorphinan (114) and the 8β,14β-methanomorphinan (115).

One of the major products of the reaction crystallised out from several of the later fractions taken during column chromatography. This product was assigned the structure (122). It is the phenolic derivative of the major product (114). Again the ring C protons helped to identify this product, as well as the accurate mass spectral data giving a molecular ion corresponding to the formula $C_{23}H_{31}NO_5$. The ^1H n.m.r. spectrum gave a multiplet at ca. δ 4.06, which was considered to arise from 5α-H deshielded by the aromatic ring. The 5β-H signal was not clearly identifiable, since it was obscured by other protons with similar chemical shift. In the 4,5-epoxide (114) 5-H resonates at δ 4.74. The 7-H signal is shifted upfield from δ 4.61 in the epoxide to 4.35 in the phenol. The phenolic proton signal at δ 6.14 clearly signified that the epoxy bridge was open. The ^{13}C n.m.r. spectrum gave the correct number and multiplicity of carbon signals consistent with the proposed structure.

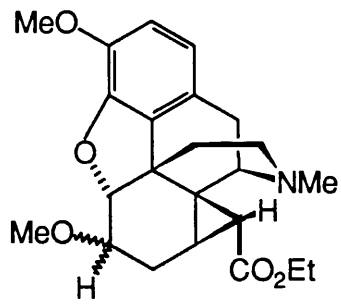


(122)

Several other products were found, but were not individually assigned structures, without some degree of speculation. Apart from the two unidentified products described earlier, the remaining compounds had either a 4,5-epoxide or a phenol group; either a 8β,14β-cyclopropane ring or a 14β-alkyl group; and were either 5,6-didehydro or 6,7-didehydro derivatives. Since reduction of a double bond is often encountered during Raney nickel desulphurisation, then it is likely that some of the remaining, non-identified products are actually dihydro derivatives of those enol ethers already identified, i.e. (114), (115), (121), (122) and (123). Reductive cleavage of the 4,5-epoxide bridge and of the cyclopropane ring may also have occurred and have contributed to the structure of the non-identified products. Table 4 shows the actual yields of the products identified and of those with tentatively assigned structures.



(124)



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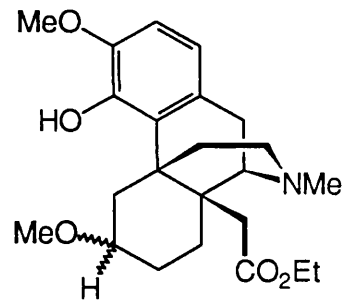
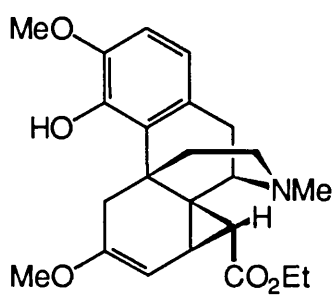


(126)



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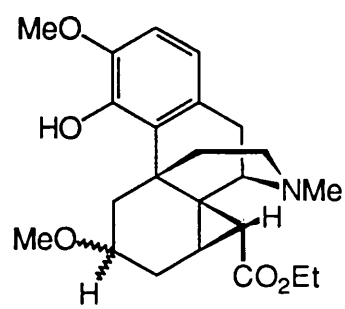


(127)

Table 4 Yields (%) of products from the large scale Raney nickel reduction of the 8α-ethoxycarbonyl-7-thia cycloadduct (49a).

Compound	Approximate Yield (%)	Compound	Approximate Yield (%)
(116)	0.6	(115)	10.7
(117)	0.1	(122)	14.8
(119)	1.3	(126) + (127)	8.3
(120)	0.2	Tentative (123)	16.4
(121)	6.2	(124) + (125)	14.6
(114)	3.0		

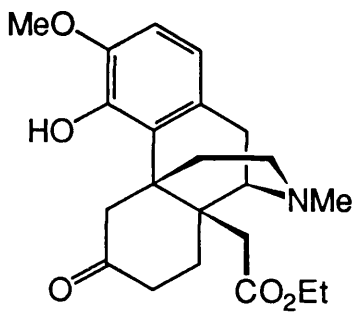
Overall yield ca. 90%

2.4.2 The ethyl ester enone (86).

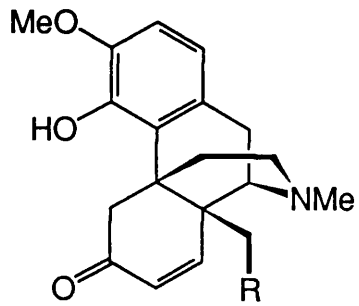
The previous experiments with the cycloadduct (49a) obviously do not provide an efficient route to 14β-alkylmorphinans. Many of the products had undergone opening of the epoxide bridge, movement of the double bond to give the thermodynamically more stable enol ethers and also subsequent hydrogenation of this double bond. So it was hoped that a simpler molecule would provide a more practical route to 14β-alkyl derivatives. The corresponding enone (86), easily produced by acid hydrolysis of the cycloadduct (see Scheme 64), offered a suitable alternative. The epoxide bridge has already been opened and the double bond cannot move, and so the possibilities for side-reactions are reduced. However, the double bond of the enone is liable to hydrogenation by the Raney nickel.

The enone (86) was thus heated with Raney nickel in ethanol for 6 h. Two products were formed in the ratio 4:1, as judged by ^{1}H n.m.r. spectroscopy. The major product was the saturated ketone (128) (60%) while the minor product was the corresponding enone (129) (15%). The ^{1}H n.m.r. signals for the mixture showed the 3-methoxy, N-methyl and ethyl groups were only slightly different for the two products, but the signals for 7-H and 8-H were clearly different. The αβ-unsaturated derivative (129) gave signals at δ 5.77 (dd, J 10.1 and 1.2 Hz, 7-H) and 7.05 (dd, J 10.1 and 0.5 Hz, 8-H). The saturated ketone (128) lacks olefinic protons and thus an accurate ratio of products was determined by integration of the signals for 1- and 2-H and for 7- and 8-H. The two products could not be separated; they gave a single spot on a t.l.c. plate. However, in the mixture, the αβ-unsaturated derivative (129) gave an i.r. absorption at 1 679 cm^{-1} for the enone group, and an absorption at 1 728 cm^{-1} for the saturated ketone (128). The ^{13}C n.m.r. spectrum gave methine signals at δ 129.7 and 153.5 for C-7 and C-8, respectively, for the enone (129). The mass spectrum showed a peak at m/z 387,

corresponding to the molecular ion of the ketone (128), and a strong peak at m/z 300, corresponding possibly to loss of ethoxycarbonylmethyl, $C_4H_7O_2$, from the ketone. When the desulphurisation experiment was repeated with acetone-deactivated Raney nickel, the only product obtained, in 55% yield, was the αβ-unsaturated derivative (129). Thus, the deactivated reagent had successfully desulphurised the thiamorphinan without reducing the 7,8-double bond.



(128)



(129) ; R= Et
(130) ; R= Me

Prolonged heating of the enone (86) with Raney nickel may have led to the pure, saturated ketone (128), but it was decided to carry out hydrogenation of the αβ-unsaturated derivative (129) with hydrogen and palladium-charcoal catalyst. However, despite repeated trials, integration of the 7- and 8-H signals in the ^1H n.m.r. (90 MHz) spectra of the reaction mixtures consistently showed that no significant reduction had occurred. Several attempts with different batches of catalyst, with and without catalytic amounts of hydrochloric acid, and even with high pressure, up to 100 psi, did not achieve reduction of the double bond. Perhaps there was some residual sulphur in the morphinan sample which poisoned the palladium catalyst. Consequently, another method was tried, namely treatment of the enone (129) with sodium dithionite in methanol (see ref. 67 for examples of dithionite mediated hydrogenations of olefins). However, the ^1H n.m.r. spectrum of the reaction mixture showed again that the double bond was intact.

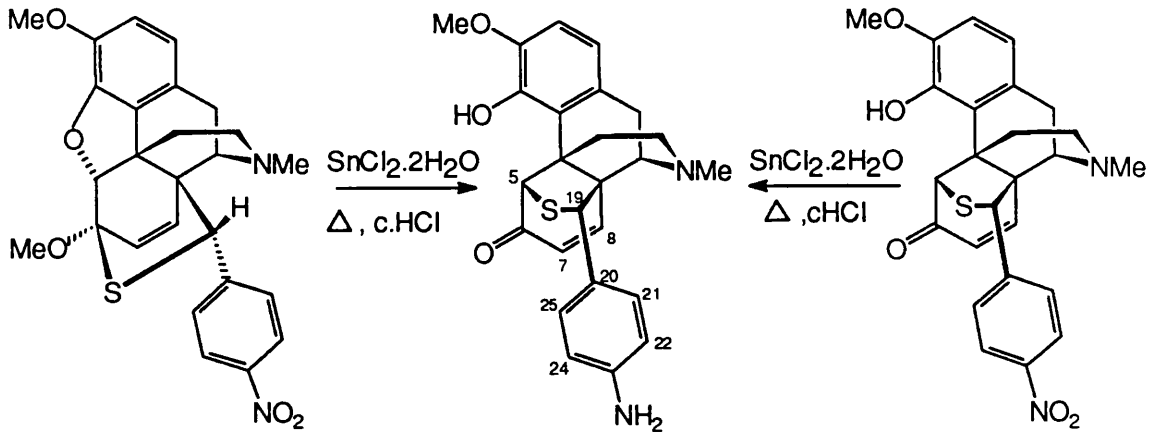
However, a reaction had occurred. The ethyl ester signals had gone and a singlet at δ 3.68 (integrating for 3 protons) had appeared, indicating that the product was the methyl ester of the αβ-unsaturated ketone, i.e. (130). Clearly, transesterification had occurred in the basic medium.

2.4.3 The 8α-p-nitrophenyl-7-thia cycloadduct (49b).

The reaction mixture from the Raney nickel desulphurisation of this cycloadduct (49b) appeared to contain only two products, as judged by t.l.c. However, the ^{1}H n.m.r. spectrum of the mixture showed several possible methoxyl and N-methyl signals, suggesting that several products had been formed despite the simplicity of the thin-layer chromatogram. It was also suggested that the nitro group had been reduced to give the corresponding amine. Because of the complexity of the mixture [cf. the desulphurisation of the 8α-ethoxycarbonyl-7-thia cycloadduct (49a)] it was decided to try to desulphurise the corresponding enone (100).

2.4.4 The (19S)-p-nitrophenyl enone (100).

This enone (100) was also found to give several products under Raney nickel desulphurisation conditions. Again, the nitro group was believed to have been reduced in some of the products. It was therefore decided to reduce the nitro group before carrying out desulphurisation by the Raney nickel. The anilino enone (131) was produced from either the cycloadduct (49b) or the corresponding enone (100), by treatment with stannous chloride in concentrated hydrochloric acid (Scheme 46). The anilino enone



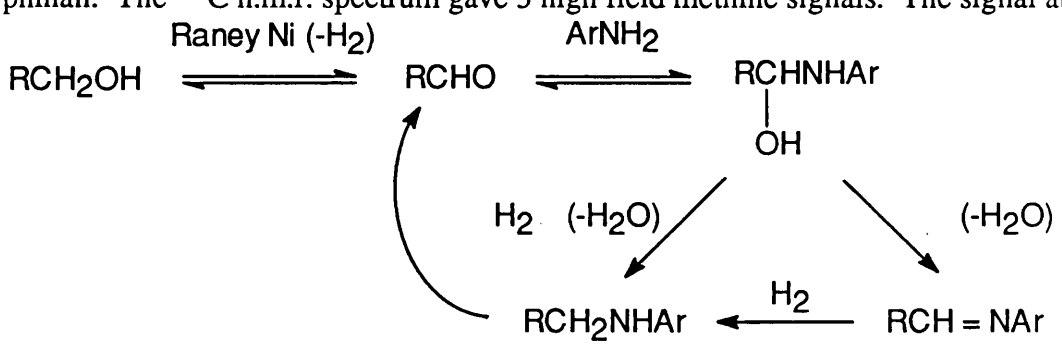
(49b) (131) (100)

Scheme 46

(131) gave a molecular ion corresponding, by accurate mass measurement, to the formula $C_{25}H_{26}N_2O_3S$. However, the microanalytical data was slightly errant. Interestingly, several signals from corresponding protons in the amine and the nitro compound had different ^1H n.m.r. chemical shifts. The protons at positions 5, 7 and 19 gave similar signals for both compounds, at ca δ 4.75, 6.02 and ca. 5.85, respectively. However, 8-H gave a doublet (J 10 Hz) at δ 4.80 for the nitro compound whereas, in the amino compound, 8-H was greatly deshielded and gave a similar doublet at δ 5.97. Compare these values with the corresponding phenyl enone (138), i.e. δ 5.78; this would indicate that the electronic nature of the aromatic ring is responsible for the chemical shift of the proton at position 8. As expected, signals for the aromatic protons of the 23-substituted phenyl ring were also altered. [See (131) for numbering system]. As expected the signals for 22- and 24-H moved upfield from δ 8.07 to 6.58, and those for 21- and 25-H, moved from δ 7.50 to 7.13 when the nitro group was reduced. The phenolic proton signal in the amine was a broad singlet at ca. δ 6.0, and the amine protons gave a very broad peak at ca. δ 3.7, which, like the phenol signal, disappeared upon addition of D_2O.

2.4.5 The (19S)-anilino enone.

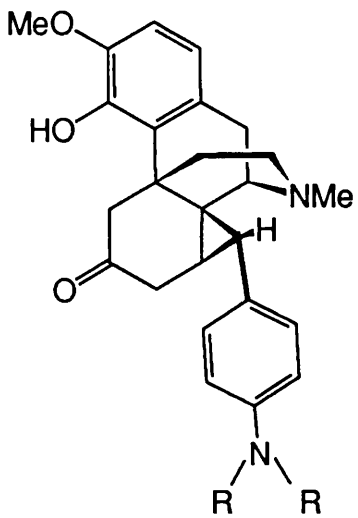
This enone (131) was heated with Raney nickel in ethanol under reflux for 18 h. From the ^1H n.m.r. spectrum it was apparent that only one product was formed. It also showed that the double bond had been reduced, but unexpectedly distinctive methyl and methylene signals were present at δ 1.13 (6H, t, J 7.0 Hz) and 3.32 (4H, q, J 7.1 Hz), respectively. These 'ethyl' signals were also present, to some extent, in spectra from the desulphurisation experiments on the nitro compounds. Rice and Kohn[68] have shown that Raney nickel can catalyse N-alkylation of aniline with alcohols (Scheme 47). The alcohol is dehydrogenated by the Raney nickel and the resultant aldehyde can then undergo attack by the nucleophilic nitrogen atom of aniline. Therefore it appeared likely that these 'ethyl' groups were from an N,N-diethyl-p-aminophenyl group attached to the morphinan. The ^{13}C n.m.r. spectrum gave 3 high field methine signals. The signal at



Scheme 47

δ 55.3 is consistent with C-9, while the signals at δ 19.3 and 27.6 may be attributed to C-8 and C-18 in the cyclopropane (132). The mass spectrum of the product gave a molecular ion peak at m/z 460 which corresponds to the structure (132). This peak corresponds to the product having a double bond or an extra ring incorporated, however the ^1H n.m.r. spectrum ruled out a 7,8-double bond and ^{13}C n.m.r. spectroscopy gave a quaternary carbon signal at δ 208.8 signifying the retention of the carbonyl group at C-6.

Therefore, the product was identified as 8β,14β-methano-18-(N,N-diethyl-p-aminophenyl)morphinan (132).



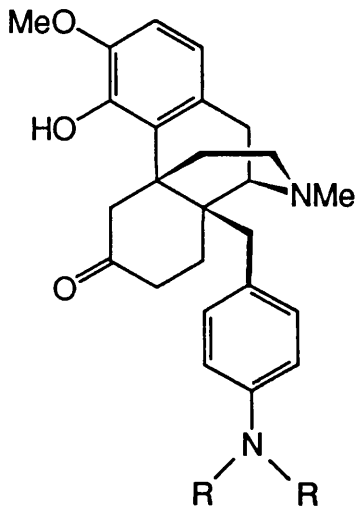
(132) ; R = Et

(133) ; R = Me

Rice and Kohn[68] reported that Raney nickel in methanol, rather than ethanol, caused no N-alkylation. They found no formaldehyde or formaldehyde derivative (see Scheme 47) when methanol was refluxed over Raney nickel. Therefore, the desulphurisation of the anilino enone (131) was carried out with Raney nickel in methanol. After being heated at reflux for 24 h, the reaction mixture was found to contain 2 products. These products were separated by preparative t.l.c. and analysed. Despite Rice and Kohn's report, both the products of the desulphurisation gave singlets at ca. δ 2.93, each integrating for 6 protons. Clearly N,N-dimethylation of the anilino group had occurred. One of the products was found to be the N,N-dimethyl analogue of (132).

This N,N-dimethyl ketone (28%) gave a molecular ion peak corresponding, by accurate mass measurement, to the formula $C_{27}H_{32}N_2O_3$ and the i.r. spectrum gave bands at 1 721 and 1 710 cm^{-1} signifying the presence of a ketonic group. This product was therefore assigned the structure (133). The other product from the desulphurisation in methanol, was found to be the 14β-(N,N-dimethyl-p-aminophenyl)methylmorphinan

(134) (20%). This structure was assigned from the following data. The ^{1}H n.m.r. spectrum showed no olefinic signals, a fact confirmed from the ^{13}C n.m.r. spectrum. This spectrum gave signals similar to those for many of the carbons in the cyclopropane derivatives (132) and (133). However, signals for 2 extra methylene carbons were observed at δ 23.1 and ca. 31.9 (with the loss of 2 methine carbon signals), which were



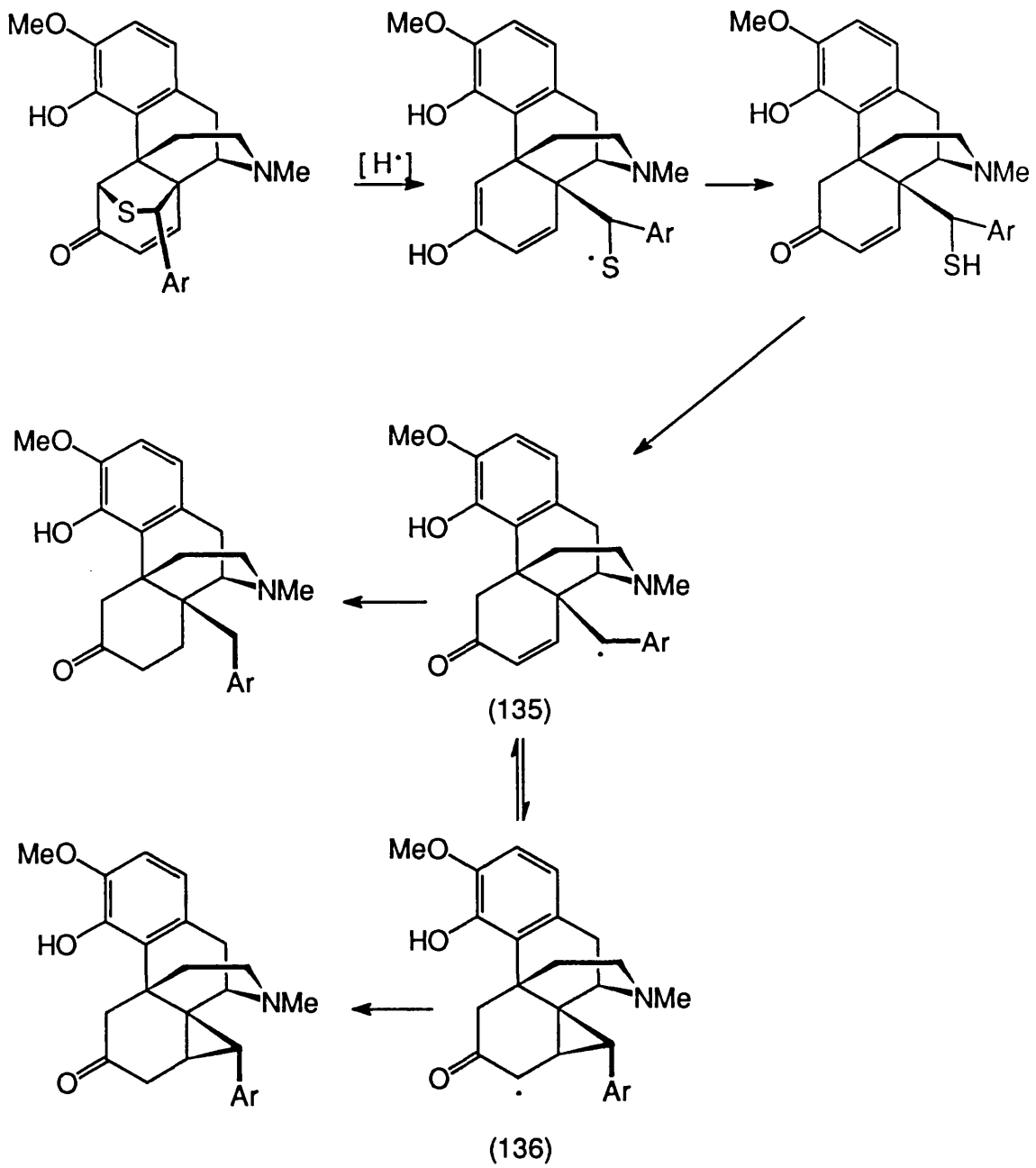
(134) ; R = Me

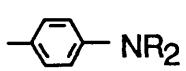
allocated to C-8 and C-18, respectively. Another significant feature of the ^{1}H n.m.r. spectra of the cyclopropane and 14β-alkyl derivatives is the relative chemical shifts of the N-methyl signals. In the cyclopropane derivatives, (132) and (133), it appears at δ 2.13 and 2.09 [see also (139), N-methyl signal at δ 2.05]. However, in the 14β-alkyl derivative (134) the N-methyl group resonates at δ 2.29. Probably, in the cyclopropane derivatives, the aminophenyl rings are held close to the NMe groups and thus shield them, whereas in the alkyl derivative (134), relatively free rotation of the aminobenzyl group occurs and the NMe group is not greatly affected by the benzene ring. In the ^{13}C n.m.r. spectra, the NMe group gives similar signals for both the cyclopropane and alkyl derivatives. The mass spectrum of the 14β-benzyl derivative (134) gave a molecular ion at m/z 434 together with fragment ion peaks at m/z 300 and 134. The last peak is probably from an ion corresponding to the 14β side-chain, $C_9H_{12}N$, and the peak at m/z

300 arises from the morphinan after loss of this side-chain. This is strong evidence for the structure (134) for this product.

In this reaction, it was possible that the 14β-alkyl derivative (134) was derived from the cyclopropane (133), by hydrogenolysis of the C(8)-C(18) bond, mediated by the Raney nickel. Therefore, the reaction was repeated but with a longer period of heating under reflux. However, after 3 days heating, the ^{1}H n.m.r. spectrum of the reaction mixture was found to be virtually identical to that obtained after 1 day. So, it was apparent that the two products (133) and (134), were formed independently during the desulphurisation reaction and that the product ratio is independent of reaction time. However, this result does not explain why the reaction in ethanol gave only one product while that in methanol gave two. Ethanol has a higher boiling point, 78.3°C, than methanol, 64.5°C, and one might have expected a more complex reaction mixture at the higher temperature.

A mechanism for the rearrangements involved in these reactions is likely to proceed through radical intermediates. It is expected that the C(5)-S(18) bond would be reduced easily and in preference to the more hindered C(19)-S(18) bond; and so a proposed mechanism for these Raney nickel desulphurisation reactions is given in Scheme 48. It is possible that the higher temperature in the 'ethanol' reaction may push the equilibrium towards cyclopropane formation, whereas in methanol the equilibrium between the two radical intermediates (135) and (136) gives rise to a mixture. Experiments employing other solvents might throw light on this difference, as might desulphurisation in ethanol at 64.5°C.



Ar =  NR_2

R = Me or Et

(assuming N,N- dialkylation occurs before desulphurisation)

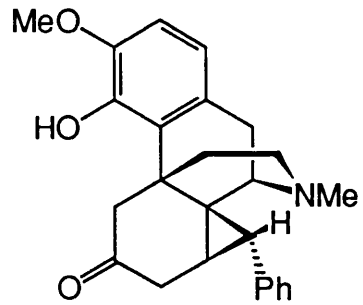
Scheme 48

2.4.6 The thiobenzaldehyde cycloadduct (49c).

Due to the results encountered in the desulphurisation experiments of the ethyl ester and p-nitrophenyl cycloadducts, it was decided to carry out the desulphurisation of the thiobenzaldehyde cycloadduct (49c) with Raney nickel deactivated with acetone. The ^{1}H n.m.r. spectrum of the reaction mixture, after heating under reflux for 8 h, appeared to show largely one product to be present. This product was not fully characterised but was tentatively assigned the structure (137) from the ^{1}H n.m.r. data. The N-methyl signal came at ca. δ 2.05, which has now been shown to be characteristic of a 8β,14β-methano aryl derivative. The doublet at ca. δ 4.1 (J 17 Hz) is attributable to 5α-H, deshielded by its proximity to the phenolic hydroxy group. These data suggest that desulphurisation has occurred with formation of a phenol. The signal at ca. δ 4.9 (dd, J 6 and 2 Hz) is attributable to 7-H in a 6,7-didehydromorphinan [cf. the corresponding signals for compounds (115) and (123)]. Although this experiment was successful in removing sulphur, it was decided to examine the desulphurisation of the corresponding enone in the hope of producing a 14β-benzyl derivative.

2.4.7 The (19S)-phenyl enone.

This enone (138) was prepared from the cycloadduct by heating with dilute hydrochloric acid; as were the other enones produced from their corresponding cycloadducts (see Scheme 64). Again acetone-deactivated Raney nickel was used to try to prevent hydrogenation of the double bond and thus possibly lead to a simpler product mixture. After 20 h heating under reflux, the only product isolated from the reaction mixture was the 8β,14β-methano-18-phenylmorphinan (139). This product was identified by comparison of its i.r. and n.m.r. data with those of the p-aminophenyl derivatives already identified. The i.r. spectrum gave a band at 1 710 cm^{-1}, consistent with a saturated ketone and the ^{1}H n.m.r. spectrum gave an N-methyl signal at δ 2.05,

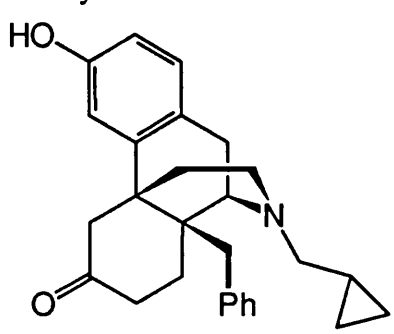


(139)

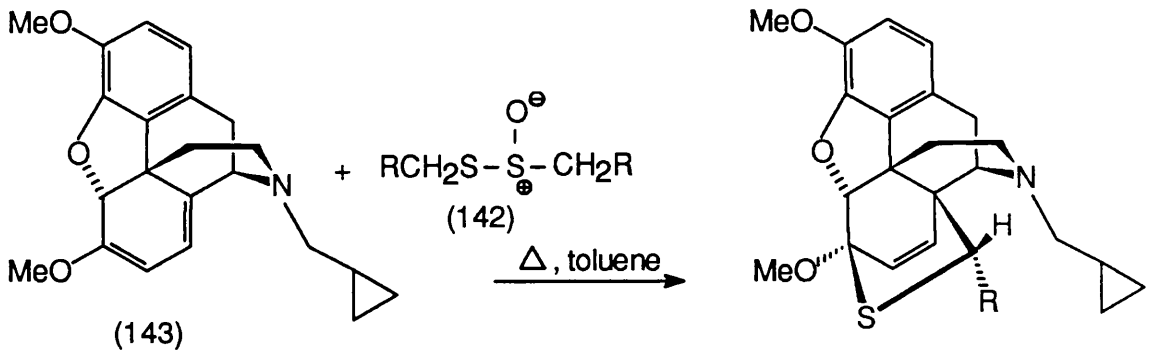
which is in good agreement with NMe signals from the other arylcyclopropyl derivatives. Accurate mass measurement of the molecular ion gave the composition $C_{25}H_{27}NO_3$ consistent with the proposed structure (139). This experiment was repeated but with freshly prepared, non-deactivated Raney nickel. The ^1H n.m.r. spectrum of this reaction mixture appeared to show two products, in approximately equal proportions. The products were not identified, but the NMe signals at δ 2.30 and 2.32 suggest that the products were both 14β-alkyl derivatives. No further work was carried out on this reaction mixture because a successful desulphurisation of the enone (138), had already been achieved to produce a single, fully-characterised product.

2.5 Recent studies leading to 14β-alkyl morphinans.

As mentioned earlier, during the course of this present project, a preliminary paper[69] appeared in 1989 describing a single compound (140) made by the desulphurisation of a thiobenzaldehyde adduct of a thebaine derivative. The compound,



(140)



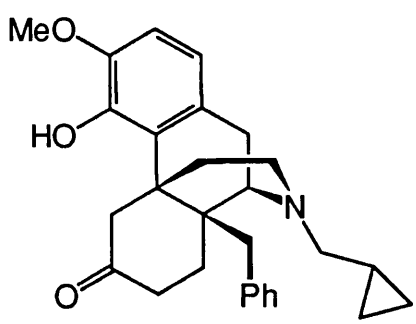
(143)

(141)

a ; R = H
b ; R = Me
c ; R = Et
d ; R = Ph

Scheme 49

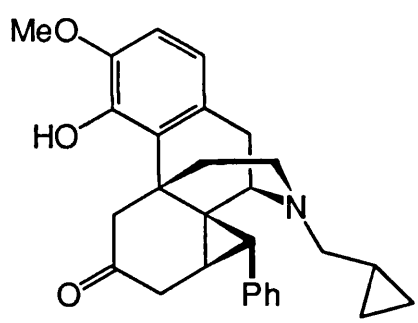
a 14β-benzylmorphinan (140) has antagonistic actions selective at the μ and κ opiate receptors. The full paper[70] was published in 1990 and the relevant information will now be given. The 7-thia cycloadducts (141a-d) were prepared from the thiosulphinates (142a-d) and N-(cyclopropylmethyl)northebaine (143) (Scheme 49). Revesz reported



(144)

that only the thiobenzaldehyde cycloadduct (141d) could be desulphurised to a single product; acidic workup after Raney nickel desulphurisation yielded the dethioketone (144d) in 25% yield. The other cycloadducts (141a-c) gave complex mixtures on similar treatment with Raney nickel. However, a successful method for the desulphurisation was developed for the rearranged phenolic enones (145) obtained by acid hydrolysis of the

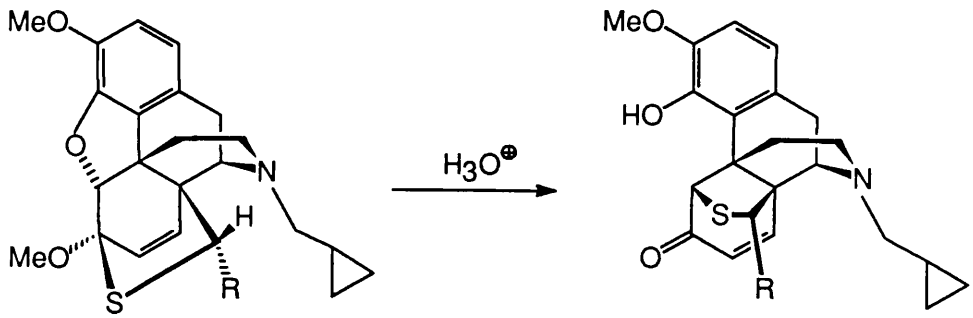
cycloadducts (Scheme 50). On treatment with lithium in liquid ammonia the enones (145a-c) gave only the mercaptans (146a-c) as a mixture of epimeric alcohols. These mercaptans could then be desulphurised easily and in high yield with Raney nickel to give the epimeric alcohols (147a-c) (Scheme 51). The phenyl enone (145d) was desulphurised with lithium in liquid ammonia to give a 1:1 mixture of the ketone (144) and the epimeric alcohols (147d) (Scheme 52). Interestingly, it was found that the enones (145a-c) could be desulphurised with Raney nickel but this method was considered unsuitable because cyclopropane derivative(s), possibly the 8β,14β-methanomorphinans (148a-c), were also produced.



a ; R = H
b ; R = Me
c ; R = Et

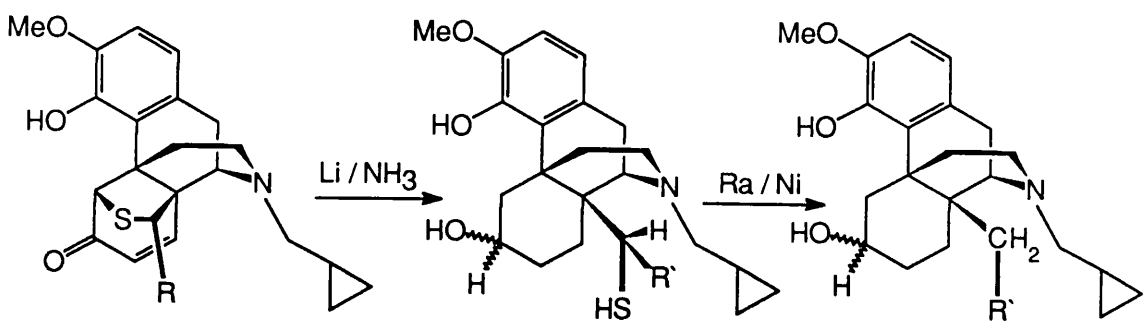
(148a-c)

These results are largely identical to those obtained by the present author. It is most unfortunate that two independent research groups had been working on the same topic and method of approach at virtually the same time.



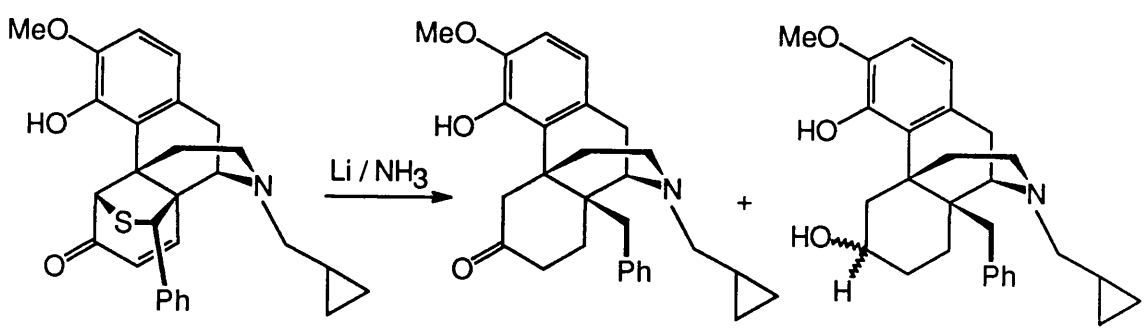
(141a-d) (145a-d)

Scheme 50



(145a-c) (146a-c) (147a-c)

Scheme 51



(145d) (144) 1 : 1 (147d)

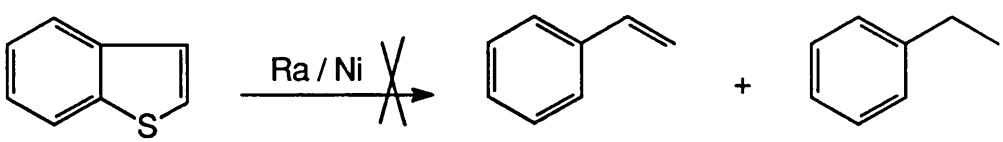
Scheme 52

a ; R = H
b ; R = Me
c ; R = Et
d ; R = Ph

2.6 Raney nickel desulphurisation of simpler thia-containing compounds.

During this project many desulphurisation experiments were carried out with Raney nickel, freshly prepared[27] from the commercially available nickel-aluminium alloy. This preparation requires much personal judgement and attention to technique and consequently the activity or quality of the Raney nickel may vary slightly over different experiments although it was always prepared as the W-2 reagent. For example, the difference between batches of Raney nickel may account for the observation that, during the desulphurisation of ethyl 5β,14β-thia-ethanomorphinan-19(R)-carboxylate (86), with W-2 Raney nickel, the 7,8-double bond of the morphinan remained intact, while another batch of reagent gave a mixture of the saturated and unsaturated dethiamorphinans (128) and (129). For these reasons, experiments were also carried out with simpler sulphur compounds. It was hoped that a suitable compound could be found to test batches of the Raney nickel for activity.

The simplest compound tested was benzothiophene (149). However, despite several attempts with different batches of Raney nickel, no sign of styrene (150) or ethylbenzene (151) was ever observed (Scheme 53). Another, simple compound was dibenzothiophene (152). However, this compound, prepared from diphenyl and

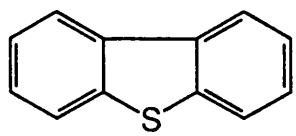


(149) (150) (151)

Scheme 53

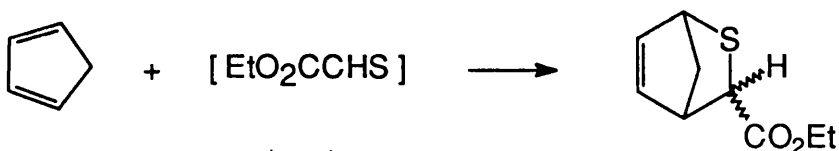
elemental sulphur by a literature method,[71] was found to be contaminated with diphenyl. The amount of the diphenyl appeared to increase when a sample of the crude dibenzothiophene (152) was treated with Raney nickel. This experiment, although

inconclusive, could be a good quality test[72] of the Raney nickel, if a pure sample of dibenzothiophene was available, since a t.l.c. system was found to separate the two compounds. T.l.c. on silver nitrate-impregnated,[73] silica plates with triple elution in hexane separated the two compounds, dibenzothiophene giving the lower R_f value due to its complexing with the silver ions in the silica.



(152)

Kirby and co-workers[52,53,56] have carried out much research on the preparation of cycloadducts of ethyl thioxoacetate (47a) to various conjugated dienes. One of these dienes was cyclopentadiene (153), and the resultant cycloadducts, referred to as compound (154), [being an ca. 6:4 mixture of the endo (155) and exo (156) cycloadducts, respectively] are relatively easy to prepare by the Bunte salt method (see Section 2.1, Scheme 31; and Scheme 54 below). These simpler thia-containing cycloadducts (154) are remotely similar to the cycloadducts of thebaine and ethyl

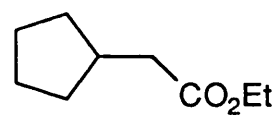


(153) (47a) (154)

Scheme 54

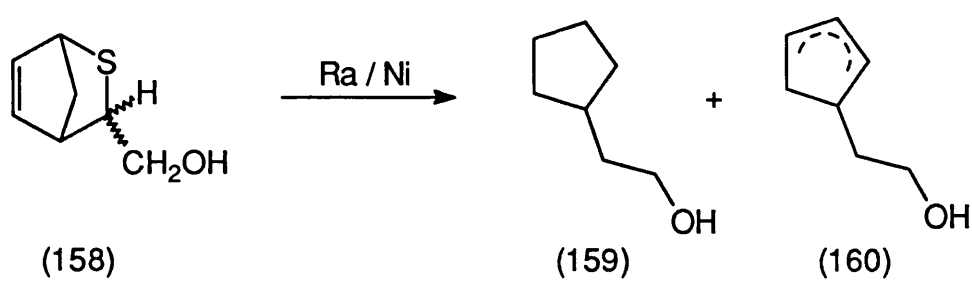
thioxoacetate and so may be a good test compound to try to desulphurise with Raney nickel. Thus the cycloadducts (154) were heated under reflux with Raney nickel and ethanol for 4 h. The only product formed, obtained as a colourless oil, was ethyl cyclopentylacetate (157) (49%). The i.r. spectrum had an absorption at 1 735 cm^{-1}, corresponding to the saturated ester, while accurate mass measurement of the ion at m/z

156 in the mass spectrum confirmed the formula, $C_9H_{16}O_2$. The ^1H n.m.r. spectrum was, as expected, very simple, but clear evidence for the presence of the ethyl ester and the cyclopentyl ring was given and the absence of olefinic protons confirmed the reduction of the double bond. Desulphurisation of the same cycloadducts (154) with deactivated Raney nickel was carried out, but the resultant ^1H n.m.r. spectrum was complex and so the material was not studied further. Also, the cyclopentadiene



(157)

cycloadducts (154) were reduced with lithium aluminiumhydride to give the corresponding alcohols (158). These alcohols gave analytical data consistent with Jaap's[74] values. Raney nickel desulphurisation of the cyclopentadiene alcohols (158), produced in a high yield, a 83:17 mixture of 2-cyclopentylethanol (159) and 2-cyclopentenylethanol derivative(s) (160), respectively, as judged by ^1H n.m.r. (90 MHz) spectroscopy (Scheme 55). However, the low resolution mass spectrum of this mixture gave a molecular ion at m/z 112, for the unsaturated derivative(s), but no molecular ion was observed for the major product, the saturated alcohol (159).



(158) (159) (160)

Scheme 55

2.7 Recovery of material after treatment with Raney nickel.

Many of the Raney nickel desulphurisation reactions carried out in this project often resulted in a relatively low yield (typically 40-60%) of desulphurised material. This is probably due to strong adsorption of the material on the nickel surface. Low yields are common in desulphurisation[75] reactions and several methods of product recovery have been tried during the present author's project. The simplest method was to filter the warm reaction mixture through a thin pad of Celite and to wash the nickel residues with hot ethanol. Another method was to dissolve the nickel residues in a mineral acid, then neutralise the resultant green solution and then to extract the desulphurised material with an organic solvent. However, only a little more material was recovered extra to that from the simple filtration method. Possibly the best method of recovery was to extract the product from the nickel residues with a suitable solvent, e.g. ethanol, in a Soxhlet apparatus. In practise most of the morphinan material was recovered within an hour or two with Soxhlet extraction.

2.8 Desulphurisation with tin hydrides

This method of desulphurisation appeared to be experimentally simple and straightforward. The tin hydrides used, triphenyltin hydride (66) and tri-n-butyltin hydride (161), and the radical initiator, azoisobutyronitrile (162) (AIBN), were all easily measured out (unlike the Raney nickel slurry), and the reactions were carried out in dry solvents, dry glassware and under a nitrogen atmosphere. However, problems arose in the workup of the reactions. One was the separation of the desired product from the by-product of desulphurisation, namely bis-tri-n-butyltin sulphide (163) or bis-triphenyltin sulphide (164). These sulphides were isolated from the reaction mixture either by crystallisation or by chromatography. However, the expected weight of the sulphides was never obtained. Perhaps the sulphides complexed with the morphinan or the reaction

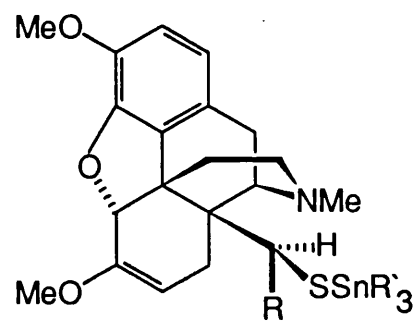
had proceeded only as far as a thiostannane intermediate, possibly (165). (However, see concluding comments in this section.) Also an excess of tin hydride was used as was recommended in the literature.[40,42] However, it was also stated that any excess of organotin hydrides is difficult to separate from the desired reaction product.

$Bu_3Sn-S-SnBu_3$

(163)

$Ph_3Sn-S-SnPh_3$

(164)



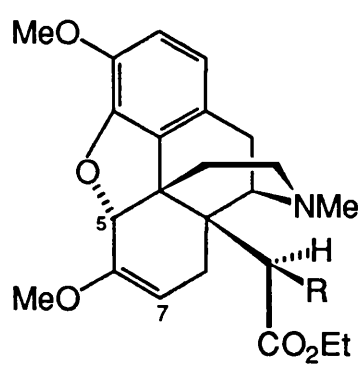
(165)

R = CO_2Et or Ph

R` = Ph or Bu

2.8.1 Triphenyltin hydride (66)

The 8α-ethoxycarbonyl-7-thia cycloadduct (49a) was heated under reflux with an excess (ca. 3.2 mol equiv.) of triphenyltin hydride and a catalytic amount of AIBN (162) in dry benzene for 24 h. After evaporation of the solvent, a few drops of dichloromethane and hexane were added to the reaction mixture to initiate crystallisation of bis-triphenyltin sulphide (164), which was filtered off. The remainder of the reaction mixture appeared to contain the 14β-subsituted morphinan (114) contaminated with phenyl-containing material. Thus, the ^{1}H n.m.r. (90 MHz) spectrum gave signals at δ 4.51 (dd, J 7 and 2 Hz, 7-H) and 4.78 (s, 5-H) in agreement with those of the dethiomorphinan (114) produced in the Raney nickel desulphurisation reaction of the same cycloadduct (49a). It is possible that the thiostannane intermediate (166) was also present. However, integration of the signal for phenyl groups, ca. δ 7.4 suggested that additional material containing phenyl groups must also have been present. Perhaps the tin hydride (66) was present as a contaminant. No further work was carried out on this mixture.

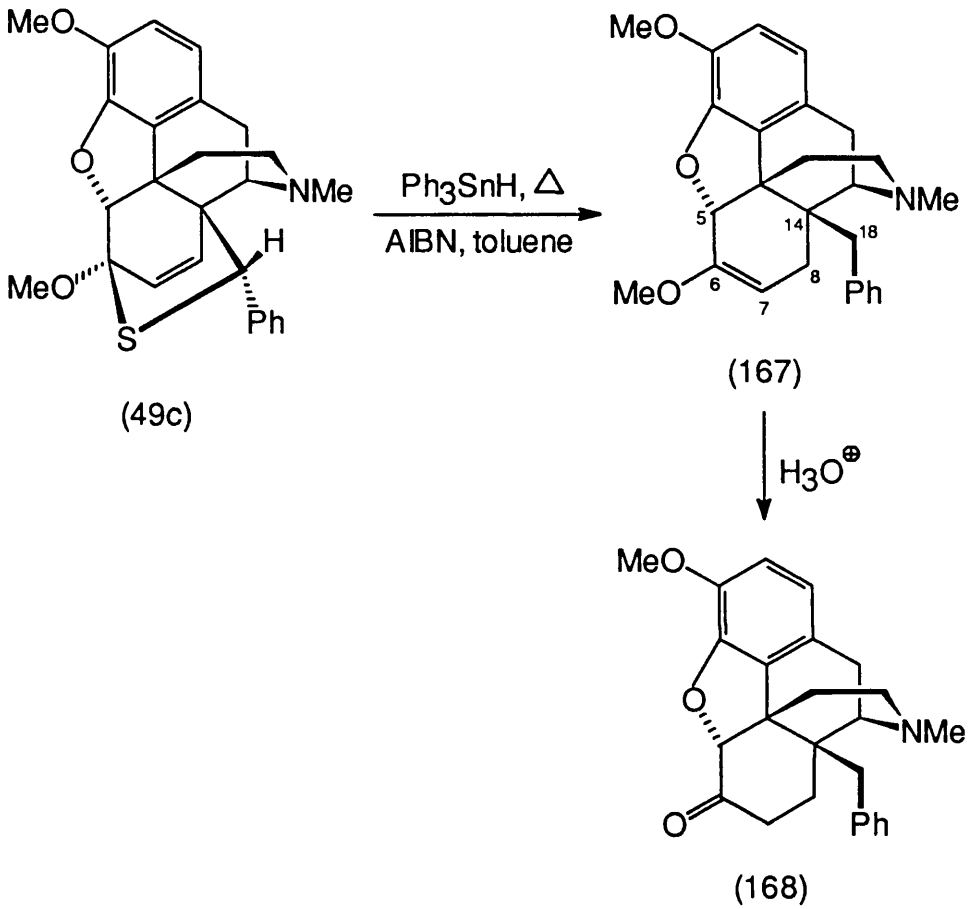


(114) ; R = H

(166) ; R = SSnPh3

The thiobenzaldehyde cycloadduct (49c) was treated in a similar way with triphenyltin hydride and AIBN with heating under reflux in dry toluene for 3 h. The

ether-light petroleum (1:9) to remove the bis-triphenyltin sulphide (164). Later fractions contained morphinan derivatives and also phenyl-containing material, as judged by ^{1}H n.m.r. spectroscopy. These fractions were rechromatographed by preparative t.l.c. to remove more contaminants. The product was found to be the, relatively pure, 14β-benzyl-6,7-didehydro-4,5α-epoxymorphinan (167) (Scheme 56). The ^{1}H n.m.r. spectrum (200 MHz) gave signals at δ 4.78 (dd, $J_{7,8\beta}$ 6.5 and $J_{7,8\alpha}$ 2.1 Hz, 7-H) and 4.15 (d, $J_{5,8\alpha}$ 1.2 Hz, 5-H), which are consistent with a 6,7-didehydro-4,5α-epoxymorphinan structure. Also, the ^{13}C n.m.r. spectrum gave methylene signals attributable to C-8 and -18. A sample of this 6,7-didehydromorphinan (167) was heated in aqueous hydrochloric acid under reflux for a few minutes. The crude product was tentatively identified as the ketone (168), as judged by ^{1}H n.m.r. spectroscopy.



(49c)

(167)

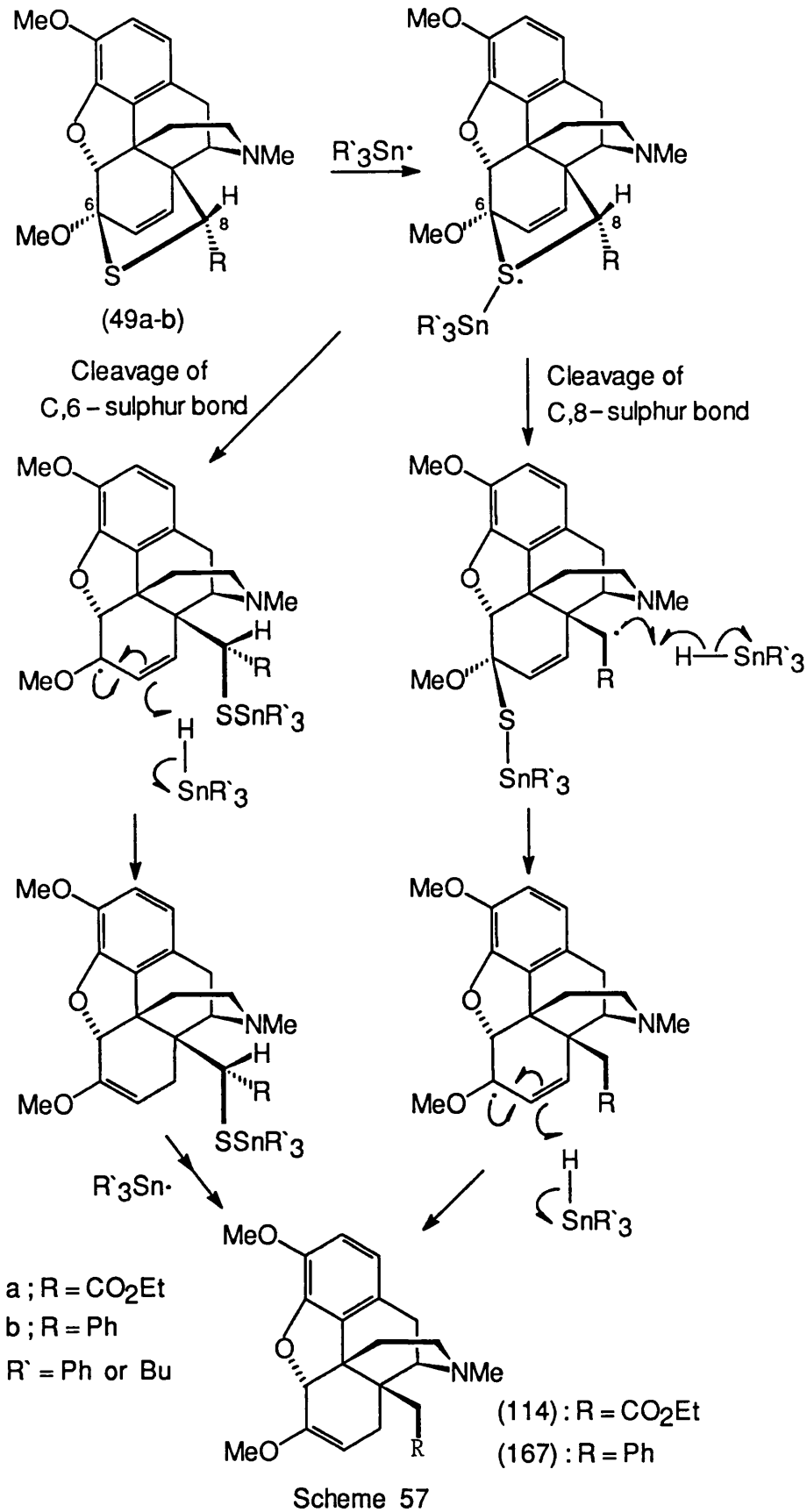
(168)

Scheme 56

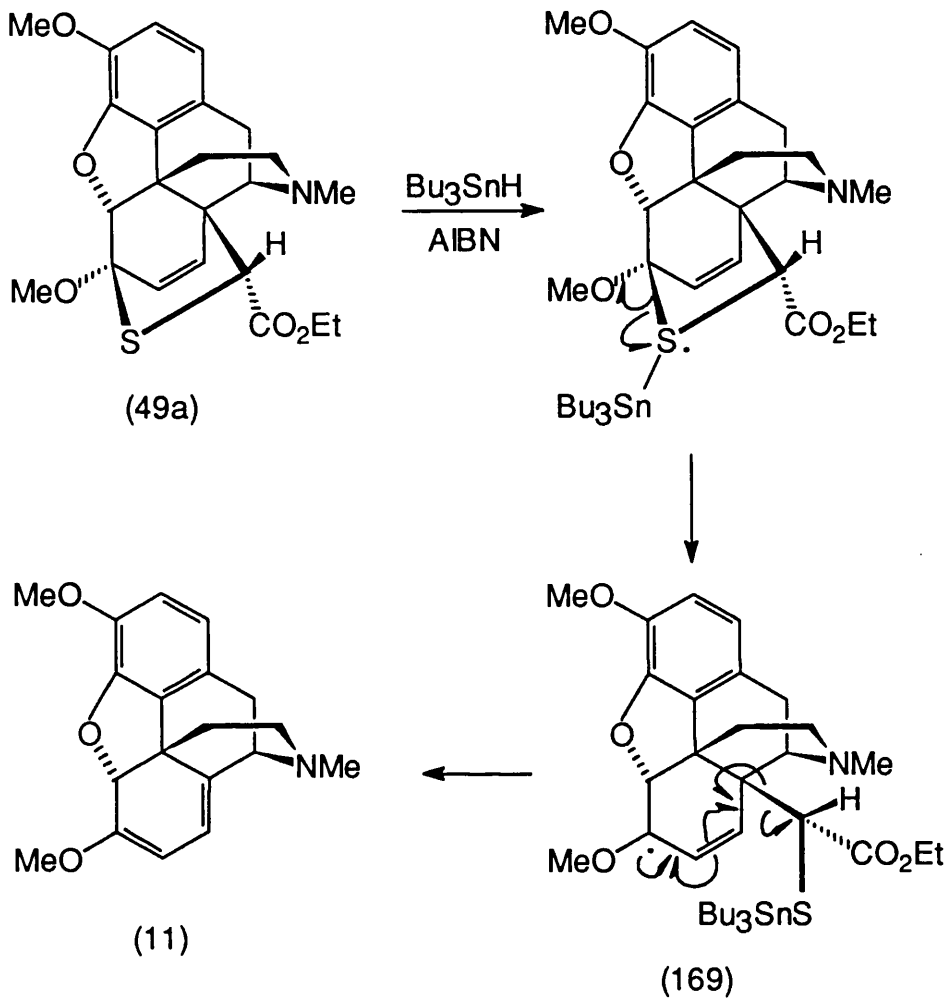
A possible mechanism for the desulphurisation with the tin hydrides is given in Scheme 57. Attack at sulphur by a tributyl- or triphenyl-tin radical could lead to cleavage of either the C(6)-S or C(8)-S bond. The former would give an allyl radical further stabilised by the methoxy group. The latter would give either a benzyl radical (R=Ph) or a radical stabilised by conjugation with a carbonyl group ($R=CO_2Et$). It is therefore difficult to decide which cleavage is the more likely. In either case, subsequent attack on these intermediates would also give stabilised radicals and ultimately the dethiomorphinans (114) and (167).

2.8.2 Tri-n-butyltin hydride (161)

Tri-n-butyltin hydride was employed in a similar way, in toluene under reflux, and, with the 8α-ethoxycarbonyl-7-thia cycloadduct (49A), the expected 6,7-didehydromorphinan (114) was produced in ca. 32% yield. However, in one attempt to desulphurise the same cycloadduct (49A), the only morphinan product was found to be thebaine (11). The ^{1}H n.m.r. and low-resolution mass spectra of this product were virtually indistinguishable from those of authentic thebaine except that the mass spectrum gave a molecular ion peak at m/z 310 instead of 311. Formally a retro-Diels-Alder reaction had taken place, perhaps resulting from collapse of the radical (169) with elimination of the group at C(14) (Scheme 58). Alternatively, reduction of the thioaldehyde liberated thermally from the cycloadduct may have occurred. This abnormal product was encountered only once and it is not clear in what way conditions must have varied on this occasion.


MeO
NMe
H
6
8
MeO
R
S
(49a-b)
R`3Sn·
R`3Sn
Cleavage of
C,6 – sulphur bond
Cleavage of
C,8 – sulphur bond
SSnR`3
SnR`3
H—SnR`3
a ; R = CO2Et
b ; R = Ph
R` = Ph or Bu
(114) : R = CO2Et
(167) : R = Ph

Scheme 57



Scheme 58

A single attempt was carried out to desulphurise the enone (86) with tri-n-butyltin hydride. The reaction mixture was found to contain tri-n-butyl-containing material and unreacted enone (86), however, another product was isolated in an impure form but was not fully identified.

Conclusions: Gutierrez[42] et al. have found that destannylation of thiostannane intermediates, such as (165) can be achieved in good yield by absorbing them onto silica gel columns and slowly eluting with pentane-dichloromethane mixtures or by aqueous hydrochloric acid hydrolysis. The products in these destannylation reactions are thiols.

In the present author's experiments, some of the products were devoid of sulphur as judged by ^{1}H and ^{13}C n.m.r. spectroscopy and by mass spectral data. Therefore it is suggested that no thiostannane products, such as (166), were ever present in the reaction mixtures and that the contaminants containing phenyl or butyl groups were simply organotin material complexing or co-running with the morphinans present.

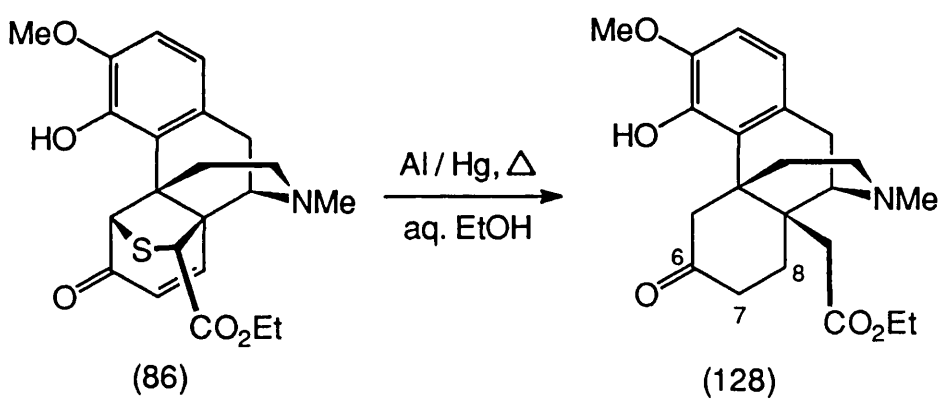
2.9 Desulphurisation with aluminium amalgam

In this method of desulphurisation, with aluminium amalgam in ethanol, the reaction is carried out under neutral conditions and so was thought to be ideal for desulphurising compounds susceptible to acid or base catalysed rearrangements. However, as Sclare had shown, the cycloadduct (49a) rearranges under neutral conditions to the acetal (53) when heated under reflux in toluene (see Introduction, Scheme 10), and during the present research the cycloadducts (49a) and (49b) have also been shown to rearrange in refluxing ethanol. Therefore this method of desulphurisation may not be as suitable as first thought. However some success was achieved.

The preparation of aluminium amalgam, despite close adherement to the literature method,[76] proved to be rather erratic in producing active reagent. As with the preparation of W-2 Raney nickel, the preparation of aluminium amalgam relied much on personal judgement, and so this method of desulphurisation would appear to be of limited use.

An attempt was made to desulphurise the 8α-ethoxycarbonyl-7-thia cycloadduct (49a) with aluminium amalgam in refluxing aqueous ethanol, but the resultant reaction mixture, as judged by ^{1}H n.m.r. (90 MHz) spectroscopy, contained the same products obtained when the cycloadduct (49a) was heated in ethanol alone for approximately the same length of time [see 'Rearrangement of the cycloadduct (49a) without added base', Section 2.2.2, p 49]. Since the cycloadduct (49a) rearranged in hot ethanol, it was not

practical to pursue this method of desulphurisation. It was decided to attempt this method of desulphurisation on the enone (86), produced by mild acid hydrolysis of the corresponding cycloadduct (49a). After several attempts with mostly starting material being recovered, a successful desulphurisation reaction was achieved. A mixture of the enone (86) and an excess of aluminium amalgam in 90% aqueous ethanol, was heated under reflux for 3 h. The only product obtained, in 62% yield, was the dethioketone (128). Accurate mass measurement of the molecular ion, m/z 387, gave the molecular formula, $C_{22}H_{29}NO_5$. The ^1H and ^{13}C n.m.r. spectra were consistent with the proposed 7,8-dihydro-6-ketomorphinan structure (128) (Scheme 59). In particular, ^{13}C n.m.r. shows the two carbonyl signals at δ 172.7 ($\underline{C}O_2Et$) and 210.7 (C-6), and the presence of eight methylene signals, four of which arise from the successful desulphurisation reaction.



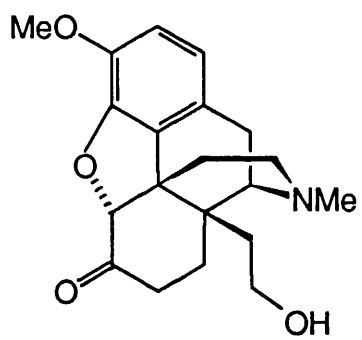
(86) (128)

Scheme 59

2.10 Attempted desulphurisation of the 8α-ethoxycarbonyl-7-thia cycloadduct (49a) using sodium in liquid ammonia

This method of desulphurisation was carried out only once, and, since it was not possible to measure the amount of sodium accurately, over-reduction of the cycloadduct (49a) was possible. However, a single product was obtained, in a low yield, which had apparently been desulphurised. The product was tentatively identified as the substituted

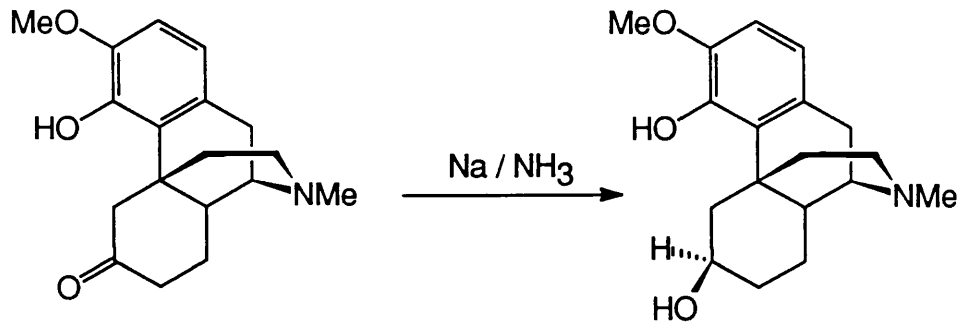
ethanol (170) from the limited data obtained and from the knowledge that esters can be reduced to alcohols by dissolving metals, i.e. by the Bouveault-Blanc method. ^{1}H N.m.r. spectroscopy (90 MHz) showed that no ester group was present, that the 7,8-double bond had apparently been reduced and that the 6-OMe group was absent. The i.r. spectrum gave absorptions at 3 525 and 1 723 cm^{-1}, suggesting the presence of an alcohol and a saturated ketone, and, with the mass spectrum giving a possible molecular ion peak at m/z 343, the proposed structure (170) is based on good evidence. This method of desulphurisation appears promising. However, the handling of small amounts of sodium



(170)

metal is quite tricky and possibly hazardous. This method would be useful only on a larger scale, when addition of an excess of sodium, leading to over-reduction, could be avoided.

An interesting feature of this product is the fact that the 6-keto and epoxide groups are still present. Ketones, such as dihydrothebainone (171), are reduced to alcohols when treated with sodium in liquid ammonia (Scheme 60). Also, the epoxide rings of codeinones are easily opened reductively. Perhaps, in the desulphurisation experiment the amount of sodium used was sufficient only to produce the dethioketoalcohol (170).

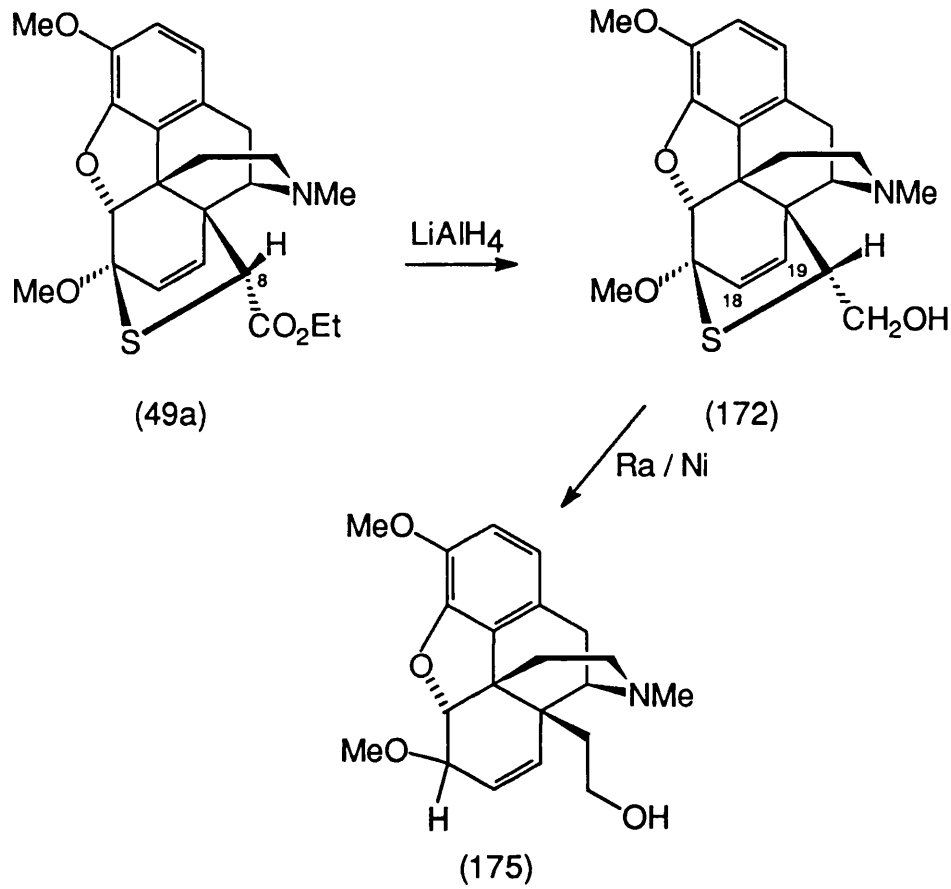


(171)

Scheme 60

2.11 Lithium aluminium hydride reduction of the 8α-ethoxycarbonyl-7-thia cycloadduct (49a)

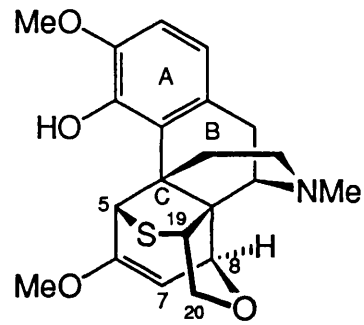
Sclare had shown that the cycloadduct (51) can rearrange under basic conditions (see Introduction, Scheme 9). It was therefore possible that, during Raney nickel desulphurisation of this cycloadduct (49a), rearrangement might occur, initiated by abstraction of the C-8 proton with base. This proton is made acidic by the electron-withdrawing ester group. It was thought likely that, by reducing the ester to the alcohol (172) with lithium aluminium hydride, the proton would no longer be acidic and the Raney nickel desulphurisation would proceed without any base-catalysed rearrangements. The envisaged route is shown in Scheme 61.



Scheme 61

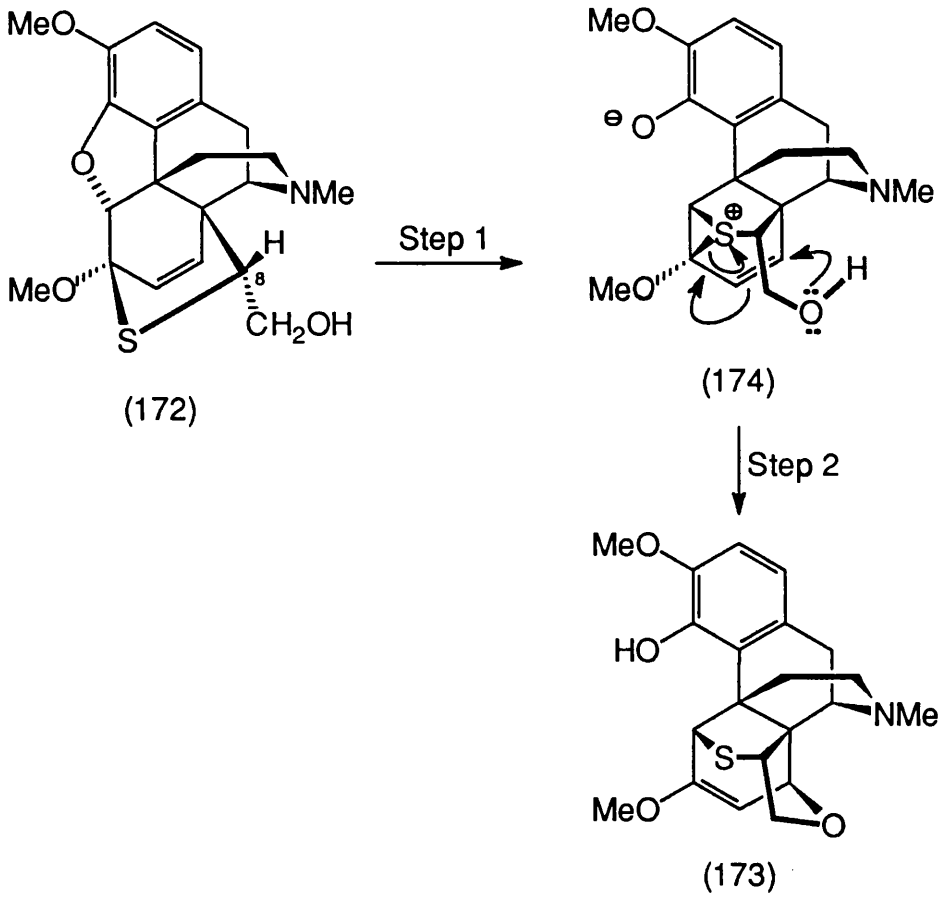
Reduction of the ester (49a) with lithium aluminium hydride gave, however, two products, as judged by ^1H n.m.r. spectroscopy and by t.l.c. of the reaction mixture. Both products lacked the ester group. As expected, the 8α-hydroxymethyl derivative (172) was found to be present, recognised by the distinctive signals of the 18,19-protons at δ 5.43 (d, J 10 Hz, 19-H) and 6.15 (dd, J 10 and 2 Hz, 18-H) and the lack of the ethyl ester signals. The other product was assigned the structure (173). This furan (173) gave a complex set of ^1H n.m.r. signals for the protons of ring C and the furan. Further, the signal at δ 5.81 for a phenol, exchangeable with D_2O, clearly implied that a rearrangement had taken place involving opening of the epoxide bridge presumably by the sulphur atom attaching itself to the carbon at position 5 (Scheme 62). The signals

that clearly identify the furan derivative are as follows; 4.10 (complex multiplet containing $J_{19,20}$ 7.8 Hz, 19-H), 4.22 (dd, $J_{7,8\alpha}$ 4.5 and $J_{5\alpha,7}$ 1.7 Hz, 7-H), 4.36 (m, 8-H), 4.42 (2H, ABq, J ca. 7.6 Hz, 20-H). The ^{13}C n.m.r. spectrum gave the correct quantity and multiplicity of carbons consistent with the furan structure (173). The molecular ion at m/z 387 (100%) in the low resolution mass spectrum was in agreement with the proposed structure (173). The ratio of the 8α-hydroxymethyl derivative (172) and the furan (173) was 78:22, respectively, as judged by the ^1H n.m.r. spectrum of the reaction mixture.



(173)

The furan (173) is isomeric with the alcohol (172). Interestingly, this reaction mixture, dissolved in deuteriochloroform, underwent complete isomerisation to the furan derivative (173), simply on standing at room temperature for several days. Although the alcohol (172) rearranged in an apparently neutral solution, it is possible that there was still some residual base, created during the workup, present in the chloroform solution and that the isomerisation was actually base catalysed. Of course, the alkaloid is a weak base itself. A possible mechanism for this isomerisation, via the episulphonium ion (174), is given in Scheme 62. If step 1 is the rate-determining step, then base cannot affect the rate. However, if step 1 is reversible then base could speed up product formation. It would be possible to determine if base does actually affect this



(172) (174) (173)

Scheme 62

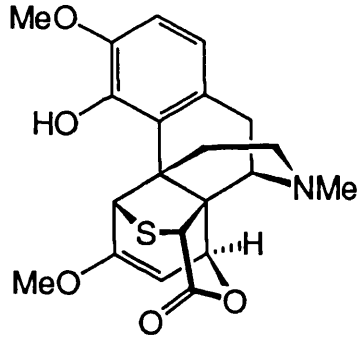
transformation but the purpose of reducing the ester (49a) to the alcohol (172) was for the sake of simplifying formation of 14β-alkyl derivatives [see (175), Scheme 61]. Formation of the furan (173), although interesting, would not necessarily simplify the desired desulphurisation process, and, also due to the lack of time, further experimental work was not carried out.

2.12 Rearrangements of the 8α-ethoxycarbonyl-7-thia cycloadduct (49a) with lithium hydroxide

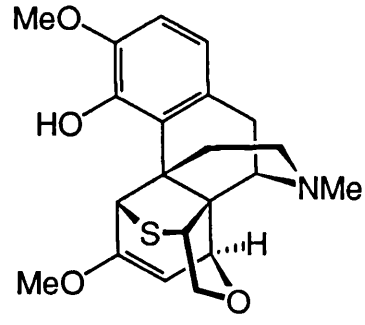
During an attempt at reduction of the 8α-ethoxycarbonyl-7-thia cycloadduct (49a) with lithium aluminium hydride ($LiAlH_4$) the only product isolated was assigned the rearranged lactone structure (176). Apparently this batch of $LiAlH_4$ was not an active reducing reagent but had been decomposed by age or moisture to give possibly, lithium hydroxide. Thus, in the attempt at 'reduction' of the ester, hydrolysis of the ester followed by rearrangement to the lactone had occurred.

Several attempts were carried out to mimic this reaction using ammonium hydroxide and sodium hydroxide with the cycloadduct (49a). However, only starting material was recovered. However, when the cycloadduct (49a) was treated in ethanol with aqueous lithium hydroxide at room temperature for 16 h, a reaction occurred. The reaction mixture, as judged by ^1H n.m.r. spectroscopy, appeared to contain three, or possibly four, products. The major product was believed to be the corresponding 8α-carboxylic acid (177), since the ^1H n.m.r. spectrum showed that the ester group was absent but the 18,19-protons were still present. This reaction mixture was separated by preparative t.l.c., however the major product isolated was found to be the rearranged lactone (176) (27%), as previously encountered. Microanalysis and accurate mass spectral data confirmed the molecular formula, $C_{21}H_{23}NO_5S$, for the lactone. The i.r. spectrum gave absorptions at 3 345 and 1 750 cm^{-1}, consistent with phenol and γ-lactone groups. The ^1H and ^{13}C n.m.r. spectra showed several signals that were similar to those of the furan (173) obtained by $LiAlH_4$ reduction of the ethyl ester cycloadduct; for examples, see Table 5. Apparently the cycloadduct acid (177) had completely isomerised to the lactone (176) on silica (Scheme 63), while the other products of the alkaline treatment, produced via a different reaction pathway (see Scheme 63), remained

as they were in the original mixture of the products. These other products are believed to have arisen by abstraction of the acidic 8-H proton of the ester, allowing cyclisation to occur to give cyclopropane derivatives. One of these cyclopropane derivatives was the ethyl ester (85) (10%) as judged by comparison of its ^1H n.m.r. spectrum with that of an authenticated sample. The other product was tentatively identified as the cyclopropane acid (178) (7%), since its ^1H n.m.r. spectrum was similar to that of the ester (85) except for the absence of the ethyl signals, and it gave a possible molecular ion peak at m/z 401. Apparently the ester (85) had undergone partial hydrolysis by the lithium hydroxide reagent (Scheme 63).



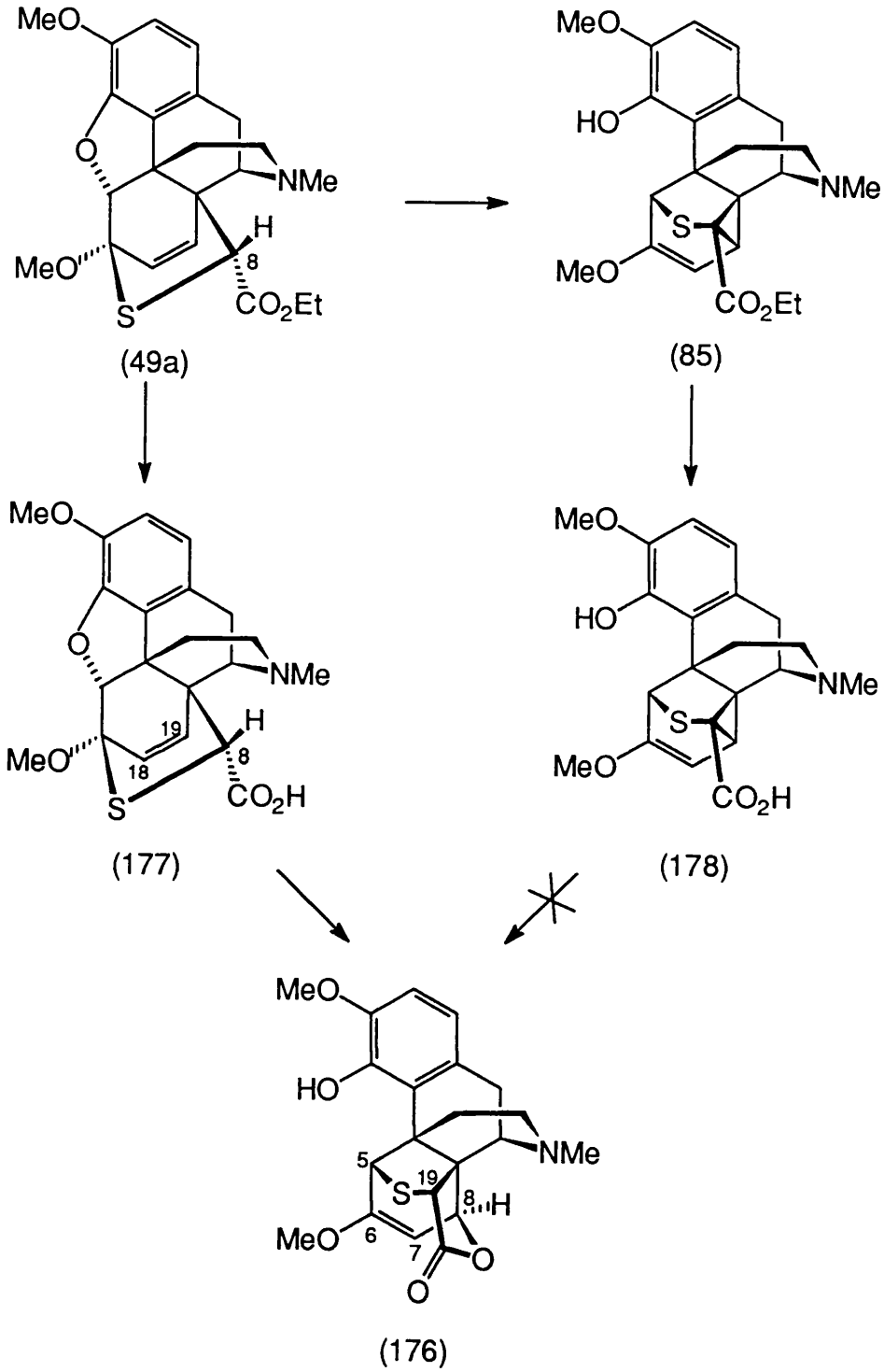
(176)



(173)

Table 5 Comparison of some ^{1}H and ^{13}C signals of the lactone (176) and the furan (173)

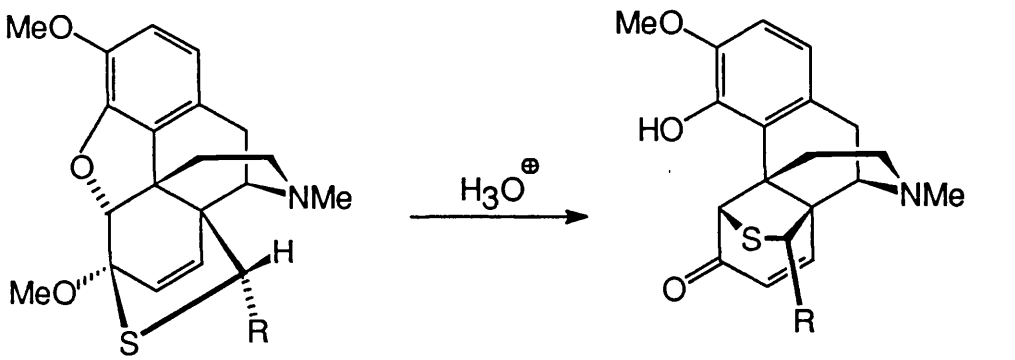
	Lactone	Furan
	^{1}H Signals (δ)	
5-H	4.50 (dd, J 1.7 and 0.6 Hz)	4.36 (m)
7-H	4.36 (dd, J 4.9 and 1.7 Hz)	4.22 (dd, J 4.5 and 1.7 Hz)
8-H	4.91 (d, J 5.0 Hz)	4.55 (d, J 4.5 Hz)
	^{13}C Signals (δ)	
C-5	46.2	48.5
C-6	167.2	165.0
C-7	89.0	90.3
C-8	82.0	80.3
C-19	ca. 54.8	55.9
C-20	176.5 (C=0)	75.0 (CH_2O)


MeO
O
NMe
H
MeO
8
S
CO2Et
(49a)
MeO
HO
NMe
S
MeO
CO2Et
(85)
MeO
O
NMe
19
H
MeO
18
8
S
CO2H
(177)
MeO
HO
NMe
S
MeO
CO2H
(178)
MeO
HO
5
NMe
19
S
8
H
MeO
6
7
O
O
(176)

Scheme 63

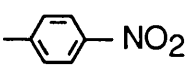
2.13 Acid-catalysed rearrangements of the ethyl ester cycloadduct (49a)

The cycloadducts (49a-c), being acetals, are sensitive to acid-catalysed hydrolysis to the corresponding enones (Scheme 64). The enones (86) and (100) were also formed in slightly basic and neutral solutions, as minor products, due to water entering the



(49a-c)

(86) R = CO_2Et

(100) R =  NO_2

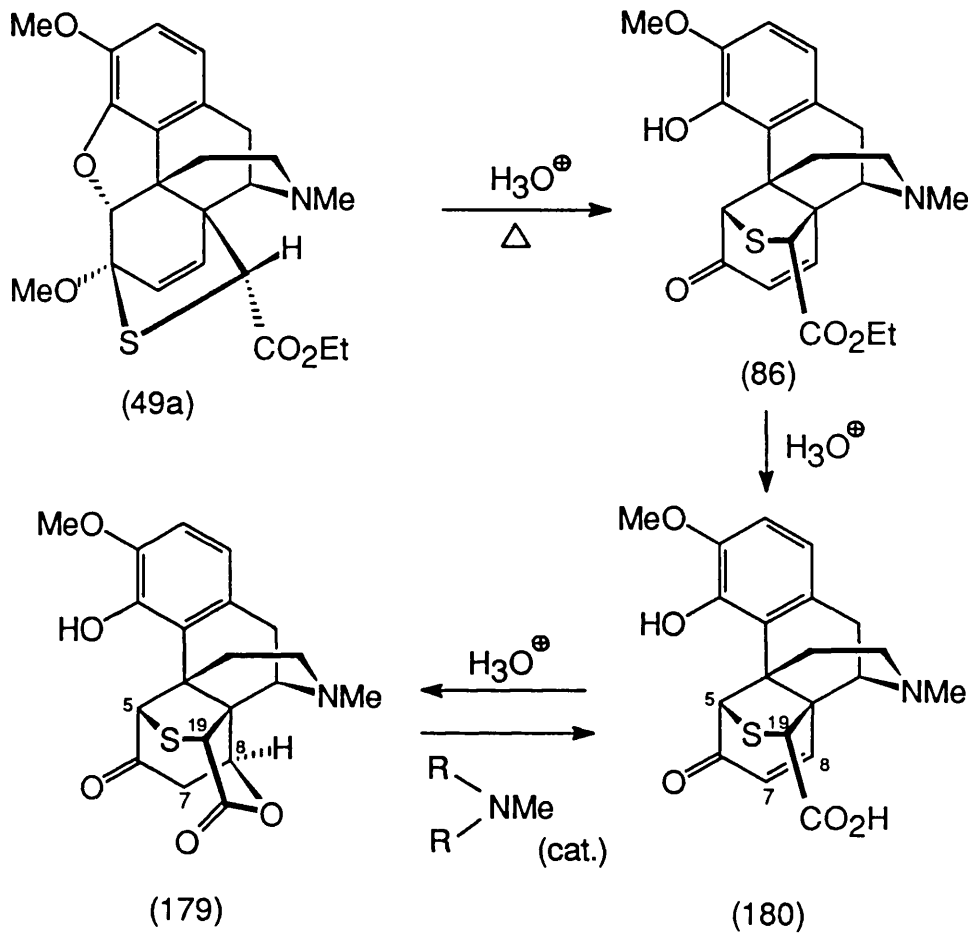
(138) R = 

Scheme 64

reaction mixture as was seen in the sodium ethoxide-catalysed rearrangement of the cycloadduct (49b). McDougall[61] also showed that the phenyl enone (138) was formed when the thiobenzaldehyde cycloadduct (49c) was heated for a long period in ethanolic sodium hydroxide. However, we found that the cycloadducts (49a-c) were hydrolysed to the enones reproducibly by heating under reflux for 5 min in ethanol and 2N hydrochloric acid (4:1; v/v). In contrast, when a solution of the cycloadduct (49a) in ethanol and acid (1:1), was stirred at room temperature for 18 h hydrolysis was only ca. 70% complete. Further, when the ethyl ester cycloadduct (49a) was heated in this mixture for 2 h, the keto-lactone (179) was formed as a single product as judged by ^{1}H and ^{13}C n.m.r. spectroscopy. Evidently the ester group in the desired enone (86) had been hydrolysed to the acid (180) which had rearranged to give the isomeric keto-lactone

(179). This lactone was identified by the singlet at δ 6.08 for the phenolic proton and also by the protons at positions 5, 8 and 19 i.e. the singlet at δ 4.65 for 5-H, the doublet (J 8.0 Hz) at 4.51 for 8-H and the singlet at 4.46 for 19-H. This spectrum had been recorded in deuteriochloroform with ca. 0.1 ml of [$^2H_6$]-dimethyl sulphoxide, added to aid solubility. However, the spectrum lacked fine resolution, probably due to poor solubility, and so the author decided to have the ^1H and ^{13}C n.m.r. spectra re-recorded. The deuterio-solution had been allowed to evaporate to dryness and then stored at room temperature in the laboratory for several weeks before the spectra were re-recorded in [$^2H_6$]-dimethyl sulphoxide. In these repeated spectra it was evident that another product was now present in addition to the lactone (179). This new product was judged to be the acid-enone (180); the ratio of lactone to acid was found to be ca. 6:1. Apparently the lactone was slowly isomerising to the acid-enone (180) (Scheme 65). When the n.m.r. spectrum was recorded in [$^2H_6$]-dimethyl sulphoxide alone, several signals were split and changed in chemical shift compared to those of the spectrum in deuteriochloroform containing a small amount of [$^2H_6$]-dimethyl sulphoxide. In [$^2H_6$]-dimethyl sulphoxide alone, the lactone (179) gave doublets at δ 6.69 (J 8.4 Hz, 1-H) and 6.84 (J 8.4 Hz, 2-H) for the aromatic protons, a singlet at 4.31 for 19-H, a doublet at 4.74 (J 7.5 Hz) for 8-H, a singlet at 4.61 for 5-H, and a singlet, greatly deshielded by the solvent, at 8.96 for the phenolic proton. No further work was carried out on this mixture but the deuterio-solution was allowed to evaporate to dryness and then stored in the laboratory. However, an i.r. spectrum was recorded several months later; this showed no absorption at ca. 1 770 cm^{-1} expected for the carbonyl group of a γ-lactone, however several overlapping bands at 1 720-1 685 cm^{-1} indicated, in conjunction with the n.m.r. data, that a carboxylic acid and an enone group were present. The acid-enone (180) was identified by signals for the protons at positions 5, 7 and 8. The olefinic signals were at δ 6.55 (d, J

ca. 9 Hz, 8-H) and 5.83 (dd, J ca. 9 and 2 Hz, 7-H) while 5-H gave a doublet δ 4.52, ($J_{5,7}$ 2Hz). The 19-H signal apparently overlapped that of the lactone. The phenolic proton gave a singlet at δ 8.64.



Scheme 65

The lactone (179) to acid (180) transformation may be base-catalysed in that the lactone itself is a base and the isomerisation might go to completion in the solid/gum state.

3. EXPERIMENTAL

General Procedures

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infra-red spectra were recorded for potassium bromide discs (unless otherwise stated) on either a Perkin-Elmer 580 or a Philips Analytical PU9800FTIR Spectrometer. Proton nuclear magnetic resonance spectra were determined on a Perkin-Elmer R32 (90 MHz) spectrometer using deuteriochloroform as solvent (unless otherwise stated). Tetramethylsilane was used as an internal standard. ^{1}H N.m.r. spectra were also recorded at 200 MHz on a Bruker WP 200 SY spectrometer, using a deuterium lock system. The chloroform ($C\underline{H}Cl_3$) in $CDCl_3$ was set at δ 7.25 as internal standard. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double-doublet; dt, double triplet; dq, double quartet, br, broad; ax, axial and eq, equitorial. Carbon nuclear magnetic resonance spectra were recorded on a Bruker WP 200 SY spectrometer at 50.3 MHz, with the solvent $CDCl_3$ signal set at δ 77.0. Chemical shifts throughout are quoted as p.p.m. downfield from tetramethylsilane. Mass spectra were obtained using a VE/Kratos MS12 spectrometer or a VG/Kratos MS90S spectrometer for high resolution in the EI mode at 70 eV.

Preparative layer chromatography was carried out on 20 x 20 cm glass plates coated with Merck Kieselgel GF_{254} of 0.1 mm thickness. Analytical thin layer chromatography (t.l.c.) was carried on commercial plates with a 0.25 mm layer of the same silica gel. Compounds were detected by u.v. light (254 nm) or by iodine vapour. Column chromatography was carried out on silica (Merck Kieselgel GF_{254} or HF_{254}) under suction applied by a water pump.

Solvents were purified in the following manner: tetrahydrofuran (THF) was first distilled from cuprous chloride and then from sodium-benzophenone; methanol and

ethanol were dried using magnesium activated with iodine; diethyl ether was dried using sodium wire. Light petroleum refers to the fraction b.p. 40-60°C.

Solutions in organic solvents were dried over anhydrous magnesium sulphate and evaporated under reduced pressure using a rotary evaporator.

Purification of triethylamine.[77] Reagent grade triethylamine was heated under reflux with potassium hydroxide pellets for 1 h, and then distilled into a flask containing more pellets. The flask was stoppered and this purified triethylamine was kept at ca. 5°C in a refrigerator and was considered pure until it became pale yellow.

Preparation of the 8α-ethoxycarbonyl-7-thia cycloadduct (49a).

Bunte salt method.

Preparation of the Bunte salt, $EtO_2CCH_2S_2O_3Na$ (80a) by the standard method.[55] A mixture of ethyl bromoacetate (181a) (14.7 g, 88 mmol) and sodium thiosulphate pentahydrate (22.2 g, 89 mmol) in 50% aqueous ethanol (100 ml) was heated under reflux for 1 h. The solution was evaporated to give a residue which was extracted with refluxing ethanol. The extracts were filtered and set aside to allow the Bunte salt to separate. The yield of the Bunte salt (80a) was 10.5 g (54%); m.p. 150-156°C (lit.,[55] 155°C).

Preparation of the cycloadducts of thebaine and the Bunte salt, $EtO_2CCH_2SSO_3Na$. The cycloadducts were prepared by the method of Sclare.[59] A mixture of calcium chloride dihydrate (0.45 g, 3.1 mmol), thebaine (11) (0.89 g, 2.8 mmol) and the Bunte salt (80a) (0.68 g, 3.1 mmol) was dissolved in ethanol-benzene (1:1) (40 ml). Distilled triethylamine (0.31 g, 3.1 mmol) was added with stirring at room temperature. Stirring was continued at room temperature for 9 days. The precipitate was filtered off and washed with ethanol (20 ml). The filtrate and washings were evaporated to dryness, and the residue was then dissolved in chloroform. The solution was washed

with saturated sodium hydrogencarbonate (5 ml) and water (10 ml). The organic layer was removed and the aqueous layer was further extracted with chloroform (3 x 30 ml). The combined organic extracts were dried and evaporated to give a sticky residue (1.20 g). The 90 MHz ^{1}H n.m.r. spectrum showed that the major product was the 7α-ethoxycarbonyl-8-thia cycloadduct (48a), along with some unreacted thebaine. The cycloadducts known to be produced in lower yields in this reaction were not detectable in this spectrum. However, t.l.c. of the residue on silica developed with diethyl ether show thebaine, $\underline{R}_f$ <0.1, and spots at $\underline{R}_f$ values of 0.36, 0.50 and 0.56 corresponding to the 7α-ethoxycarbonyl-8-thia (48a), 7β-ethoxycarbonyl-8-thia (84) and 8α-ethoxycarbonyl-7-thia (49a) cycloadducts, respectively. The residue (ca. 1.0 g) was chromatographed on a silica column using chloroform-diethyl ether (7:3) as eluent. The faster running, 8α-ethoxycarbonyl-7-thia cycloadduct (49a), as judged by ^{1}H n.m.r, spectroscopy, had hydrolysed to give the enone (86) as well as another, unidentified compound, while it was eluted from the column. The middle-running, 7β-ethoxycarbonyl-8-thia cycloadduct (84) (48 mg) gave the following ^{1}H n.m.r. signals; δ_H (90 MHz; $CDCl_3$) 1.28 (t, J 7 Hz, $OCH_2C\underline{H}_3$), 1.5-1.9 (m, contains $15_{eq.}$-H), 2.37 (s, NMe), 3.58 (m), 3.1-3.5 (m, $15_{ax.}$-, 9-, 10α- and 10β-H), 3.59 (s, 6-OMe), 3.75 (s, 7-H), 3.82 (s, 3-OMe), 4.23 (q, J 7 Hz, $OC\underline{H}_2CH_3$), 5.56 (d, J ca. 2 Hz, 5-H), 5.80 (d, J 9 Hz, 19-H), 5.99 (dd, J 9 and 2 Hz, 18-H), 6.53 (d, J ca. 8 Hz, 1-H) and 6.63 (d, J 8 Hz, 2-H). The slower running, major product, the 7α-ethoxycarbonyl-8-thia cycloadduct (48a) (0.46 g) had m.p. 114-117°C (lit.,[56] 116-118°C) (from propan-2-ol); $\upsilon_{max.}$ (KBr) 1 751, 1 720, 1 629, 1 600, 1 500 and 1 394 cm^{-1}; δ_H (90 MHz; $CDCl_3$) ($CHCl_3$ signal at δ 7.29) 1.25 (t, J 8 Hz, $OCH_2C\underline{H}_3$), 1.85 (dm, J ca. 12 Hz, $15_{eq.}$-H), 2.40 (s, NMe), 2.5-2.9 (m, $15_{ax.}$- and 10α-H), 3.27 (d, J 18 Hz, 10β-H), 3.47 (d, J 7 Hz, 9-H), 3.68 (s, 6-OMe), 3.85 (s, 3-OMe), 4.02 (s, 7-H), 4.16 (q, J 8 Hz, $OC\underline{H}_2CH_3$), 4.58 (s, 5-H), 5.89 (ABq, J 9 Hz, 18- and 19-

H), 6.57 (d, J 8 Hz, 1-H) and 6.63 (d, J 8 Hz, 2-H). The foregoing n.m.r. data agree well with literature values.[56,59]

Sulphenyl chloride method

Preparation of ethoxycarbonylmethanesulphenyl chloride[78] (81). Ethyl mercaptoacetate (182) (6.36 g, 53 mmol) was added dropwise with stirring to a suspension of N-chlorosuccinimide (7.70 g, 58 mmol) in benzene (150 ml) at room temperature. A yellow colour signifying the formation of the sulphenyl chloride developed soon after addition of the thiol had commenced. N-Chlorosuccinimide was purified by washing with water, drying in vacuo over P_2O_5 and then crystallisation from benzene.

Preparation of the 7α-ethoxycarbonyl-8-thia cycloadduct (48a). After stirring for 2 h, the above mixture was filtered through a pad of Celite such that the filtrate, the sulphenyl chloride solution, was added dropwise with stirring during 50 min, to a solution of thebaine (11) (13.7 g, 44 mmol) and distilled triethylamine (5.8 g, 57 mmol) in benzene-methanol (1:1) (300 ml) at room temperature.[56] After a further 30 min, aqueous sodium carbonate (200 ml) was added to the mixture and the layers were separated. The aqueous layer was extracted 3 times with dichloromethane and the combined extracts were washed with water, dried and evaporated to yield the cycloadduct (48a) (10.2 g, 54%). The ^1H n.m.r. spectrum of crystallised material (from propan-2-ol) was consistent with the literature[56] data (see p 123).

Preparation of the 8α-ethoxycarbonyl-7-thia cycloadduct (49a). The 7α-ethoxycarbonyl-8-thia cycloadduct (48a), (0.43 g, 1.0 mmol) [or a mixture of all three cycloadducts (48a), (84) and (49a)] was heated under reflux in toluene (60 ml) for 8 h.[56] Evaporation of the solution and crystallisation of the residue from propan-2-ol, gave the 8α-ethoxycarbonyl-7-thia adduct (49a) (0.32 g, 75%), m.p. 123-127°C (lit.,[56] 125-

128°C); $\upsilon_{max.}$ (KBr) 1 730, 1 630, 1 600, 1 505 and 1 401 cm^{-1}; δ_H (90 MHz; $CDCl_3$) ($CHCl_3$ signal at δ 7.32) 1.28 (t, J 7 Hz, $OCH_2\underline{CH_3}$), 1.8-2.3 (m, $15_{ax.}$- and $15_{eq.}$-H), 2.41 (s, NMe), 2.3-2.7 (m, $16_{ax.}$-, $16_{eq.}$- and 10α-H), 3.24 (d, J 19 Hz, 10β-H), 3.62 (s, 6-OMe), 3.72 (d, partially obscured by 6-OMe signal, 9-H), 3.82 (s, 3-OMe), 4.14 (q, J 7 Hz, $O\underline{CH_2}CH_3$), 4.99 (d, J 2 Hz, 5-H), 5.27 (s, 8-H), 5.77 (d, J 9 Hz, 19-H), 6.23 (dd, J 9 and 2 Hz, 18-H), 6.63 (d, J 8 Hz, 1-H) and 6.68 (d, J 8 Hz, 2-H); these values agreed well with those reported; m/z 429 (M) (100%) and 230 (94).

Preparation of the Bunte Salt, $4\text{-}NO_2C_6H_4CH_2S_2O_3Na$ (80b). The method of Price and Twiss[57] was used as follows. A mixture of p-nitrobenzyl bromide (181b) (31 g, 0.14 mol) and sodium thiosulphate pentahydrate (40 g, 0.19 mol) in 50% aqueous ethanol (200 ml) was heated under reflux for 1.5 h. The solution was then evaporated, and the residue was extracted with refluxing ethanol. The extracts were filtered and then cooled to allow the Bunte salt, sodium p-nitrobenzyl thiosulphate (80b) (20 g, 51%) to crystallise out.

Preparation of the 8α-p-nitrophenyl-7-thia cycloadduct (49b) of thebaine (11) from the Bunte salt, $4\text{-}NO_2C_6H_4CH_2S_2O_3Na$ (80b). The method of Sheldrake[60] was used as follows. Distilled triethylamine (0.80 g, 7.9 mmol) was added dropwise with stirring to the Bunte salt (80b) (2.30 g, 7.9 mmol), thebaine (11) (2.50 g, 8.0 mmol) and calcium chloride dihydrate (1.16 g, 7.9 mmol) in ethanol (20 ml) and benzene (60 ml). The mixture was stirred at room temperature for 6 days. The mixture was acidified with 2N hydrochloric acid and the layers separated. The aqueous layer was extracted with chloroform (3 x 30 ml) and the combined extracts were washed with brine (50 ml), dried and evaporated. The ^1H n.m.r. spectrum of the resultant residue showed the 8α-p-nitrophenyl-7-thia cycloadduct (49b) and the 7α-p-nitrophenyl-8-thia cycloadduct (48b) to be present in an approximate 1:1 mixture. This residue was heated in toluene under

reflux for 1 h. The solution was evaporated to dryness to give a pale yellow solid, which was recrystallised from ethanol, to yield the pure regioisomeric 7-thia cycloadduct (49b) (1.81 g, 47%), m.p. 193-196°C (decomp.) [lit.,[60] 195-196°C (decomp.)]; $\upsilon_{max.}$ (KBr) 1 628, 1 599, 1 518, 1 500, 1 452, 1 438 and 1 347 cm^{-1}; δ_H (90 MHz; $CDCl_3$) 2.38 (s, NMe), 3.18 (d, J 19 Hz, 10β-H), 3.69 (s, 6-OMe), 3.83 (s, 3-OMe), 5.11 (br s, 5-H), 5.17 (d, J 9 Hz, partly obscured by 5-H signal, 19-H), 5.82 (s, 8-H), 6.39 (d, J 9 Hz, 18-H), 6.50 (d, J 8 Hz, partly obscured by 18-H signal, 1-H), 6.53 (d, J 8 Hz, 2-H), 7.54 and 8.08 (4H, ABq, J 9 Hz, aryl'-H).

Preparation of dibenzyl disulphide (183). The disulphide was prepared by a standard method involving iodine oxidation of the thiol, as follows. Sodium hydroxide (3.4 g, 85 mmol) and a small amount of potassium iodide (ca. 50 mg) were added to water (80 ml) and swirled to effect complete dissolution. Ethanol (80 ml) was added followed by benzyl mercaptan (184) (10 ml, 85 mmol). Iodine (5.4 g, 43 mmol) was then added in portions with shaking over 30 min. Precipitation of the disulphide occurred immediately upon addition of iodine. The reaction mixture was left standing for 1 h, then the precipitate was filtered off and washed with ethanol (100 ml). The dibenzyl disulphide (183) (6.5 g, 65%), had m.p. 58-60°C (lit.,[79] 59-60°C); δ_H (90 MHz; $CDCl_3$) 3.60 (s, SCH_2) and 7.28 (s, ArH), and was considered pure enough to use directly in the next stage.

Preparation of S-benzyl phenylmethanethiosulphinate (82). The thiosulphinate was prepared by a general method.[58] Thus, 29% w/w peracetic acid (2.10 g, 8.05 mmol) in dichloromethane (20 ml) was added dropwise with stirring during 5 min to a solution of dibenzyl disulphide (183) (1.98 g, 8.05 mmol) in dichloromethane (20 ml) cooled in ice-water. The cooling bath was removed after 1 h. The reaction mixture was stirred overnight at room temperature and then treated with saturated aqueous sodium

hydrogencarbonate until effervescence ceased. This mixture was extracted with dichloromethane (3 x 50 ml), and the combined organic extracts were washed with water (2 x 50 ml), dried and then evaporated to give a pink solid. Crystallisation from diethyl ether yielded the thiosulphinate (82) (1.31 g, 62%), m.p. 63-65°C (lit., 65-67°C). The ^{1}H n.m.r. spectrum gave the following signals, in good agreement with Jaap's[74] results; δ_H (90 MHz, $CDCl_3$) 4.25 and 4.28 (2 x s, SCH_2 and $SOCH_2$) and 7.30 and 7.34 (2 x s, ArH).

Preparation of the thiobenzaldehyde cycloadduct (49c) from S-benzyl phenylmethanethiosulphinate (82) and thebaine (11). A variation of the method of Baldwin et al.[58] was used as follows. A 1:1 mol ratio (cf. Baldwin 10-20:1) of the diene trap, thebaine, to the thiosulphinate was used. Thus, thebaine (11) (1.32 g, 4.2 mmol) and the thiosulphinate (82) (1.21 g, 4.2 mmol) in dry toluene (12 ml), under a nitrogen atmosphere, were heated under reflux for 1 h. At this time, t.l.c. on silica plates developed with dichloromethane-methanol (9:1) showed only the desired cycloadduct (49c), R_f 0.9, and no thebaine, R_f 0.3. Evaporation of the toluene gave a reddish oil which was dissolved in dichloromethane (20 ml). This solution was washed successively with saturated brine (10 ml), and water (10 ml), and then dried and evaporated to give the thioaldehyde cycloadduct (49c) (1.40 g, 77%) as an oily gum; m.p. 182-185°C (lit.,[58] 182-183°C) (from diethyl ether); m/z 433 (M) (10%) and 311 (M-C_7H_6S) (21). The ^{1}H n.m.r. spectrum of the oil obtained after evaporation of the toluene gave the following signals; δ_H (90 MHz; $CDCl_3$) 2.36 (s, NMe), 2.90 (d, J 6 Hz, 9-H or part of 10α-H signal), 3.15 (d, J 19 Hz, 10β-H), 3.65 (s, 6-OMe), 3.78 (s, 3-OMe), 5.05 (d, J ca. 2 Hz, 5-H), 5.19 (d, J 8 Hz, 19-H), 5.72 (s, 8-H), 6.31 (dd, J ca. 9 and 2 Hz, 18-H), 6.50 (d, J 8 Hz, 1-H), 6.60 (d, J 8 Hz, 2-H) and 7.15-7.50 (m, Ph).

Base catalysed rearrangement of the ethyl ester 7-thia cycloadduct (49a). The ethyl ester cycloadduct (49a) (275 mg, 0.64 mmol) was dissolved in dry ethanol (10 ml). Ethanolic sodium ethoxide [0.6 ml of a solution prepared from sodium (12.2 mg) in ethanol (2 ml); 0.16 mmol, 25% mol equiv.] was added and the mixture was refluxed under nitrogen for 26 h. The reaction mixture was evaporated to dryness. The residue was dissolved in water (5 ml) and then extracted with dichloromethane (3 x 10 ml). The combined extracts were washed once with water (5 ml), dried and evaporated to yield a yellow residue. This residue was chromatographed on silica plates, developed with methanol-dichloromethane (1:9). [N.B. The enone (86), has a typical R_f value of 0.6]. The cyclopropane ester (85), R_f 0.35, (178 mg, 65%) had m.p. 224-225°C (from propan-2-ol/dichloromethane) [Found: C, 63.8; H, 6.6; N, 3.3; S, 7.2; m/z 429.1608 (68%), 414.1392 (100) and 310.1436 (77). $C_{23}H_{27}NO_5S$ requires C, 64.4; H, 6.4; N, 3.3; S, 7.5%; M, 429.1610; (M-CH_3), 414.1375 and (M-$C_4H_7O_2S$), 310.1443; respectively.]; $\upsilon_{max.}$ (KBr) 3 420, 1 710, 1 635, 1 485 and 1 280 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.29 (t, J 7.1 Hz, OCH_2CH_3), 1.48 (br d, J ca. 9 Hz, $15_{eq.}$-H), 2.13 (td, J 12 and 2.4 Hz, $16_{ax.}$-H), 2.27 (dd, J ca. 9 and 3 Hz, possibly td partly obscured by the NMe signal, $15_{ax.}$-H), 2.35 (s, NMe), 2.56 (d, J 6.9 Hz, 8-H), ca. 2.56 (m, signals partly obscured by 8-H signal, $16_{eq.}$-H), 2.87 (dd, J 17.7 and 5.8 Hz, 10α-H), 3.14 (d, J 18.0 Hz, 10β-H), 3.40 (s, 6-OMe), 3.58 (d, J 5.3 Hz, 9-H), 3.81 (s, 3-OMe), 4.21 and 4.24 (q ABq, J 7.1 and 10.6 Hz, OCH_2CH_3), 4.38 (d, J 2.4 Hz, 5-H), 4.61 (dd, J 6.9 and 2.5 Hz, 7-H), 5.82 (s, OH, exch. with D_2O), 6.64 (d, J 8.4 Hz, 1-H) and 6.66 (d, J 8.4 Hz, 2-H); δ_C (50.3 MHz; $CDCl_3$) 14.1 (OCH_2CH_3), 28.2 (C-10 or -15), 29.1 (C-15 or -10), 31.7 (C-8), 41.0 (C-14), 42.1 (NMe), 45.2 and 45.8 (C-13 and -19), 47.1 (C-16), 49.6 (C-5), 53.4 (C-9), 55.2 (6-OMe), 55.9 (3-OMe), 61.6 (OCH_2CH_3), 86.4 (C-7), 108.8 (C-2), 118.1 (C-1), 124.5 (C-11), 131.3 (C-12), 142.8 (C-3), 144.3 (C-4), 158.0 (C-6) and 170.6 (CO_2Et).

LDA-mediated rearrangment of the ethyl ester 7-thia-cycloadduct (49a).

Diisopropylamine (96 mg, 0.95 mmol) in dry tetrahydrofuran (2 ml) was cooled to -78°C in a dry ice-acetone bath and then n-butyllithium (0.6 ml, 1.6 M, 0.96 mmol) was added through a rubber septum from a syringe. The cycloadduct (49a) (196 mg, 0.45 mmol), in dry tetrahydrofuran (3 ml), was added likewise, with stirring, to the lithium diisopropylamide (LDA) solution.. This mixture was stirred for 30 min at -78°C and then the cooling bath was removed and the mixture stirred for a further 30 min. A few drops of dilute hydrochloric acid and water (5 ml) were added to the mixture, which was then extracted with dichloromethane. The combined extracts were dried and evaporated to yield a residue which, as judged by ^1H n.m.r. spectroscopy (90 MHz) contained the cycloadduct (49a) and the ketocyclopropane (94) in the ratio ca. 1:4. Preparative t.l.c. of this residue on silica plates developed with diethyl ether gave the cycloadduct (49a), R_f 0.7, and the ketocyclopropane (94), R_f 0.1 (Found: m/z 415.1450 (11%). $C_{22}H_{25}NO_5S$ requires M, 415.1453); δ_H (200 MHz; $CDCl_3$) 1.31 (t, J 7.1 Hz, OCH_2CH_3), 1.67 (br d, J 10.1 Hz, $15_{eq.}$-H), 1.91 (t, J 2.7 Hz, 8-H), 2.06 (dd, J 20.1 and 2.9 Hz, 7α-H), 2.56 (s, NMe), 2.79 (dd, J 20.1 and 2.7 Hz, 7β-H), 3.21 (dd, 18.6 and 5.9 Hz, 10α-H), 3.50 (br d, J 18.6 Hz, 10β-H), ca. 3.76 (d, J ca. 6 Hz, obscured by 3-OMe signal, 9-H), 3.79 (s, 3-OMe), 4.28 (q, J 7.1 Hz, OCH_2CH_3), 4.36 (s, 5-H), ca. 6.2 (v br s, OH, exch. with D_2O) and 6.71 (s, 1- and 2-H); δ_C (50.3 MHz; $CDCl_3$) 14.0 (OCH_2CH_3), 26.0 (C-10), 26.3 (C-8), 29.9 (C-15), 32.1 (C-7), 38.9 (C-14), 40.7 (C-18), 41.0 (NMe), 45.7 (C-13), 46.0 (C-16), 54.5 (C-5 or -9), 56.0 (3-OMe), 56.6 (C-9 or -5), 62.7 (OCH_2CH_3), 110.3 (C-2), 119.2 (C-1), 121.9 (C-11), ca. 128.5 (C-12), 142.6 (C-3), 145.3 (C-4), 168.9 (CO_2Et) and 196.9 (C-6).

Attempted LDA mediated rearrangement of the ethyl ester 7-thia-cycloadduct (49a) formation of the butyl ketone (95). A solution of diisopropylamine (177 mg, 1.75 mmol) in dry THF (10 ml) was cooled to -78°C (acetone-solid carbon dioxide bath) under a stream of nitrogen. n-Butyllithium in THF (1.1 ml, 1.6 M) was added through a septum from a syringe, with stirring. The cycloadduct (49a) (300 mg, 0.70 mmol), dissolved in dry THF (5 ml), was then added from a syringe, and the stirring was continued at -78°C for 1 h. The cooling bath was removed and the reaction mixture was stirred for a further 2 h. Water (5 ml) was added and the mixture was evaporated to give a gum. Water (5 ml) was added and the mixture was then extracted with dichloromethane (4 x 20 ml). The combined organic extracts were washed with water (10 ml), dried and evaporated. The ^1H n.m.r. spectrum (90 MHz) of the residue showed the presence of two major products, in approximately equal quantities, one of them the cyclopropane ethyl ester (85). This residue was purified by preparative t.l.c. using silica plates, with diethyl ether as eluent. The slower running spot (R_f 0.2) was the cyclopropane ethyl ester (85), while the faster running spot (R_f 0.8) was found to be the butyl ketone (95) (47 mg, 15%), m.p. 105-110°C (from dichloromethane-diethyl ether); (Found: m/z 441.1959. $C_{25}H_{31}NO_4S$ requires M, 441.1974); $\upsilon_{max.}$ ($CHCl_3$) 1 709, 1 500, 1 450 and 1 440 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 0.88 (t, J 7.5 Hz, 24-CH_3), ca. 1.27 (complex m, 23-H), ca. 1.51 (complex m, 22-H), 1.81 (d, J ca. 13 Hz, $15_{eq.}$-H), 2.16 (m, $16_{ax.}$-H), 2.31 (s, NMe), ca. 2.4 (m, 21-, 10α-, $15_{ax.}$- and $16_{eq.}$-H), 3.20 (d, J 18.6 Hz, 10β-H), 3.57 (s, 6-OMe), ca. 3.58 (d, obscured by 6-OMe signal, 9-H), 3.79 (s, 3-OMe), 4.96 (d, J 1.6 Hz, 5-H), 5.30 (s, 19-H), 5.77 (d, J 9.1 Hz, 8-H), 6.08 (dd, J 9.2 and 1.6 Hz, 7-H), 6.55 (d, J 8.2 Hz, 1-H) and 6.62 (d, J 8.2 Hz, 2-H); δ_C (50.3 MHz; $CDCl_3$) 13.8 (C-24), 22.2 (C-22 or -23), 22.3 (C-23 or -22), 25.9 (C-10), 33.6 (C-15), 42.4 (C-21), 43.3 (NMe), 45.2 (C-16), 46.2 and 48.0 (C-13 or -14), 53.4 (6-OMe), 55.8 (C-8 or -

9), 56.3 (3-OMe), 58.5 (C-9 or -8), 89.5 (C-6), 93.2 (C-5), 113.1 (C-2), 119.2 (C-1), 126.6 (C-18 or -19), 127.2, 131.2 and 132.3 (C-11 or -12), 136.1 (C-19 or -18), 141.8 (C-3), 146.9 (C-4) and 196.7 (C-20).

Preparation of the ketocyclopropane (94) by mild acid hydrolysis of the corresponding enol ether (85). The cyclopropane enol ether (85) (55 mg, 0.13 mmol) dissolved in ethanol (5 ml) and 0.4 M hydrochloric acid (5 ml), was stirred at room temperature for 25 min. The reaction mixture was evaporated to low volume and then diluted with 5% aqueous sodium hydrogencarbonate (5 ml). This mixture was extracted with dichloromethane (3 x 5 ml) and the combined extracts were washed once with water (5 ml), dried and evaporated to yield the ketocyclopropane (94) as a gum, (37 mg, 69%); δ_H (90 MHz; $CDCl_3$) 1.25 (t, J 7 Hz, OCH_2CH_3), 1.58 (br d, J 7 Hz, $15_{eq.}$-H), 2.47 (s, NMe), 3.09 (dd, J 18 and 6 Hz, 10α-H), 3.40 (d, J 18 Hz, 10β-H), 3.72 (s, 3-OMe), 4.20 (q, J 7 Hz, OCH_2CH_3), 4.27 (s, 5-H), ca. 5.9 (br s, OH, exch. with D_2O) and 6.64 (s, 1- and 2-H), in good agreement with 200 MHz spectrum (see p 128 for values and also for ^{13}C values); m/z 415 (M) (4%) and 230 (100).

Preparation of ethyl 7,8-didehydro-3,6β-dimethoxy-17-methyl-4,6α-epoxy-5β,14β-thiaethanomorphinan-(19R)-carboxylate (53). The 4,6α-epoxy acetal (53) was prepared by the method of Sclare.[59] Thus, the ethyl ester 7-thia cycloadduct (49a) dissolved in chlorobenzene was heated under reflux for 30 h. Evaporation of the solvent yielded a 1:4 mixture of the cycloadduct and the 4,6α-epoxy acetal. Preparative t.l.c. of the resultant residue on alumina plates developed with diethyl ether-light petroleum (65:35) gave the cycloadduct, R_f 0.7, and the 4,6α-epoxy acetal, R_f 0.6. This acetal gave, in good agreement with Sclare's values, δ_H (90 MHz; $CDCl_3$) ($CHCl_3$ signal at δ 7.29) 1.26 (t, J 7 Hz, OCH_2CH_3), 2.42 (s, NMe), 3.61 (s, 6-OMe), 3.81 (s, 3-OMe), 4.14

(qABq, J 7 and 10 Hz, OCH_2CH_3), 5.27 (dd, J 10 and 2 Hz, 7-H), 5.55 (s, 19-H), 6.08 (d, J 10 Hz, 8-H), and 6.67 (s, 1- and 2-H).

Base catalysed rearrangement of the 4,6α-epoxy acetal (53). The acetal (53) (96 mg, 0.23 mmol) was dissolved in dry ethanol (200 ml). Ethanolic sodium ethoxide [0.9 ml of a solution prepared from sodium (12 mg) in ethanol (10 ml); 20% mol equiv.] was added to the acetal solution and the mixture was heated under reflux, and under nitrogen for 20 h. The reaction mixture was evaporated to low volume (ca. 25 ml) and then water (25 ml) and saturated brine (10 ml) were added. This mixture was extracted with dichloromethane (3 x 30 ml). The combined extracts were dried and evaporated to yield a gum (71 mg). This gum, as judged by ^1H n.m.r. spectroscopy (90 MHz), contains the 6α-ethyl-6β-methyl acetal (96) and the 4,6α-epoxy acetal (53) in the ratio of ca. 3:1. The acetal (96) gave δ_H (90 MHz; $CDCl_3$) ($CHCl_3$ signal at δ 7.30) 0.74 (t, J 7 Hz, 6α-OCH_2CH_3), ca. 1.28 (t, J 7 Hz, $CO_2CH_2CH_3$), 2.37 (s, NMe), 3.25 (s, 6β-OMe), 3.82 (s, 3-OMe), ca. 4.15 (q, J 7 Hz, $CO_2CH_2CH_3$), 4.49 (d, J 3 Hz, 5-H), 5.04 (s, 19-H), 5.58 (dd, J 10 and 3 Hz, 7-H), ca. 5.85 (br s, OH, exch. with D_2O), 5.98 (d, J 10 Hz, 8-H), and 6.66 (ABq, 1- and 2-H).

Rearrangement of the ethyl ester 7-thia cycloadduct (49a) in ethanol. The cycloadduct (49a) (63 mg, 0.147 mmol) was heated in dry ethanol (40 ml) under reflux, and under nitrogen for 2 h. Evaporation of the solvent yielded a residue which, as judged by ^1H n.m.r. (90 MHz) spectroscopy, contained the cycloadduct (49a) (62%), the 4,6α-epoxy-6β-methyl acetal (53) (25%) and the 6α-ethyl-6β-methyl acetal (96) (12%). This reaction mixture was heated again in dry ethanol (40 ml), under nitrogen, and refluxed for a further 3 h. As judged by ^1H n.m.r. (90 MHz) spectroscopy, the reaction mixture (total 5 h heating at reflux) contained the cycloadduct (49a) (54%), the 4,6α-epoxy-6β-methyl acetal (53) (19%), (96) the 6α-ethyl-6β-methyl acetal (19%) (96) and now also

the 6,6-diethyl acetal (97) (8%). After heating in ethanol under reflux for 20 h total, the reaction mixture contained the compounds (53) and (97) in the ratio 29:54, respectively, and now another product was present, the 4,6α-epoxy-6β-ethyl acetal (98) comprising 17% of the mixture. Finally, after a total of 45 h heating in ethanol under reflux, the reaction mixture contained, as judged by ^{1}H n.m.r. spectroscopy (90 MHz) only the 6,6-diethyl acetal (97) and the 4,6α-epoxy-6β-ethyl acetal (98) in the ratio ca. 1:1. The n.m.r. signals used for identification of the foregoing reaction products are listed in Section 2.2.2, p 51.

Attempts to produce 6,6-dialkyl acetals e.g. (97) from the 8α-ethoxycarbonyl-7-thia cycloadduct (49a) using hydrogen chloride gas. The general approach was to dissolve the 7-thia cycloadduct (49a) in dry ethanol and then to bubble dry hydrogen chloride gas into this solution for 30-40 min. After a period of heating at reflux, excess triethylamine was added to neutralise the acid and then the reaction mixture was evaporated to low volume, diluted with water and extracted with dichloromethane. The organic extracts were dried and evaporated and then a ^{1}H n.m.r. spectrum (90 MHz) was taken to determine the result of the reaction.

1. With 5 h at reflux only the ethyl ester enone (86) was present.
2. Molecular sieves (5A) was added to the same reaction mixture, which was heated at reflux for 3 h; again only the enone (86) was present.
3. Fractionally distilled triethyl orthoformate was added to the same reaction mixture and after 90 min at reflux, the cycloadduct was still present. However, a small high-field triplet at ca. δ 0.98, may indicate the presence of a 6α-ethyl-6β-alkyl acetal.

4. The same conditions as immediately above (3) were repeated with longer periods of heating. However, after heating at reflux for 6 h only the cycloadduct was present; again, heating at reflux for 24 h produced only the enone.

Preparation of 7,8-didehydro-6,6-diethoxy-4-hydroxy-3-methoxy-17-methyl-19(S)-p-nitrophenyl-5β,14β-thiaethanomorphinan (99). The p-nitrophenyl cycloadduct (49b) (173 mg, 0.36 mmol) was dissolved in dry ethanol (60 ml). Sodium ethoxide [0.7 ml of 0.045 M solution, prepared from sodium (26 mg) in ethanol (25 ml), 3.16×10^{-5} mol, ca. 9% mol equiv.] was added and the mixture was then heated under reflux for 51 h, under a nitrogen atmosphere and then left to stand at room temperature overnight. A yellow crystalline solid crystallised out from the reaction mixture. The mother liquer was decanted off and the crystals were washed twice with ethanol. The crystals were found to be pure 6,6-diethyl acetal (99) (157 mg, 81%), m.p. 196-197°C (from ethanol) (Found: C, 64.5; H, 6.3; N, 5.2; S, 6.3. $C_{29}H_{34}N_2O_6S$ requires C, 64.7; H, 6.4; N, 5.2; S, 6.0%); (Found: m/z 492.1705. $C_{27}H_{28}N_2O_5S$ requires M-EtOH, 492.1719. No M found.); $\upsilon_{max.}$ (KBr) 3 540, 1 593, 1 520, 1 487, 1 345 and 1 280 cm^{-1}; δ_H (100 MHz; $CDCl_3$) 0.69 (t, J 7 Hz, 6α-OCH_2CH_3), 1.21 (t, J 7 Hz, 6β-OCH_2CH_3), 1.7-2.2 (m, $15_{eq.}$ and $16_{ax.}$-H), 2.34 (s, NMe), 2.4-2.9 (m, 9-, 10α-, $15_{ax.}$- and $16_{eq.}$-H), 3.00 (d, J 18 Hz, 10β-H), 3.60 (m, 6-OCH_2CH_3), 3.78 (s, 3-OMe), 4.60 (d, J 3 Hz, 5-H), 4.90 (d, J 10 Hz, 8-H), 5.59 (s, 19-H), 5.69 (d, J 3 Hz; part of dd J 10 and 3 Hz, partially obscured by 19-H signal; 7-H), 5.83 (s, OH, exch. with D_2O), 6.56 (d, J 8 Hz, 1-H), 6.64 (d, J 8 Hz, 2-H), 7.65 (2H, d, J 9 Hz, 21- and 25-H) and 8.12 (2H, d, J 9 Hz, 22- and 24-H). The mother liquer and ethanol washings were combined and evaporated to yield a yellow residue. The ^1H n.m.r. spectrum (90 MHz) showed that this residue was the corresponding enone (100).

Shorter period of time of reflux. The above reaction was repeated but with heating for only ca. 20 h. The reaction mixture, as judged by ^1H n.m.r. (90 MHz) spectroscopy contained the starting cycloadduct (49b), the diethyl acetal (99) and the 6α-ethyl-6β-methyl acetal (101). This mixed acetal (101) gave m.p. 197-199°C (from methanol-benzene); (Found: m/z 492.1715. $C_{27}H_{28}N_2O_5S$ requires M-EtOH, 429.1718. No M found.); $\upsilon_{max.}$ (KBr) 3 540, 1 593, 1 517, 1 488, 1 442, 1 344 and 1 284 cm^{-1}; $\upsilon_{max.}$ ($CHCl_3$) 3 685, 3 540, 1 595, 1 519, 1 484, and 1 347 cm^{-1}; $\upsilon_{max.}$ ($CHCl_3$, diluted sample) absorptions are not affected; δ_H (200 MHz; $CDCl_3$) 0.73 (t, J ca. 7 Hz, 6α-OCH_2CH_3), 2.37 (s, NMe), 3.30 (s, 6β-OMe), ca. 3.53 (m, 6α-OCH_2CH_3), 3.80 (s, 3-OMe), 4.59 (m, 5-H), 4.87 (d, 10.2 Hz, 8-H), 5.56-5.65 (m, 7- and 19-H), 6.52 (d, J 8.3 Hz, 1-H), 6.61 (d, J 8.3 Hz, 2-H), ca. 7.61 (d, J 8.9 Hz, 21- and 25-H), and 8.08 (d, J 8.9 Hz, 22- and 24-H); δ_C (50.3 MHz; $CDCl_3$) signals are virtually identical to the other p-nitrophenyl acetals, with δ 47.9 (6β-OMe).

Treatment of the diethyl acetal (99) with a catalytic amount of sodium methoxide. Similar experimental conditions were carried out as described above. Thus after 47 h at reflux in methanol-benzene, the componds present were the diethyl acetal (99) and the 6β-ethyl-6α-methyl acetal (102), in the ratio 2:3, respectively. The diethyl acetal (99) gave the following signals, δ_H (200 MHz; $CDCl_3$) 0.75 (t, J 7.0 Hz, 6α-OCH_2CH_3), 1.27 (t, J 7.2 Hz, 6β-OCH_2CH_3), 2.39 (s, NMe), ca. 3.55 (m, 6α-OCH_2CH_3), ca. 3.65 (m, 6β-OCH_2CH_3), 3.81 (s, 3-OMe), 4.61 (s, 5-H), 4.89 (d, J 10.2 Hz, 8-H), 5.56-5.69 (m, 7- and 19-H), 5.83 (s, OH, exch. with D_2O), 6.54 (d, J 8.3 Hz, 1-H), 6.67 (d, J 8.3 Hz, 2-H), ca. 7.63 (d, J ca. 9 Hz, 21- and 25-H), and 8.10 (d, J ca. 9 Hz, 22- and 24-H); δ_C (50.3 MHz; $CDCl_3$) 14.4 (6α-OCH_2CH_3), 15.4 (6β-OCH_2CH_3), 25.3 (C-10), 30.6 (C-15), 42.5 (NMe), 46.8 (C-16), 50.6 (C-13 or -14), 51.9 (C-19), 53.6 (C-14 or -13), 55.4 (C-5 or -9), 55.7 (6α-OCH_2CH_3), 55.7 (3-OMe), 56.1 (C-9 or -5), 56.7 (6β-

OCH_2CH_3), 100.9 (C-6), 108.4 (C-2), 118.0 (C-1), 122.6 (C-21 and -25), ca. 127.4 (C-7 or -8), ca. 128.6 (C-11), 129.6 (C-12), 131.2 (C-22 and -24), ca. 132.6 (C-8 or -7), 143.8-147.0 (C-3, -4, -20 and -23). The 6β-ethyl-6α-methyl acetal (102) gave, m.p. 180-181°C (from ethanol); δ_H (200 MHz; $CDCl_3$) 1.28 (t, J 7.0 Hz, 6β-OCH_2CH_3), 2.39 (s, NMe), 2.80 (6α-OMe), ca. 3.65 (m, 6β-OCH_2CH_3), 3.82 (s, 3-OMe), 4.61 (s, 5-H), 4.92 (d, J 10.2 Hz, 8-H), 5.56-5.69 (m, 7- and 19-H), 5.88 (s, OH, exch. with D_2O), 6.53 (d, J 8.3 Hz, 1-H), 6.64 (d, J 8.3 Hz, 2-H), ca. 7.63 (d, J ca. 9 Hz, 21- and 25-H), and 8.10 (d, J ca. 9 Hz, 22- and 24-H). m/z 492 (M-MeOH).

Treatment of the 6α-ethyl-6β-methyl acetal (101) with a catalytic amount of sodium methoxide. Similar experimental conditions were carried out as previously described. Thus after 17 h at reflux in methanol-benzene, the ^1H n.m.r. spectrum (90 MHz) of the reaction mixture, shows the presence of the starting mixed acetal (101) and the dimethyl acetal (103) in the approximate ratio of 1:1.

Preparation of 7,8-didehydro-6,6-dimethoxy-4-hydroxy-3-methoxy-17-methyl-19(S)-p-nitrophenyl-5β,14β-thiaethanomorphinan (103). The p-nitrophenyl cycloadduct (49b) (245 mg, 0.51 mmol) was dissolved in dry benzene (10 ml) and dry methanol (10 ml). Sodium metal (2.4 mg, 0.10 mmol, 20% mol equiv.) was added and the mixture then refluxed under a nitrogen atmosphere for 24 h. After the mixture had cooled, water (5 ml) was added and then this mixture was evaporated to dryness. Water (5 ml) was added to the residue and the mixture was extracted with dichloromethane (3 x 10 ml). The combined organic extracts were washed once with water (10 ml), dried and evaporated to yield the phenolic acetal (103) as a yellow gum (170 mg, 65%), m.p. 123-124°C (as needles from methanol) (Found: C, 59.9; H, 5.7; N, 5.0. No satisfactory fit could be found: $C_{27}H_{30}N_2O_6S$ requires C, 63.5; H, 5.9; N, 5.5%. $C_{27}H_{30}N_2O_6S.2MeOH$ requires C, 60.1; H, 6.7; N, 4.9%. $C_{27}H_{30}N_2O_6S.2H_2O$

requires C, 59.3; H, 6.3; N, 5.1%.) (Found m/z 478.1587. $C_{26}H_{26}N_2O_5S$ requires M-MeOH, 478.1562); $\upsilon_{max.}$ (KBr) 3 440, 1 597, 1 525, 1 490, 1 350 and 1 280 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.85 (dd, J ca. 12 and 3 Hz, $15_{eq.}$-H), 1.97 (td, J 11.9 and 4.0 Hz, $16_{ax.}$-H), 2.38 (s, NMe), 2.47-2.85 (m, 9-, 10α-, $15_{ax.}$- and $16_{eq.}$-H), 2.78 (s, 6α-OMe), 3.10 (d, J 18.0 Hz, 10β-H), 3.32 (s, 6β-OMe), 3.82 (s, 3-OMe), 4.61 (d, J 2.2 Hz, 5-H), 4.92 (d, J 10.2 Hz, 8-H), 5.59 (s, 19-H), 5.62 (dd, J 10.2 and 2.3 Hz, 7-H), 5.87 (s, OH, exch. with D_2O), 6.52 (d, J 8.3 Hz, 1-H), 6.63 (d, J 8.3 Hz, 2-H), 7.62 (2H, d, J 8.8 Hz, 21- and 25-H), and 8.08 (2H, d, J 8.8 Hz, 22- and 24-H); δ_C (50.3 MHz; $CDCl_3$) 25.3 (C-10), 30.4 (C-15), 42.5 (NMe), 46.8 (C-16), 48.2 and 48.9 (6,6-OMe), 50.6 (C-13 or -14), 51.9 (C-19), 53.8 (C-14 or -13), 55.4 (C-9 and -5), 56.2 (3-OMe), 101.3 (C-6), 108.9 (C-2), 117.8 (C-1), 122.7 (C-21 and -25), 126.7 (C-7 or -8), 128.0 (C-11 or -12), 129.9 (C-12 or -11), 131.2 (C-22 and -24), 133.2 (C-8 or -7), and 143.9, 145.1, 146.5 and 147.1 (C-3, -4, -20 and -23).

Prolonged treatment of the dimethyl acetal (103) with a catalytic amount of sodium ethoxide. With a total of 8 d at reflux, the only product was the 6α-ethyl-6β-methyl acetal (101), as judged by ^1H n.m.r. (90 MHz) spectroscopy.

Treatment of the dimethyl acetal (103) with a ca.1.2 mole excess of sodium ethoxide. The dimethyl acetal (103) (90 mg, 0.176 mmol) was dissolved in dry benzene (5 ml). Sodium (5 mg, 0.217 mmol, 1.23 mol equiv.) dissolved in dry ethanol (5 ml), was added to the dimethyl acetal solution. The resultant reaction mixture was then heated under reflux, under a nitrogen atmosphere. After 5 min at reflux, the reaction mixture changed from yellow to purple; after 20 h, the solution was yellow; however, when heating was stopped after 28 h, the reaction mixture became purple on cooling to room temperature. A few small lumps of solid carbon dioxide were added to the reaction mixture and then water (5 ml) was added. This mixture was evaporated to low volume

and then extracted with dichloromethane (3 x 20 ml). The combined extracts were washed with water, dried and evaporated to yield a residue, which by ^{1}H n.m.r. spectroscopy appeared to contain only starting material (103) and possibly some of the corresponding enone (100).

Attempted LDA mediated rearrangement of the 8α-p-nitrophenyl-7-thia cycloadduct (49b). A solution of diisopropylamine (80 mg, 0.79 mmol) in dry THF (5 ml) was cooled to -78°C (acetone-solid carbon dioxide bath) under a stream of nitrogen. n-Butyllithium in THF (0.5 ml, 1.6 M, 0.80 mmol) was added through a rubber septum from a syringe, with stirring. The cycloadduct (49b) (300 mg, 0.63 mmol), dissolved in dry benzene-dry THF (1:1) (10 ml), was then added from a syringe, and the stirring was continued at -78°C for 1 h. The cooling bath was removed and the reaction mixture was stirred for a further 1 h then diluted with water (5 ml) and evaporated to dryness. Water (10 ml) was added to the residue, which was then extracted with dichloromethane (4 x 20 ml). The combined extracts were washed with water, dried and evaporated. The ^{1}H n.m.r. spectrum (90 MHz) of the resultant residue showed that most of the material was recovered as unreacted cycloadduct.

Solvolysis of the 8α-p-nitrophenyl-7-thia cycloadduct (49b) in ethanol. A solution of the cycloadduct (49b) (94 mg, 0.2 mmol) in ethanol (33 ml) was heated under reflux for 2 d, with a silica gel drying tube attached to the condenser. The diethyl acetal (99) (33%) crystallised out from the reaction mixture. The mother liquer yielded the corresponding enone (100) (ca. 67%). This experiment was repeated under a nitrogen atmosphere and with more regard to keeping the apparatus and solvent dry. In this case the diethyl acetal was produced essentially free of the enone.

Shorter period of time at reflux. The above reaction was repeated with heating at reflux for 25 h. The diethyl acetal (99) was present along with the 6β-ethyl-6α-methyl

acetal (102), as judged by ^{1}H n.m.r. spectroscopy. See the sodium alkoxide catalysed rearrangements, previously described, for analytical data on these acetals.

Solvolysis of the dimethyl acetal (103) in ethanol. The dimethyl acetal (103) in ethanol-benzene, was heated under reflux for ca. 4 d. The only product was the diethyl acetal (99), as judged by ^{1}H n.m.r. spectroscopy.

Solvolysis of the phenolic diethyl acetal (99) in refluxing methanol. The diethyl acetal (99) (51 mg, 9.5 x 10^{-5} mol) was dissolved in dry benzene (5 ml) and dry methanol (5 ml). The solution was heated under reflux and under a nitrogen atmosphere for 20 h. Evaporation of the solvent yielded a pale yellow powder. Assuming that no starting diethyl acetal (99) is now present, the ^{1}H n.m.r. spectrum (90 MHz) showed the presence of three products. They were the 6α-ethyl-6β-methyl acetal (101) (ca. 70%), the 6β-ethyl-6α-methyl acetal (102) (ca. 20%) and the 6,6-dimethyl acetal (103) (ca. 10%). This reaction mixture was dissolved in 1:1 benzene-methanol mixture (10 ml) and heated under reflux for a further 20 h. Again, a pale yellow powder appeared on evaporation of the solvent. The ^{1}H n.m.r. spectrum (90 MHz) gave the 6α-ethyl-6β-methyl acetal (101) (ca. 60%), the 6β-ethyl-6α-methyl acetal (102) (ca. 20%) and the dimethyl acetal (103) (ca. 20%). This experimental procedure was repeated giving, after 60 h at reflux, the ratio of (101):(102):(103) as ca. 50%:20%:30%. After 10 days total reflux, the dimethyl acetal (103) was solely present along with some of the corresponding enone (100). See p 134 and 135 for analytical data relating to the acetals (101), (102) and (103), respectively.

Solvolysis of the 6α-ethyl-6β-methyl acetal (101) in ethanol. The mixed acetal (101) was heated under reflux for 18 h. An ca. 1:1 mixture of the mixed acetal (101) and the diethyl acetal (99) was observed, as judged by ^{1}H n.m.r. spectroscopy.

Raney nickel desulphurisation of the ethyl ester 7-thia cycloadduct (49a). A mixture of W-2 Raney nickel[27] (1.2 g of slurry) and the cycloadduct (49a) (165 mg, 0.38 mmol) in dry ethanol (35 ml) was stirred and heated under reflux, under a nitrogen atmosphere, for 3 h. The entire reaction mixture was filtered through a pad of Celite and the filtrate evaporated to yield a gum (80 mg). This gum appeared to consist of only two products, (114) and (115), in the ratio 45:55 respectively, as judged by ^{1}H n.m.r. (90 MHz) spectroscopy. Preparative t.l.c. of this gum on silica plates developed with diethyl ether gave, as the faster running band, R_f 0.45, ethyl 6,7-didehydro-3,6-dimethoxy-4,5α-epoxy-17-methylmorphinan-14β-ylacetate (114), m.p. 72-74°C (of a solidified gum). [Found: m/z 399.2038 (100%) and 312.1611 (27). $C_{23}H_{29}NO_5$ requires M, 399.2045 and (M-$C_4H_7O_2$), 312.1599]; $\upsilon_{max.}$ (KBr) 1 728, 1 663, 1 551 and 1 443 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.24 (t, J 7.1 Hz, OCH_2CH_3), 1.52 (br d, J ca. 8 Hz, 15 $_{eq.}$-H), 1.85 (dd, J 16.5 and 1.4 Hz, 8β-H), 2.07 (dd, J 16.5 and 6.8 Hz, 8α-H), 2.29 (s, NMe), 2.31-2.52 (m, 10α- and $16_{eq.}$-H), 2.76 (d, J 14.0 Hz, 18-H), 3.03 (d, J 19.6 Hz, 10β-H), 3.18 (d, J 12.8 Hz, 18-H), 3.20 (d, partially obscured by d at δ 3.18, 9-H), 3.45 (s, 6-OMe), 3.80 (s, 3-OMe), 4.04 and 4.08 (qABq, J 7.1 and 10.6 Hz, OCH_2CH_3), 4.61 (dd, J 6.7 and 2.0 Hz, 7-H), 4.74 (d, J 1.3 Hz, 5-H), 6.59 (d, J 8.2 Hz, 1-H) and 6.66 (d, J 8.2 Hz, 2-H); δ_C (50.3 MHz; $CDCl_3$) 14.2 (OCH_2CH_3), 20.4 (C-10), 27.7 and 30.1 (C-8 and -18), 36.4 (C-15), 41.2 (C-14), 43.1 (NMe), 45.5 (C-13), 45.6 (C-16), 54.3 (6-OMe), 56.3 (3-OMe), 59.9 (OCH_2CH_3), 60.2 (C-9), 87.3 (C-7), 96.7 (C-5), 113.4 (C-2), 118.1 (C-1), 126.8 (C-11), 130.9 (C-12), 143.1 (C-3), 144.3 (C-4), 151.4 (C-6) and 173.1 (C-19). The slower running band, R_f ca. 0.2, was found to be the ethyl (18R)-6,7-didehydro-3,6-dimethoxy-4,5α-epoxy-8β,14β-methano-17-methylmorphinan-18-ylacetate (115), m.p. 153-156 °C (from propan-2-ol); δ_H (200 MHz; $CDCl_3$) 1.28 (t, J 7.1 Hz, OCH_2CH_3), 1.42 (d, J 3.7 Hz, 18-H), 1.76 (br d, J ca. 12 Hz, $15_{eq.}$-H), 2.05 (dd, J 5.8 and 3.8 Hz, 8-

H), 2.29 (s, NMe), 3.13 (d, J 18.4 Hz, 10β-H), 3.44 (s, 6-OMe), 3.83 (s, 3-OMe), 4.14 and 4.16, (qABq, J 7.1 and 10.8 Hz, OCH_2CH_3), 4.57 (s, 5-H), 5.03 (d, J 5.9 Hz, 7-H), 6.68 (d, J 8.2 Hz, 1-H) and 6.72 (d, J 8.2 Hz, 2-H); δ_C (50.3 MHz; $CDCl_3$) 14.3 (OCH_2CH_3), 22.9 (C-10), 25.4 (C-8), 34.2 (C-15), 37.0 (C-18), 42.8 (NMe), 43.2 (C-13 or -14), 46.9 (C-16), 54.8 (6-OMe), 55.3 (C-9), 56.6 (3-OMe), 60.6 (OCH_2CH_3), 84.8 (C-7), 98.6 (C-5), 114.1 (C-2), 119.2 (C-1), ca. 127.8 (C-11), ca. 131.4 (C-12), 142.8 (C-3), 143.6 (C-4), 150.0 (C-6) and 171.6 (C-19), signal for C-13 or -14 was too weak to be identified. m/z 397 (M) (60%), 382 (29), 324 (37), 310 (39), 86 (62) and 84 (100).

Larger scale Raney nickel desulphurisation of the ethyl ester 7-thia-cycloadduct (49a). A mixture of W-2 Raney nickel[27] (14 g of slurry in ethanol at pH ca. 7) and the cycloadduct (49a) (3.0 g, 7.0 mmol) in ethanol (50 ml) was stirred and heated under reflux for 3 h. The entire reaction mixture was transferred by decantation to a Soxhlet thimble (3 x 10 cm) and the nickel residues were extracted with refluxing ethanol (200 ml) during 2 h. The extract was then filtered through a pad of Celite (CAUTION:- the nickel residues must be kept moist). Evaporation of the filtrate yielded a gum (2.6 g). This gum was chromatographed on a silica column (ca. 3 x 20 cm) and ca. 20-25 ml fractions were taken. Elution with diethyl ether-light petroleum (1:10) gave 5 fractions containing only solvent. Elution with the solvents in the ratio 1:5 gave 4 fractions again containing only solvent. With the solvent ratio at 3:10, the next 5 fractions (A-E), which were combined, contained the 4 products (116), (117), and 2 unknowns (119) and (120). T.l.c. on silica plates developed with diethyl ether gave the 2 major compounds (116) and (119), R_f 0.64 and 0.66, respectively. The next 5 fractions (F-J) together contained 3 products (121), (114) and (115). On the same t.l.c. system as before, the product (114) has R_f 0.45, while products (121) and (115) have lower values. The subsequent 4 fractions (K-N) together gave the 3 products (122), (121) and (115). The combined

fractions (O-Q) contained the didehydro product (115) as the only significant product. The eluent was then changed to diethyl ether. The resulting fractions (R-W) apparently contained 2 products (115) and (123). No further material was eluted from the column.

Fractions A-E. These combined fractions were evaporated to yield a residue (74 mg) which was chromatographed by preparative t.l.c. on silica plates. With triple elution in diethyl ether-hexane (3:7), the faster running band (23 mg), containing two, co-running, dethioacetals (116) and (117) in the ratio 82:18, gave the following n.m.r. signals. The major component, the 6β-ethyl-6α-methyl acetal (116) gave δ_H (200 MHz; $CDCl_3$) 1.19 and 1.22 (overlapping t, J 7.1 Hz, 6α-$OCH_2\underline{C}H_3$ and $CO_2CH_2\underline{C}H_3$), 1.61 (br d, J ca. 11 Hz, $15_{eq.}$-H), 2.15 (td, J 12.1 and 5.0 Hz, $16_{ax.}$-H), 2.36 (s, NMe), 3.03 (br d, J 18.5 Hz, 10β-H), 3.42 (s, 6β-OMe), 3.85 (s, 3-OMe), 3.98-4.17 (m, 6α-$O\underline{C}H_2CH_3$ and $CO_2\underline{C}H_2CH_3$), 4.68 (d, J 1.2 Hz, 5-H), 5.60 (dd, J 10.3 and 1.2 Hz, 7-H), 5.89 (d, J 10.6 Hz, 8-H), 6.51 (d, J 8.2 Hz, 1-H) and 6.61 (d, J 8.2 Hz, 2-H); δ_C (50.3 MHz; $CDCl_3$) 14.2 and 14.9 (6β-$OCH_2\underline{C}H_3$ and $CO_2CH_2\underline{C}H_3$), 20.6 (C-10), 30.4 (C-18), 37.2 (C-15), 41.2 (C-14), 43.7 (NMe), 46.2 (C-16), 47.5 (C-13), 49.6 (6β-OMe), 56.2 (6β-$O\underline{C}H_2CH_3$), ca. 57.2 (3-OMe), 59.4 (C-9), 59.8 ($CO_2\underline{C}H_2CH_3$), 92.9 (C-5), 95.9 (C-6), 114.5 (C-2), 118.7 (C-1), ca. 127.2 (C-11), 132.0 (C-7), 132.3 (C-12), 136.8 (C-8), 141.9 (C-3), ca. 145.2 (C-4) and 172.7 ($\underline{C}O_2Et$). The minor component, believed to be the 6,6-diethyl acetal (117) gave similar ^1H and ^{13}C signals except for the following; δ_H 3.83 (s, 3-OMe), 5.61 (dd, J 10.4 and 1.2 Hz, 7-H) and 5.88 (d, J 10.3 Hz, 8-H); the mass spectrum of the mixture gave (assignments are tentative) m/z 457 [M, 13% (117)] and 443 [M, 76% (116)]. The slower running band (43 mg), containing 2, co-running unidentified products (119) and (120), in the ratio 86:14, gave the following n.m.r. signals. The major component gave δ_H (200 MHz; $CDCl_3$) 1.19 (t, J 7.1 Hz, $OCH_2\underline{C}H_3$), 1.62 (dd, J 12.9 and ca. 2.5 Hz, $15_{eq.}$-H), 2.17 (td, J 10.8 and ca. 3 Hz,

$16_{ax.}$-H), 2.33 (s, NMe), 2.92 (br d, J 18.4 Hz, 10β-H), 3.69 (s, 6-OMe), 3.84 (s, 3-OMe), 3.92 (br d, J 5.7 Hz, 9-H), 4.02 (complex multiplet, $OC\underline{H}_2CH_3$), 4.33 (1H, d, J 9.7 Hz), 4.69 (1H, d, J 9.7 Hz), 5.70 (1H, d, J 13.4 Hz), 6.15 (1H, d, J 13.4 Hz), 6.57 (d, J 8.2 Hz, 1-H) and 6.69 (d, J 8.2 Hz, 2-H); δ_C (50.3 MHz; $CDCl_3$) 14.1 ($OCH_2\underline{C}H_3$), 20.8 (C-10), 31.3 (C-18), 37.0 (C-15), 43.2 (NMe), 45.9 (C-14), 46.0 (C-16), 47.4 (C-13), 51.5 (CH), 56.3 (6-OMe), 59.5 (3-OMe), 60.1 ($O\underline{C}H_2CH_3$), 61.8 (C-9), 81.8 (CH_2), 93.7 (CH), 113.3 (C-2), 118.6 (C-1), 121.2 (CH), 127.5 (C-11), 131.2 (C-12), 142.3 (C-3), 145.8 (C-4), 148.1 (C), 166.3 (C) and 172.9 (C-19). The minor component gave similar ^1H and ^{13}C signals except for the following; δ_H 2.37 (s, NMe), 3.67 (s, 6-OMe), 3.84 (s, 3-OMe), 5.68 (1H, d, J 13.4 Hz) and 6.13 (1H, d, J 13.4 Hz); and δ_C 113.8 (C-2), 119.0 (C-1) and 172.6 (C-19); the mass spectrum of the mixture gave (assignments are tentative) m/z 429 [M, 12% (minor)], 415 [M, 80% (major)], 342 [(M-$C_4H_7O_2$), 37 (minor)], 328 [(M-$C_4H_7O_2$), 19 (major)] and 230 (100).

Fractions F-J. On standing overnight, these combined fractions produced a small amount of crystals which were filtered off. These crystals were combined with those formed from the combined fractions of K-N and analysed (see Fractions K-N for data). The filtrate from fractions F-J was evaporated to yield a residue (242 mg) which was shown to contain, as judged by ^1H n.m.r. (90 MHz) spectroscopy, the 3 compounds (121), (114) and (115) in the ratio of 50:35:15. The major product, tentatively assigned as the 5,6-didehydro-4-hydroxymorphinan (121), gave the following ^1H n.m.r. signals, (90 MHz; $CDCl_3$) 1.23 (t, J 7 Hz, $OCH_2C\underline{H}_3$), 2.30 (s, NMe), 3.56 (s, 6-OMe), 3.78 (s, 3-OMe), 4.05 (q, J 7 Hz, $OC\underline{H}_2CH_3$), 5.40 (s, 5-H), 5.95 (br s, OH) and 6.61 (m, 1- and 2-H). The other 2 products (114) and (115) were identical to the two desulphurised products obtained from the small scale desulphurisation experiment (see page 139 for

analytical data). They were the 6,7-didehydro-4,5α-epoxymorphinan (114) and the 8β,14β-methanomorphinan ethyl 18-carboxylate (115).

Fractions K-N. These fractions were combined and allowed to stand overnight. The crystals that formed were combined with those from fractions F-J. These crystals (230 mg) were found to be the pure 6,7-didehydro-4-hydroxymorphinan (122), m.p. 166-168°C (from methanol) [Found: m/z 401.2210 and 314.1748. $C_{23}H_{31}NO_5$ requires M, 401.2202 and (M-$C_4H_7O_2$), 314.1756]; δ_H (200 MHz; $CDCl_3$) 1.26 (t, J 7.1 Hz, OCH_2CH_3), 1.59 (br d, J ca. 11 Hz, $15_{eq.}$-H), 1.91 (td, J 11.9 and 4.7 Hz, $16_{ax.}$-H), 1.9-2.4 (m, contains 8α- and 8β-H), 2.26 (s, NMe), 2.52 (d, J 13.8 Hz, 18-H), 2.80 (dd, J 18.4 and 6.1 Hz, 10α-H), 2.94 (d, J 18.2 Hz, 10β-H), 3.15 (d, J 5.9 Hz, 9-H), 3.22 (dd, J 13.9 and 1.5 Hz, 18-H), 3.44 (s, 6-OMe), 3.81 (s, 3-OMe), ca. 4.06 (m, obscured by OCH_2CH_3 signal, 5α-H), 4.11 and 4.14 (qABq, J 7.1 and 10.7 Hz, OCH_2CH_3), 4.35 (dt, J 5.4 and 2.3 Hz, 7-H), 6.14 (s, OH, exch. with D_2O), 6.59 (d, J 8.3 Hz, 1-H) and 6.67 (d, J 8.3 Hz, 2-H); δ_C (50.3 MHz; $CDCl_3$) 14.4 (OCH_2CH_3), 23.6 (C-10), 27.9 (C-8), 32.7 (C-5 and -18), 34.7 (C-15), 39.0 and 39.2 (C-13 and -14), 43.0 (NMe), 46.4 (C-16), 53.9 (6-OMe), 56.0 (3-OMe), 56.5 (C-9), 59.8 (OCH_2CH_3), 90.5 (C-7), 108.3 (C-2), 117.9 (C-1), 126.2 (C-11), 131.6 (C-12), 144.2 and 144.3 (C-3 and -4), 153.5 (C-6) and 173.6 (C-19). The filtrate from the crystals was evaporated down to yield a residue (264 mg). This residue was found to contain 3 compounds, the 6,7-didehydro-4-hydroxymorphinan (122), the 5,6-didehydro-4-hydroxymorphinan (121) and the 8β,14β-methanomorphinan ethyl 18-carboxylate (115) in the approximate ratio 7:2:1, respectively.

Fractions O-Q. These fractions were combined and evaporated to yield a residue (866 mg). This residue appeared to contain, as judged by ^1H n.m.r. (90 MHz) spectroscopy, 4 products. One of them was the 8β,14β-methanomorphinan ethyl 18-

carboxylate (115); the remaining 3 compounds are believed to be the dihydro derivatives of the enol ethers already identified [see (114), (121) and (122) in the 'Results and Discussion' Section 2.4.1, page 72].

Fractions R-W. These fractions were combined and evaporated to yield a residue (611 mg). This residue was crystallised from propan-2-ol. These crystals appeared to contain 2 products, as judged by ^{1}H n.m.r. (90 MHz) spectroscopy. They are believed to be the phenolic 6,7-didehydro-8β,14β-methanomorphinan (123) and the 4,5α-epoxy-8β,14β-methanomorphinan (115), present in the ratio 3:1, respectively. The phenolic morphinan (123) gave the following ^{1}H n.m.r. signals; δ_H (90 MHz; $CDCl_3$) 1.26 (t, J 7 Hz, $OCH_2\underline{CH_3}$), 2.27 (s, NMe), 3.33 (s, 6-OMe), 3.80 (s, 3-OMe), 4.13 (q, J 7 Hz, with fine splitting, $OCH_2\underline{CH_3}$), 4.69 (dd, J 6 and 2 Hz, 7-H), 6.15 (br s, OH), 6.62 (d, J 8Hz, 1-H) and 6.66 (d, J 8 Hz, 2-H). The 4,5α-epoxy morphinan (115) has similar chemical shifts of the appropriate signals, except that the 6-OMe singlet appears at δ 3.44.

Raney nickel desulphurisation of the ethyl ester 5β,14β-thiaethanomorphinan (86). The thiaethanomorphinan (86) (157 mg, 0.38 mmol) and W-2 Raney nickel[27] (0.8 g of slurry) in ethanol (12 ml), were stirred and heated under reflux for 6 h. The entire reaction mixture was transferred to a Soxhlet thimble and the nickel residues were extracted with refluxing ethanol (50 ml) during 1 h. The resultant green solution was evaporated to dryness. The resultant residue (167 mg) was chromatographed by preparative t.l.c. on silica plates developed with diethyl ether. The major band, R_f 0.4, yielded a gum (110 mg) which was found to contain 2 products, as judged by ^{1}H n.m.r. spectroscopy (90 MHz), in the ratio 4:1. The major product was the 14β-alkyl ketone (128) (see page 144 for analytical data) and the minor product was the α,β-unsaturated derivative (129) (see following experiment for analytical data).

Preparation of ethyl 7,8-didehydro-4-hydroxy-3-methoxy-17-methyl-6-oxomorphinan-14β-ylacetate[80] (129). Freshly prepared W-2 Raney nickel[27] was deactivated in dry acetone with heating under reflux for 90 min. The acetone was decanted off and the nickel was washed several times with dry ethanol. The 5β,14β-thiaethanomorphinan (86) (148 mg, 0.36 mmol) was heated in ethanol (10 ml) with deactivated Raney nickel (W-2) (1.3 g of slurry) under reflux for 6 h. T.l.c. of the reaction mixture at this time on silica, developed with diethyl ether, gave a spot at R_f 0.4 for the desulphurised enone, with no visible spot at R_f 0.5 corresponding to the starting material. The entire reaction mixture was transferred by decantation to a Soxhlet thimble (1 x 5 cm) and the nickel residues were extracted with refluxing ethanol (50 ml) during 2 h. The extract was then filtered through a pad of Celite (CAUTION - keep moist). Evaporation of the filtrate yielded a greenish yellow gum (100 mg), which was chromatographed on a short silica column using diethyl ether as eluent. Evaporation of the solvent yielded the desulphurised enone (129) as a white foam (76 mg, 55%). This enone (129) had m.p. >213°C (decomp.) (from propan-2-ol); $\upsilon_{max.}$ (KBr) 3 410, 1 729, 1 679, and 1 262 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.25 (t, J 7.1 Hz, OCH_2CH_3), 2.32 (s, NMe), ca. 2.60 (d, J ca. 18 Hz, 5β-H), ca. 2.75 (br d, J ca. 15 Hz, 10α-H), ca. 3.02 (d, J ca. 19 Hz, 10β-H), 3.80 (s, 3-OMe), 4.12 (q, J 7.1 Hz, OCH_2CH_3), 4.28 (d, J 18 Hz, 5α-H), 5.77 (dd, J 10.1 and 1.2 Hz, 7-H), ca. 6.10 (br s, OH, exch. with D_2O), 6.58 (dt, J 8.3 and 0.9 Hz, 1-H), 6.64 (d, J 8 Hz, 2-H) and 7.05 (dd, J 10.1 and 0.5 Hz, 8-H); δ_C (50.3 MHz; $CDCl_3$) 14.2 (OCH_2CH_3), 24.8 (C-10), 29.7 (C-15), 37.3 (C-18), 42.1 (C-5), 42.7 (NMe), 47.0 (C-16), 56.1 (3-OMe), 56.4 (C-9), 60.5 (OCH_2CH_3), 108.8 (C-2), 118.4 (C-1), 129.7 (C-7), 143.8 (C-3 or -4), ca. 145.0 (C-4 or -3), 153.5 (C-8) and 171.9 (CO_2Et), signals for C-6, -11, -12, -13 and -14 were too weak to identify; m/z 385 (M) and 298 ($M-C_4H_7O_2$).

Attempted hydrogenation of the 7,8-didehydromorphinan (129). The 7,8-didehydromorphinan (129) (230 mg, 0.60 mmol) was dissolved in warm methanol (10 ml). The catalyst, 10% palladium on charcoal (50 mg), was added and the mixture was then stirred under a hydrogen atmosphere for 72 h. The reaction mixture was filtered through a pad of Celite and the filtrate was then evaporated to dryness. The ^1H n.m.r. spectrum of the residue showed that only starting material was present.

Attempted hydrogenation of the 7,8-didehydromorphinan (129) in the presence of acid. The 7,8-didehydromorphinan (129) (73 mg, 0.19 mmol) was dissolved in ethanol (5 ml). The catalyst, 10% palladium on charcoal (30 mg), was added to the solution along with 2N hydrochloric acid (0.3 ml). This mixture was stirred under a hydrogen atmosphere for 20 h. The reaction mixture was filtered through a thin pad of Celite and the filtrate was evaporated to dryness. The residue was dissolved in water (5 ml) and then extracted with dichloromethane (3 x 10 ml). The combined extracts were dried and evaporated to give a residue (62 mg). The ^1H n.m.r. spectrum showed only starting material to be present.

Attempted high pressure hydrogenation of the 7,8-didehydromorphinan (129). A solution of the 7,8-didehydromorphinan (129) (200 mg, 0.52 mmol) in ethanol (30 ml) and 2N hydrochloric acid (0.5 ml) was prepared. The catalyst, 10% palladium on charcoal (100 mg), was added to the hydrogenation bomb and then covered with the solution of the morphinan. The hydrogenation bomb was evacuated and then flushed with hydrogen. This process was repeated, then the pressure was set at 100 psi and the mixture shaken for 2.5 h. The reaction mixture was filtered through a pad of Celite and then evaporated to dryness. The residue was dissolved in water (15 ml), then a dilute sodium hydrogencarbonate solution was added until the mixture was slightly basic. This was extracted several times with dichloromethane. The combined extracts were washed

3 times with water, dried and evaporated. The ^1H n.m.r. spectrum showed only starting material to be present.

Attempted reduction of ethyl 7,8-didehydro-4-hydroxy-3-methoxy-17-methyl-6-oxomorphinan-14β-ylacetate (129) with dithionite. The 7,8-didehydromorphinan (129) (87 mg, 0.23 mmol) was dissolved in warm methanol (10 ml). 1.0 M Sodium hydrogencarbonate (2 ml) was added, causing precipitation to occur. Sodium dithionite (210 mg, 1.21 mmol) was added and then this mixture was heated under reflux for 1 h, during which time the precipitate apparently did not dissolve. The reaction mixture was evaporated to dryness and the residue was dissolved in dichloromethane (10 ml) and water (10 ml). The yellow aqueous layer was further extracted with dichloromethane (4 x 30 ml), and the combined extracts were dried and evaporated. Preparative t.l.c. of the resultant residue on silica, with diethyl ether as eluent, gave several bands, the major band being at R_f ca. 0.5. Elution of this band with diethyl ether gave a white residue, the ^1H n.m.r. spectrum of which showed that this fraction contained the methyl ester equivalent of the starting material. The methyl ester (130) (40 mg, 47%) had m.p. 171-173°C (from propan-2-ol); [Found: m/z 371.1725 (42%) and 298.1426 (100). $C_{21}H_{25}NO_5$ requires M, 371.1733 and (M-$C_3H_5O_2$), 298.1443]; $\upsilon_{max.}$ (KBr) 1 723, 1 675, 1 655, 1 485 and 1 432 cm^{-1}; δ_H (90 MHz; $CDCl_3$) ($CHCl_3$ signal at δ 7.28) 2.37 (s, NMe), 3.68 (s, CO_2Me), 3.82 (s, 3-OMe), 4.31 (d, J 18 Hz, 5α-H), 5.83 (d, J 10 Hz, 7-H), 6.14 (br s, OH, exch. with D_2O), 6.58 (d, J 8 Hz, 1-H), 6.69 (d, J 8 Hz, 2-H) and 7.08 (d, J 10 Hz, 8-H).

Attempted Raney nickel desulphurisation of the 8α-p-nitrophenyl-7-thia cycloadduct (49b). A mixture of the 7-thia cycloadduct (49b) (230 mg, 0.48 mmol) and freshly prepared W-2 Raney nickel[27] (2.2 g of slurry) in ethanol (30 ml), was heated under reflux for 40 min. T.l.c. of the reaction mixture at this time, using silica plates

developed with diethyl ether and with detection by iodine vapour, showed a major spot at R_f 0.5 with a minor spot at R_f <0.1, with no visible spot at R_f 0.75 corresponding to the starting material. The reaction mixture was filtered through a pad of Celite. The nickel residues were washed several times with hot ethanol and the combined filtrates were evaporated to yield a yellow gum (146 mg). The ^1H n.m.r. spectrum of this gum gave several possible 3-OMe, 6-OMe and NMe signals suggesting multiple products. However, a broad but clear triplet at ca. δ 1.22 suggests that the amino group, presumably produced during the reaction, had undergone N,N-diethylation. No further work was carried out on this gum.

Preparation of [19(S)-(4-aminophenyl)]-7,8-didehydro-4-hydroxy-3-methoxy-17-methyl-6-oxo-5β,14β-thiaethanomorphinan (131).

(a) From the p-nitrophenyl enone

The p-nitrophenyl enone (100) (1.30 g, 2.80 mmol) was dissolved, with heating, in ethanol (50 ml) and then added to a mixture of stannous chloride dihydrate (3.0 g, 13.3 mmol) in concentrated hydrochloric acid (5 ml, 36% w/w) and ethanol (20 ml). The resultant mixture was heated under reflux for 1 h and was then evaporated to low volume. Water (25 ml) was added and the resultant mixture was carefully treated with saturated aqueous sodium hydrogencarbonate until effervescence ceased and the solution was slightly alkaline. The solution was extracted with dichloromethane (3 x 40 ml) and the combined extracts were washed with water (2 x 40 ml) and dried. Evaporation of the solvent yielded the required anilino enone (131) as a yellow crystalline solid (0.85 g, 70%), m.p. 296-298°C (decomp.) (from aqueous dimethyl sulphoxide, the crystals being washed several times with diethyl ether; or from benzene-methanol) (Found: C, 67.6; H, 6.0; N, 6.3; m/z 434.1663 (100%). $C_{25}H_{26}N_2O_3S$ requires C, 69.1; H, 6.0; N, 6.4%; M, 434.1664); $\upsilon_{max.}$ (KBr) 3 450, 1 670, 1 620, 1 510, 1 485, and 1 280 cm^{-1}; δ_H (200

MHz; $CDCl_3$) 1.60 (dd, J 12.7 and 3.5 Hz, $15_{eq.}$-H), 2.10 (td, J 13 and ca. 4 Hz, $16_{ax.}$-H), 2.42 (s, NMe), 2.55 (m, $15_{ax.}$-H, $16_{eq.}$-H and 10α-H), 3.07 (d, J 5.7 Hz, 9-H), 3.14 (d, J 18.8 Hz, 10β-H), 3.77 (s, 3-OMe), 4.72 (d, J ca. 1 Hz, 5-H), 5.76 (s, 19-H), 5.95 (d, J 9.9 Hz, 8-H), 6.02 (dd, J 9.9 and 1.6 Hz, 7-H), ca. 6.0 (v br s, OH, exch. with D_2O), 6.58 (m, 1-, 2-, 22- and 24-H), and 7.13 (d, J 8.3 Hz, 21- and 25-H); δ_C (50.3 MHz; $CDCl_3$) 25.3 (C-10), 29.5 (C-15), 42.6 (NMe), 45.8 (C-16), 52.2 (C-14), 53.2 and 55.0 (C-5 or -18), 55.6 (C-13), 55.9 (3-OMe), 59.3 (C-9), 108.7 (C-2), 114.6 (C-22 and -25), 117.9 (C-1), 124.6 and 125.0 (C-11 or -20), 130.8 (C-21 and -25), 130.9 (C-7), 142.7, 144.7 and 145.9 (C-3, -4 and -23) and 194.8 (C-6), signal for C-12 was too weak or obscured to be identified.

(b) From the p-nitrophenyl cycloadduct

The same experimental procedure and relative quantities were used as before, except that the p-nitrophenyl enone (100) was replaced with the p-nitrophenyl cycloadduct (49b). The ^1H n.m.r. specrum (90 MHz) gave identical signals and melting point, to that of the enone produced in the previous experiment. The yield of the anilino enone (131) was 65%.

Raney nickel desulphurisation of the anilinoenone (131) in ethanol. Under a nitrogen atmosphere, the anilino enone (131) (134 mg, 0.31 mmol) and W-2 Raney nickel[27] (1.0 g of slurry) were stirred in ethanol (12 ml) and heated under reflux for 18 h. The entire reaction mixture was transferred by pipette to a Soxhlet thimble (1 x 5 cm) and the nickel residues were extracted with refluxing ethanol (50 ml) during 90 min. The extract was filtered through a pad of Celite and then evaporated to yield a deep red residue (92 mg). Preparative t.l.c. of this residue on silica plates developed with diethyl ether gave the 8β,14β-methano-18-(N,N-diethyl-p-aminophenyl)morphinan (132); δ_H (200 MHz; $CDCl_3$) 1.13 [t, J 7.0 Hz, $N(CH_2CH_3)_2$], 1.37 (m, 8-H), 2.01 (m), 2.13 (s,

NMe), 2.25 (dd, J 18.9 and 4.4 Hz, 7α-H), 2.27 (d, J 18.9 Hz, 5β-H), 2.55 (d, J 5.0 Hz, 18-H), 2.71 (d, J 0.9 Hz, possibly part of dd, 7β-H), 3.00 (dd, J 18.4 and ca. 6.0 Hz, 10α-H), 3.18 (s, possibly part of d, 10β-H), 3.32 [q, J 7.1 Hz, $N(C\underline{H}_2CH_3)_2$], 3.82 (s, 3-OMe), 4.38 (d, J 18.9 Hz, 5α-H), ca. 5.85 (v br s, OH), 6.62 (d, J 8.8 Hz, 21- and 23-H), 6.65 (d, J ca. 7.4 Hz, 1-H), 6.69 (d, J 8.3 Hz, 2-H) and 7.17 (d, J 8.6 Hz, 20- and 24-H); δ_C (50.3 MHz; $CDCl_3$) 12.5 [$N(CH_2\underline{C}H_3)_2$], 19.3 (C-8), 27.6 (C-18), 28.8 (C-10), 31.4 (C-14), 33.6 (C-15), 37.0 (C-13), 38.0 (C-7), 41.5 (NMe), 44.3 [$N(\underline{C}H_2CH_3)_2$], 44.7 (C-5), 47.1 (C-16), 55.3 (C-9), 56.0 (3-OMe), 109.2 (C-2), 111.7 (C-21 and -23), 119.3 (C-1), 123.8 (C-11 or -19), 125.2 (C-19 or -11), 130.0 (C-20 and -24), 131.0 (C-12), 143.3 (C-22), 144.8 (C-3), 146.5 (C-4) and 208.8 (C-6); m/z 460 (M) (13%) and 230 ($C_{15}H_{20}NO$ or $C_{14}H_{16}NO_2$) (100).

Raney nickel desulphurisation of the anilinoenone (131) in methanol. Under a nitrogen atmosphere, the anilino enone (131) (108 mg, 0.25 mmol) and W-2 Raney nickel[27] (1.5 g of slurry) were stirred in methanol (15 ml) and heated under reflux for 24 h. The reaction mixture was filtered through a pad of Celite. The nickel residues were washed several times with hot methanol and the combined filtrates were evaporated to dryness. Preparative t.l.c. of the resultant residue, on silica plates developed with diethyl ether, gave two bands with R_f values 0.4 and 0.1. The faster running product, the 14β-(N,N-dimethyl-p-aminophenyl)methylmorphinan (134) (22 mg, 20%) gave δ_H (200 MHz; $CDCl_3$) 2.29 (s, NMe), 2.63 (d, J 15.2 Hz, 5β-H), 2.94 (s, NMe_2), 3.79 (d, J 2.6 Hz), 3.81 (s, 3-OMe), 4.21 (dd, J 15.8 and ca. 1.5 Hz, 5α-H), 6.22 (s, OH), 6.54 (d, J 8.3 Hz, 1-H), 6.65 (d, J 8.3 Hz, 2-H), 6.71 (d, J 8.8 Hz, 21- and 23-H) and 7.19 (d, J 8.2 Hz, 20- and 24-H); δ_C (50.3 MHz; $CDCl_3$) 23.1 (C-8), 26.3 (C-10), 31.7 and 32.1 (C-15 or -18), 38.2 (C-7), 40.6 and 40.7 (NMe_2), 42.4 (NMe), 44.2 (C-13), 44.9 (C-5), 46.6 (C-16), 55.4 (C-9), 56.1 (3-OMe), 108.7 (C-2), 112.2 (C-21 and -23), 118.1 (C-1), 126.7 (C-

11), 131.5 (C-20 and -24), 131.8 (C-12), 144.3 (C-3), 149.1 (C-4) and 211.9 (C-6), signals for C-13, -19 and -22 were too weak to identify; m/z 434 (M) (7%), 300 (M-$C_9H_{12}N$) (9), 230 (27) and 134 ($C_9H_{12}N$) (100). The slower running product, the 8β,14β-methano-18-(N,N-dimethyl-p-aminophenyl)morphinan (133) (30 mg, 28%) [Found: m/z 432.2398 (18%) and 230.1167 (100). $C_{27}H_{32}N_2O_3$ requires M, 432.2413 and (M-$C_{13}H_{16}NO$), 230.1181]; $\upsilon_{max.}$ ($CHCl_3$) 3 515, 3 400, 3 018, 1 752 (w), 1 721 (s), 1 710 (s), 1 614, 1 520 and 1 480 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.31 (m, 8-H), 2.01 (m), 2.09 (s, NMe), 2.27 (d, J 18.5 Hz, 5β-H), 2.28 (d, J 19.2 Hz, possibly dd, J 19.2 and ca. 3 Hz, 7β-H), 2.58 (br d, J 19.4 Hz, 7α-H), 2.92 (s, NMe_2), 3.82 (s, 3-OMe), 4.36 (d, J 18.5 Hz, 5α-H), ca. 6.1 (v br s, OH), 6.58-6.73 (m, 1-, 2-, 21- and 23-H) and 7.29 (d, J 8.5 Hz, 20- and 24-H); δ_C (50.3 MHz; $CDCl_3$) 19.9 (C-8), 27.5 (C-18), 29.5 (C-10), 35.6 (C-15), 37.2 (C-13), 38.2 (C-7), 40.7 (NMe_2), 42.0 (NMe), 44.8 (C-5), 47.4 (C-16), 55.0 (C-9), 56.1 (3-OMe), 108.9 (C-2), 112.3 (C-20 and -24), 119.1 (C-1), ca. 125.8 and ca. 126.4 (C-11 or -19), 130.2 (C-21 and -23), ca. 132.3 (C-12), 143.4 (C-22), 144.7 (C-3), 149.2 (C-4), signal for C-6 not given since low field spectrum, >δ 185, was not printed.

Raney nickel desulphurisation of the anilinoenone (131) in methanol with prolonged reflux. The same conditions were used as before, except that the reaction mixture was stirred and heated under reflux for 72 h. After the normal work-up, the 90 MHz, ^1H n.m.r. spectrum of the reaction mixture showed a spectrum virtually identical to that of the previous reaction, except that the 17-NMe signal of the 14β-(N,N-dimethyl-p-aminophenyl)methylmorphinan (134) appeared smaller. No further work was carried out on this reaction mixture.

Raney nickel desulphurisation of the phenyl enone (138). Freshly prepared W-2 Raney nickel[27] was deactivated in dry acetone with heating under reflux for 2 h. The

acetone was decanted off and the nickel was washed several times with dry ethanol. Under a nitrogen atmosphere, deactivated W-2 Raney nickel (1.59 g of slurry) and the phenyl enone (49c) (142 mg, 0.34 mmol) in dry ethanol (30 ml) were stirred and heated under reflux for 20 h. The entire reaction mixture was transferred to a Soxhlet thimble (1 x 5 cm) and the nickel residues were extracted with refluxing dry ethanol (50 ml) during 90 min. The extract was evaporated to yield a residue which was chromatographed by preparative t.l.c. on silica plates developed with diethyl ether, to give, at R_f 0.2, the 4-hydroxy-8β,14β-methano-3-methoxy-17-methyl-18-phenyl-morphinan-6-one (139) (34 mg, 26%) as a gum. (Found: m/z 389.1979 (14%) and 230 ($C_{14}H_{16}NO_2$) (100), $C_{25}H_{27}NO_3$ requires M, 389.1991); $\upsilon_{max.}$ (CCl_4) 3 525, 1 710, 1 483, 1 435 and 1 280 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.46 (ddd, J 5.1, 5.1 and ca. 2.0 Hz, 8-H), 1.95-2.10 (m, $15_{ax.}$- and $16_{ax.}$-H), 2.05 (s, NMe), 2.29 (d, J 18.9 Hz, 5β-H), 2.31 (d, J 18.9 Hz or possibly dd, J 18.9 and ca. 4.6 Hz, partially obscured by 5β-H signal, 7α-H), 2.39 (br d, J 5.1 Hz, 18-H), 2.57 (t, J 3.0 Hz, part of δ 2.60, dd J ca. 12 and 3.0 Hz, $16_{eq.}$-H), 2.67 (d, J ca. 5 Hz, 9-H), 2.75 (d, J ca. 1.0 Hz; possibly part of δ 2.68, dd, J ca. 19 and 1 Hz, partially obscured by signal at δ 2.65, 7β-H), 2.89 (dd, J 18.0 and 5.3 Hz, 10α-H), 3.10 (d, J 17.7 Hz, 10β-H), 3.83 (s, 3-OMe), 4.40 (d, J 19.0 Hz, 5α-H), ca. 5.8 (v br s, OH, exch. with D_2O), 6.66 (d, J 8.2 Hz, 1-H), 6.71 (d, J 8.4 Hz, 2-H) and 7.17-7.45 (m, Ph); δ_C (50.3 MHz; $CDCl_3$) 19.6 (C-8), 28.0 (C-10), 28.4 (C-18), 32.4 (C-14), 34.9 (C-15), 37.1 (C-13), 38.0 (C-7), 41.8 (NMe), 44.8 (C-5), 47.1 (C-16), 55.1 (C-9), 56.1 (3-OMe), 109.0 (C-2), 119.2 (C-1), 125.4 (C-11), 126.4 (C-22), 127.9 (C-20 and -24), 129.5 (C-21 and -23), 131.5 (C-12), 138.0 (C-19), 143.4 (C-3), 144.8 (C-4) and 209.9 (C-6).

Acid treatment of the nickel residues. The nickel residues were treated with dilute hydrochloric acid until they had dissolved. The resultant green solution was

treated with saturated sodium hydrogencarbonate solution until effervescence ceased. This aqueous mixture was extracted several times with dichloromethane and the combined extracts were dried and evaporated. From the resultant residue a weak, 90 MHz, ^{1}H n.m.r. spectrum of the cyclopropyl ketone (139) was obtained.

Preparation of dibenzothiophene (152). Dibenzothiophene (152) was prepared by a method out-lined by Gilman and Jacoby.[71] However, the exact experimental procedure was not followed and hence the dibenzothiophene produced was contaminated with the starting material, diphenyl, as indicated by the ^{1}H n.m.r. spectrum, the mass spectrum and the t.l.c. of the reaction product. The ^{1}H n.m.r. of the reaction product gave complex multiplets at δ 7.32-7.70, 7.83 and 8.15 in the ratio ca. 4.5:1:1, respectively; cf. 2:1:1 for pure dibenzothiophene. The mass spectrum gave a peak for the molecular ion of dibenzothiophene (m/z 184) and also one for diphenyl (m/z 154). The t.l.c. of the product gave conclusive evidence for the presence of diphenyl. Silica plates were bathed in a 0.1 M aqueous silver nitrate solution and then dried in an oven for several hours. T.l.c. of the reaction product on these silver nitrate impregnated silica plates, with triple elution in hexane, gave spots for diphenyl and dibenzothiophene at R_f values 0.2 and 0.1, respectively.

Raney nickel desulphurisation of dibenzothiophene (152). Freshly prepared W-2 Raney nickel[27] and dibenzothiophene (152) (100 mg) [contaminated with ca. 34% diphenyl] in ethanol (15 ml), were heated under reflux for 90 min. The entire reaction mixture was transferred by pipette to a Soxhlet thimble (1 x 5 cm) and the nickel residues were extracted with refluxing ethanol (50 ml) during 2 h. The extract was then filtered through a pad of Celite and the filtrate was then evaporated to yield a gum. The ^{1}H n.m.r. spectrum (90 MHz) of this gum showed the presence of dibenzothiophene (152)

(12%) and diphenyl (88%). Desulphurisation had occurred although the reaction was clearly incomplete.

Under similar experimental conditions it was found that benzothiophene (149) did not desulphurise.

Preparation of cyclopentadiene (153). Cyclopentadiene (153) was prepared from the thermally induced, retro-Diels-Alder reaction of dicyclopentadiene. Thus, dicyclopentadiene was heated under reflux and, using a Vigreux fractionating column, the cyclopentadiene is distilled off at a head temperature ≤40°C. The cyclopentadiene monomer was collected in a flask cooled in ice-water. The monomer (153) was used preferrably within 30 min of distillation.

Preparation of the cycloadducts (155) and (156) from cyclopentadiene (153) and the Bunte salt, $EtO_2CCH_2S_2O_3Na$ (80a). The method of Kirby and co-workers[53] was used as follows. Distilled triethylamine (2.10 g, 21 mmol) was added at room temperature with stirring to a mixture of the Bunte salt (80a) (1.32 g, 6.0 mmol), calcium chloride dihydrate (1.38 g, 9.4 mmol) and cyclopentadiene (153) (0.4 g, 6.1 mmol) (see preparation of cyclopentadiene) in ethanol (17 ml). Stirring was continued at room temperature for 24 h. 2N Hydrochloric acid was added slowly until the precipitate of calcium sulphite had dissolved and the mixture was slightly acidic. This mixture was extracted with chloroform (3 x 30 ml) and the combined extracts were washed successively with saturated aqueous sodium hydrogencarbonate and brine, and then dried and evaporated to yield a mixture of the endo (155) and exo (156) cycloadducts as a yellow oil. The ^1H n.m.r. spectrum of this oil gave signals arising from both stereoisomeric adducts (see below). A portion of this oil (ca. 0.5 ml) was chromatographed by preparative t.l.c. on silica plates using diethyl ether-light petroleum (1:9) as eluent. The faster running isomer, the exo cycloadduct (156), (71 mg), gave the

following signals; δ_H (90 MHz; $CDCl_3$) 1.25 (t, J 7 Hz, $OCH_2\underline{CH_3}$), 1.65 and 1.90 (m, ABq, J ca. 9 Hz, 7-CH_2), 3.28 (s, 3-H), 3.53 (br s, 4-H), 4.10 (br s, 1-H), 4.21 (q, J 7 Hz, OCH_2CH_3), 5.93 (m, 5- or 6-H) and 6.37 (dd, J 6 and 3 Hz, 6- or 5-H); the slower running isomer, the endo cycloadduct (155), (105 mg), gave δ_H (90 MHz; $CDCl_3$) ca. 1.1 (t, J 7 Hz, $OCH_2\underline{CH_3}$), 1.54 (m, ABq, 7-CH_2), 3.65 (br s, 4-H), ca. 3.97 (br s, 1-H), 4.02 (q, J 7 Hz, OCH_2CH_3), 4.31 (d, J 4 Hz, 3-H), 5.78 (dd, J 6 and 3 Hz, 5- or 6-H) and 6.38 (dd, J 6 and 3 Hz, 6- or 5-H). The ratio of endo:exo cycloadducts was thus ca. 6:4 (cf.[53] 7:3).

Raney nickel desulphurisation of the ethyl ester cyclopentadiene cycloadducts (154). A mixture of the cycloadducts (154) (0.48 g, 2.61 mmol) and W-2 Raney nickel[27] (4.3 g of slurry) in ethanol (40 ml) were heated under reflux for 2 h. The entire reaction mixture was filtered through a pad of Celite and the nickel residues were washed several times with hot ethanol (200 ml). The filtrate and washings were combined and evaporated to yield, as a clear oil, ethyl cyclopentylacetate (157) (0.20 g, 49%), b.p. ca. 20°C (0.12 mm Hg) [lit., 191-192°C (1 atm)] (Found: m/z 156.1148. $C_9H_{16}O_2$ requires M, 156.1150); $\upsilon_{max.}$ (thin film) 1 735 cm^{-1}; δ_H (90 MHz; $CHCl_3$) 1.20 (t, J 7 Hz, $OCH_2\underline{CH_3}$), 1.4-2.0 (m, cyclopentane ring), 2.24 (m, $\underline{CH_2}CO_2Et$) and 4.04 (q, J 7 Hz, OCH_2CH_3).

Lithium aluminium hydride reduction of the cyclopentadiene cycloadducts (154). A solution of the cycloadducts (154) (0.58 g, 3.2 mmol) in dry diethyl ether (30 ml) was added slowly over 30 min, to a stirring mixture of lithium aluminium hydride (0.41 g, 11 mmol) and dry diethyl ether (30 ml) maintained in an ice-water bath. After the mixture had been stirred for a further 2.5 h, water (20 ml) was added. The ether layer was decanted off and the aqueous layer was further extracted with diethyl ether (2 x 30 ml). The combined ether layers were washed successively with saturated brine and water, and

then dried and evaporated to yield the alcohols (158) as an oil (0.24 g, 53%); δ_H (90 MHz; $CDCl_3$) 1.48 (m, $7CH_2$), 3.0-3.6 (complex m, containing the OH signal, exch. with D_2O; $C\underline{H}_2OH$; 4-H; 3-$H_{\underline{endo/exo}}$), 3.6-4.1 (complex m, containing 1-H and 3-$H_{\underline{endo/exo}}$), 5.55-5.75 (dd, J 7 and 3 Hz, 6- or 5-$H_{\underline{endo}}$), 5.75-6.95 (m, 6- or 5-$H_{\underline{exo}}$), 6.1-6.4 (complex m, 5- or 6-$H_{\underline{endo}}$ and 5- or 6-$H_{\underline{exo}}$); m/z 142 (M) (8%) and 66 (100).

Raney nickel desulphurisation of the sulphur-containing cyclopentadiene alcohols (158). A mixture of W-2 Raney nickel[27] (6.3 g of slurry) and the alcohols (158) (0.20 g, 1.41 mmol) in ethanol (45 ml) was stirred and heated under reflux for 45 min. The entire reaction mixture was filtered through a pad of Celite and the nickel residues washed with hot ethanol (45 ml). The filtrate and washings were combined and evaporated to yield a colourless mobile oil. Purification of this oil by Kugelrohr distillation (b.p. ca. 90°C at 0.6 mmHg), gave in high yield (>90%) a mixture of 2-cyclopentylethanol (159) and a 2-cyclopentenylethanol derivative (160) in the ratio of 83:17 respectively, as judged by ^1H n.m.r. spectroscopy. 2-Cyclopentylethanol[81] gave δ_H (90 MHz; $CDCl_3$) 0.9-1.3 (m, $C\underline{H}_2CH_2OH$), 1.3-2.1 (m, cyclopentane ring) and 3.62 (t, J 7 Hz, $CH_2C\underline{H}_2OH$). The 2-cyclopentenylethanol derivative[82] (160) gave similar signals together with δ 2.1-2.5 (m, allyl-H) and 5.4-5.8 (m, vinyl-H). The low resolution mass spectrum of the purified oil (containing the 83:17 mixture of products) gave m/z 112 [M (3%) (160)], 83 [M-CH_3O (7) (159)], 81 [M-CH_3O (28) (160)], 69 (84) and 68 (100). No M (159) was observed. T.l.c. of this oil on silica plates developed with diethyl ether-petroleum ether (2:3) and with detection by iodine vapour, showed no sulphur-containing alcohol to be present, R_f 0.1, however, a colourless spot, R_f 0.8, probably indicated the presence of the two desulphurised products.

Triphenyltin hydride desulphurisation of the 8α-ethoxycarbonyl-7-thia cycloadduct (49a). Under a nitrogen atmosphere, a mixture of the 7-thia cycloadduct (49a) (316 mg, 0.74 mmol), triphenyltin hydride (66) (0.82 g, 2.34 mmol), and azoisobutyronitrile (162) (ca. 25 mg, 0.018 mmol) in dry benzene (10 ml) was heated under reflux for 24 h. The reaction mixture was evaporated to yield a brown gum. A few drops of dichloromethane and hexane were added to this gum which caused crystallisation of white platelet crystals. These crystals were found to be bis-triphenyltin sulphide (164), m.p. 132-134°C (lit.,[38] 144.0-144.5°C) (Found: C, 59.3; H, 4.25. $C_{36}H_{30}SSn_2$ requires C, 59.1; H, 4.1%.); δ_H (90 MHz; $CDCl_3$) 7.0-7.9 (m, $SnPh_3$); m/z [734 (0.4%), 733 (0.3), 732 (0.6), 731 (0.4), 730 (0.4) and 729 (0.3); M], 699, 654 and 351 (100). The rest of the reaction mixture was believed to contain, as judged by ^1H n.m.r. spectroscopy, ethyl 6,7-didehydro-3,6-dimethoxy-4,5α-epoxy-17-methyl-morphinan-14β-ylacetate (114) contaminated with phenyl-containing material. It is possible that the thiostannane intermediate (166) was the product recovered, however it is believed, with reference to literature observations, that this is not the case in this instance. Hence, the morphinan (114) gave the following signals, δ_H (90 MHz; $CDCl_3$) 1.13 (t, J 7 Hz, OCH_2CH_3), 2.22 (s, NMe), 2.80 (d, J 9 Hz), 3.34 (s, 6-OMe), 3.68 (s, 3-OMe), 3.96 (q, J 7 Hz, OCH_2CH_3), 4.51 (dd, J 7 and 2 Hz, 7-H), 4.78 (s, 5-H), 6.51 (d, J 8 Hz, 1-H), 6.57 (d, J 8 Hz, 2-H) and 6.8-7.9 (m, contains Ph). These signals are in agreement with the morphinan (114) obtained from the Raney nickel desulphurisation experiment of the same cycloadduct (see p 139).

Triphenyltin hydride desulphurisation of the thiobenzaldehyde cycloadduct (49c). A mixture of the thiobenzaldehyde cycloadduct (49c), (149 mg, 0.34 mmol), triphenyltin hydride (66) (0.36 g, 1.03 mmol) and azoisobutyronitrile (162) (5 mg, 3.7×10^{-5} mol) in dry toluene (10 ml) was heated under reflux for 3 h. The reaction mixture was

evaporated to yield a residue, which was chromatographed on a short silica column eluted with diethyl ether-light petroleum (1:9). Early fractions contained only aromatic material, presumably the triphenyltin sulphide (164). Later fractions contained morphinan material contaminated with phenyl-containing material, as judged by ^1H n.m.r. spectroscopy. These fractions were combined and evaporated to a gum which was chromatographed twice by preparative t.l.c. on silica plates developed with diethyl ether. The band with R_f value of ca. 0.6, contained relatively pure (the integral for the phenyl protons however was too large) 14β-benzyl-6,7-didehydro-4,5α-epoxymorphinan (167) (81 mg, <59%); δ_H(200 MHz; $CDCl_3$) 2.39 (s, NMe), 2.60 (d, J 12 Hz, PhCH_2?), 3.03 (d, J 18 Hz, 10β-H), 3.58 (s, 6-OMe), 3.75 (d, J 6 Hz), 3.85 (3-OMe), 3.95 (d, J 12.5 Hz, PhCH_2?), 4.78 (dd, J 6.5 and 2.1 Hz, 7-H), 4.85 (d, J 1.2 Hz, 5-H), 6.59 (d, J 8 Hz, 1-H), 6.67 (d, J 8 Hz, 2-H) and 7.1-7.4 (m, Ph); δ_C (50.3 MHz; $CDCl_3$) 20.3 (C-8), 25.5 (C-10), 29.8 and 30.4 (C-15 and -18), 42.8 (NMe), 45.9 (C-16), 54.5 (6-OMe), 56.4 (3-OMe), 58.0 (C-9), 87.8 (C-7), 96.8 (C-5), 113.1 (C-2), 118.2 (C-1), 125.9 (C-22), 127.8 and 130.7 (C-20, -21, -23 and -24), 137.6 or 139.8 (C-19), 143.2 (C-3), 144.4 (C-4), and 151.9 (C-6), signals for C-11, -12, -13 and 14 were too weak or obscured to identify.

Acid hydrolysis of the enol ether (167). The enol ether (167), contaminated with phenyl-containing material, was dissolved in ethanol (5 ml) and 2N hydrochloric acid (5 ml). This mixture was heated under reflux for 1 h. The reaction mixture was evaporated to yield a gum which was dissolved in deuteriochloroform. The product was tentatively identified as the ketone (168) as judged by ^1H n.m.r. spectroscopy (200 MHz); δ_H 3.90 (s, 3-OMe), 4.65 (s, 5-H), ca. 6.72 (m, 1- and 2-H) and 7.2-7.9 (m, contains Ph of ketone).

Tri-n-butyltin hydride desulphurisation of the 8α-ethoxycarbonyl-7-thia cycloadduct (49a). A mixture of the 7-thia cycloadduct (49a) (0.45 g, 1.05 mmol), tri-n-butyltin hydride (161) (2.91 g, 10 mmol) and azoisobutyronitrile (162) (95 mg, 0.70 mmol) in dry toluene (5 ml), was heated under reflux, under a nitrogen atmosphere, for 20 h. T.l.c. of the reaction mixture on silica plates developed with diethyl ether gave a large white spot, R_f 0.8, a faint spot at R_f 0.5 (the 7-thia cycloaduct gives a typical R_f value of 0.5 in this solvent system), and a spot at R_f 0.4 corresponding to a product. The reaction mixture was evaporated to give a liquid (ca. 3 ml) which was chromatographed on a silica column. Elution with light petroleum removed the faster running product, this being the bis-tri-n-butyltin sulphide (163); δ_H (90 MHz; neat) 0.6-0.9 (m) and 0.9-2.0 (br m); m/z [584 (0.4%), 583 (0.3), 582 (1.5), 581 (0.9), 580 (1.8), 579 (1.2), 578 (1.7), 577 (0.6), and 576 (0.7); M-C_2H_5]. Elution with diethyl ether then removed the remainder of the product from the column. This ethereal solution contained a single morphinan product contaminated with butyl-containing material as judged by ^1H n.m.r. spectroscopy. This mixture was chromatographed by preparative t.l.c. on silica developed with diethyl ether. This chromatographic procedure was repeated to produce a butyl-free sample of the morphinan. This was found to be the ethyl 6,7-didehydro-4,5α-epoxymorphinan-14β-yl acetate (114) (136 mg, 32%), as judged by comparison of the 90 MHz ^1H n.m.r. spectrum of this sample with that of the 200 MHz spectrum of (114), obtained from the Raney nickel desulphurisation reaction of the same 7-thia cycloadduct (see p 139 for analytical data).

An attempt at tri-n-butyltin hydride desulphurisation of the 8α-ethoxycarbonyl-7-thia cycloadduct (49a). On one attempt to carry out this reaction (see previous experiment), the reaction mixture was found to contain only thebaine (11), contaminated with butyl-containing material, as judged by ^1H n.m.r. (90 MHz) spectroscopy. The

mass spectrum of this product gave a molecular ion at m/z 310. This value is out by one mass unit from that of authentic thebaine (m/z 311).

Attempted tri-n-butyltin hydride desulphurisation of the ethyl ester enone (86). A mixture of the enone (86) (146 mg, 0.35 mmol), tri-n-butyltin hydride (161) (0.25 ml, 0.89 mmol) and azoisobutyronitrile (162) (23 mg, 0.017 mmol) in toluene (20 ml) was heated under reflux for 3 days. T.l.c. of the reaction mixture on silica developed with diethyl ether appeared to show starting material still to be present, R_f 0.5, with tri-n-butyl-containing material at R_f 0.9. The reaction mixture was evaporated to a gum which was chromatographed on a silica column. Light petroleum eluted the tri-n-butyl-containing material, δ_H (90 MHz; $CDCl_3$) 0.7-1.0 (m) and 1.0-2.0 (br m). The column was then eluted exhaustively with diethyl ether. This ethereal eluate was evaporated to give a residue which was further chromatographed by preparative t.l.c. on silica plates developed with diethyl ether-light petroleum (1:1). The lower band gave unreacted enone (86) (27 mg), while the upper band gave, as judged by ^1H n.m.r. spectroscopy, the non-desulphurised 7,8-dihydro ketone. The ^1H n.m.r. spectrum of this compound was weak and still showed strong signals for butyl groups, however, the signals were tentatively assigned as follows: δ_H (90 MHz; $CDCl_3$), 2.34 (s, NMe), 3.81 (s, 3-OMe), 4.17 (m, OCH_2CH_3), 4.38 (s, 5-H), 5.46 (s, 19-H), 5.80 (s, OH), and 6.59 (s, 1- and 2-H).

Preparation of aluminium amalgam. Aluminium amalgam was prepared by the method described in Vogel's Textbook of Practical Organic Chemistry, 4th Ed.[76]

Attempted desulphurisation of the 8α-ethoxycarbonyl-7-thia cycloadduct (49a) using aluminium amalgam. The cycloadduct (49a) (300 mg, 0.70 mmol) and aluminium amalgam (2 g of aluminium foil) in ethanol (50 ml) and water (5 ml) were stirred and heated under reflux for 25 h. The entire reaction mixture was filtered through a pad of

Celite. The aluminium amalgam residues were washed several times with boiling ethanol and the combined filtrate and washings were evaporated to a foam (245 mg). The ^1H n.m.r. spectrum (90 MHz) of this foam was virtually identical with that obtained from refluxing a solution of the cycloadduct (49a) in ethanol for 20 h (see pages 52 and 131). This signified that desulphurisation had not occurred during this particular reaction. This reaction was not repeated.

Desulphurisation of the ethyl ester enone (86) using aluminium amalgam. The enone (86) (450 mg, 1.1 mmol) and aluminium amalgam[76] (from 5 g of aluminium foil) in ethanol (45 ml) and water (5 ml) were stirred and heated under reflux for 3 h. The entire reaction mixture was filtered through a pad of Celite. The aluminium amalgam residues were washed several times with refluxing ethanol (100 ml) and the combined filtrate and washings were evaporated to give a residue (472 mg). Preparative t.l.c. of this residue on silica plates developed with diethyl ether gave no starting material (R_f 0.6), but the band at R_f 0.3 gave the dethioketone (128) (264 mg, 62%) as a gum [Found: m/z 387.2036 (57%) and 300.1598 (100). $C_{22}H_{29}NO_5$ requires M, 387.2046 and (M-$C_4H_7O_2$), 300.1599]; δ_H (200 MHz; $CDCl_3$) 1.24 (t, J 7.1 Hz, OCH_2CH_3), 1.55 (m, $15_{eq.}$-H), 2.28 (s, NMe), 2.74 (d, J 13.3 Hz, 18-H), ca. 2.67 (dd, J ca. 19 and ca. 6 Hz, 10α-H), 2.95 (d, J 18.6 Hz, 10β-H), 3.20 (d, J 5.4 Hz), 3.75 (s, 3-OMe), 4.12 (q, J 7.1 Hz, OCH_2CH_3), 4.23 (dd, J 15.7 and ca. 1.8 Hz, 5α-H), ca. 6.0 (br s, OH, exch. with D_2O), 6.55 (d, J 8.3 Hz, 1-H) and 6.62 (d, J 8.3 Hz, 2-H); δ_C (50.3 MHz; $CDCl_3$) 14.2 (OCH_2CH_3), 23.2 (C-8), 28.1 (C-10), 32.0 (C-15), 33.9 (C-18), 37.9 (C-7), 40.2 (C-14), 42.6 (NMe), 43.6 (C-13), 44.5 (C-5 or -16), 46.2 (C-16 or -5), 55.9 (3-OMe), 56.7 (C-9), 60.1 (OCH_2CH_3), 108.8 (C-2), 118.1 (C-1), 124.3 (C-11), 130.6 (C-12), 144.1 (C-3 or -4), 144.8 (C-4 or -3), 172.7 (C-19) and 210.7 (C-6).

Attempted desulphurisation of the 8α-ethoxycarbonyl-7-thia cycloadduct (49a) using sodium in liquid ammonia. Sodium-dried ammonia (ca. 15 ml) was distilled into a flask containing the cycloadduct (49a) (108 mg, 0.25 mmol) in dry THF (10 ml). Sodium metal (a couple of small pieces) was added with stirring to the THF-ammonia solution, during 15 min. A deep blue colour appeared immediately upon addition of the sodium pieces, signifying the presence of ammonia-solvated electrons. The reaction mixture was stirred for a further 45 min and then the ammonia was allowed to evaporate off overnight. The resultant residue was chromatographed on silica plates. The product, in low yield, was tentatively identified as the substituted ethanol (170). The following data were obtained for this compound, δ_H (90 MHz; $CDCl_3$) 2.28 (s, NMe), 3.85 (s, 3-OMe), 6.64 (d, J ca. 8 Hz, 1-H) and 6.72 (d, J ca. 8 Hz, 2-H); $\upsilon_{max.}$ ($CHCl_3$) 3 525, 1 723, 1 485, 1 462, 1 440, 1 280 and 1 220 cm^{-1}; m/z 343 (M, $C_{20}H_{25}NO_4$) (12%), 206 (25), 44 (48) and 42 (100).

Lithium aluminium hydride reduction of the 8α-ethoxycarbonyl-7-thia cycloadduct (49a). In an ice-water bath and under a nitrogen atmosphere, the ester (49a) (200 mg, 0.47 mmol) in tetrahydrofuran (20 ml) was added dropwise with stirring over 20 min to a mixture of lithium aluminium hydride (35 mg, 0.93 mmol) in tetrahydrofuran (20 ml). The cooling bath was then removed and the reaction mixture was stirred for a further 1 h. Distilled water was added until foaming ceased. This mixture was left to stand overnight and then filtered. The filtrate was evaporated to low volume and then extracted with dichloromethane (3 x 30 ml). The combined extracts were washed with water (20 ml), dried and evaporated to yield a yellowish foam (169 mg). T.l.c. of this foam on silica developed with diethyl ether and with iodine vapour detection, showed that no starting material (49a), R_f 0.6, was present, however, two spots at R_f 0.3 and 0.2 showed that two products had been formed. These products were found

to be the 8α-methylalcohol (172) and the isomeric furan (173) in the ratio of 78:22, respectively. The 8α-methylalcohol (172), R_f 0.2, gave the following ^{1}H n.m.r. signals, (90 MHz; $CDCl_3$) 2.38 (s, NMe), 3.55 (s, 6-OMe), 3.75 (s, 3-OMe), 4.75 (t, J 6 Hz, 8-H), 4.94 (d, J 2 Hz, 5-H), 5.43 (d, J 10 Hz, 19-H), 6.15 (dd, J 10 and 2 Hz, 18-H), 6.55 (d, J 8 Hz, 1-H) and 6.62 (d, J 8 Hz, 2-H). Analytical data for the furan (173), R_f 0.3, will be given below.

Isomerisation of the 8α-methylalcohol (172) to the furan (173). A solution of the above mixture of (172) and (173), on standing at room temperature for several days, had been found to isomerise completely to give the furan derivative (173), m.p. 286-288°C (from ethanol); $\upsilon_{max.}$ (KBr) 3 280, 1 658, 1 615, 1 583, 1 485, 1 438, 1 358, 1 333, 1 280, 1 223 and 1 150 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.54 (ddd, J 13.1, 3.4 and 1.5 Hz, $15_{eq.}$-H), 2.01 (td, J 12.3 and 3.6 Hz, $16_{ax.}$-H), 2.36 (s, NMe), 2.42 (d br d, J 12.4 and ca. 5 Hz; possibly td, partially obscured by NMe signal; $16_{eq.}$-H), 2.77 (td, J 13.0 and 5.5 Hz, $15_{ax.}$-H), 2.93 (dd, J 18.7 and 6.6 Hz, 10α-H), 3.11 (s; possibly part of doublet, J ca. 5 Hz, partially obscured by 10β-H signal; 9-H), 3.16 (d, J 18.6 Hz, 10β-H), 3.45 (s, 6-OMe), 3.82 (s, 3-OMe), 4.10 (dd, J 7.8 and 0.9 Hz, 19-H), 4.22 (dd, $J_{7,8\alpha}$ 4.5 and $J_{5\alpha,7}$ 1.7 Hz, 7-H), 4.36 (m, 8-H), 4.42 (2H, ABq, J ca. 7.6 Hz, 20-H), 4.55 (d, J 4.5 Hz, 5-H), 5.81 (s, OH, exch. with D_2O), 6.64 (d, J 8.4 Hz, 1-H) and 6.67 (d, J 8.4 Hz, 2-H); δ_C (50.3 MHz; $CDCl_3$) 25.1 (C-15), 32.3 (C-10), 43.4 (NMe), 45.9 (C-16), 48.5 (C-5), 50.6 (C-13), 53.4 (C-9), 55.1 (6-OMe), 55.9 (C-19), 56.0 (3-OMe), 62.3 (C-14), 75.0 (C-20), 80.3 (C-8), 90.3 (C-7), 108.7 (C-2), 118.1 (C-1), 127.2 (C-11), 130.3 (C-12), 142.6 (C-3), 144.0 (C-4) and 165.0 (C-6); m/z 387 (M, 100%)

Lithium hydroxide induced hydrolysis and rearrangement of the 8α-ethoxycarbonyl-7-thia cycloadduct (49a). A mixture of the cycloadduct (49a) (250 mg, 0.58 mmol) in ethanol (10 ml) and aqueous lithium hydroxide (3 ml of 1.6 M solution;

4.8 mmol) was stirred at room temperature for 16 h. The dark red reaction mixture was evaporated to low volume, acidified, to give a yellow neutral solution, and then extracted with dichloromethane. The combined extracts were evaporated to yield a residue which was shown by ^{1}H n.m.r. (90 MHz) spectroscopy to contain apparently three or possibly four products. The major product at this stage was tentatively identified as the cycloadduct acid (177) with the following ^{1}H n.m.r. signals, δ_H (90 MHz; $CDCl_3$) 2.58 (s, NMe), 3.40 (s, 6-OMe), ca. 3.76 (s, 3-OMe), 4.96 (br s, 5-H), 5.10 (br s, 8-H), 5.79 (d, J 10 Hz, 19-H), 6.08 (d, J 10 Hz, 18-H) and 6.65 (s, 1- and 2-H). T.l.c. of the combined extracts on silica plates developed with methanol-dichloromethane (1:9) showed that no starting cycloadduct (49a), R_f ca. 0.8, was present. However, three spots are detected by iodine vapour at R_f 0.1, 0.2 and 0.6. The major product, with R_f 0.6, was the lactone (176) (62 mg, 27%) [the major product from the combined extracts had apparently isomerised completely to give the lactone (176)], m.p. 256-259°C (decomp.) (from dichloromethane and ethanol) (Found: C, 62.6; H, 5.9; N, 3.5%; m/z 401.1312 (78%) and 310.1434 (100). $C_{21}H_{23}NO_5S$ requires C, 62.8; H, 5.8; N, 3.5%; M, 401.1297 and (M-$C_2H_3O_2S$), 310.1443); $\upsilon_{max.}$ (KBr) 3 345, 1 750, 1 650, 1 488 and 1 282 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.59 (ddd, J 13.1, ca. 3 and 1.6 Hz, $15_{eq.}$-H), 1.99 (td, J ca. 11.7 and ca. 3.5 Hz, $16_{ax.}$-H), 2.33 (s, NMe), 2.39 (dd, J 5.5 and ca. 1 Hz; possibly td, partially obscured by $15_{ax.}$-H signal; $16_{eq.}$-H), 2.56 (dd, J 12.7 and 5.4 Hz; possibly td, partially obscured by $16_{eq.}$-H signal; $15_{ax.}$-H), 2.94 (dd, J 18.7 and 6.2 Hz, 10α-H), 3.18 (d, J ca. 18.5 Hz, 10β-H), 3.21 (d, J 6.3 Hz, 9-H), 3.46 (s, 6-OMe), 3.83 (s, 3-OMe), 4.36 (dd, J 4.9 and 1.7 Hz, 7-H), 4.50 (dd, J 1.7 and 0.6 Hz, 8-H), 4.51 (s, 19-H), 4.91 (d, J 5.0 Hz, 5-H), 5.81 (s, OH, exch. with D_2O), 6.66 (d, J ca. 8 Hz, 1-H) and 6.69 (d, J ca. 8-Hz, 2-H); δ_C (50.3 MHz; $CDCl_3$) 24.4 (C-10), 31.6 (C-15), 43.1 (NMe), 45.4 (C-16), 46.2 (C-5), 51.5 (C-14), 54.5 and 55.1 (C-9 and -19), 55.4 and 56.0 (3-OMe

and 6-OMe), 58.4 (C-13), 82.0 (C-8), 89.0 (C-7), 109.1 (C-2), 118.4 (C-1), 125.2 (C-11), 129.3 (C-12), 142.4 (C-3), 144.4 (C-4), 167.2 (C-6) and 176.5 (C-20). The spot with $\underline{R}_f$ 0.2 was found to be the cyclopropane ester derivative (85) (24 mg, 10%), as judged by ^{1}H n.m.r. spectroscopy. The spot with $\underline{R}_f$ 0.1 was judged to be the cyclopropane acid derivative (178) (17 mg, 7%), since its ^{1}H n.m.r. spectrum closely resembled that of the cyclopropane ester except that no distinctive signals for an ethoxy group were present. The cyclopropane acid gave the following data; δ_H (90 MHz; $CDCl_3$) 2.70 (s, NMe), 3.39 (s, 6-OMe), 3.83 (s, 3-OMe), 4.31 (d, J ca. 2 Hz, 5-H), 4.62 (dd, J ca. 7 and ca. 2 Hz, 7-H) and 6.65 (s, 1- and 2-H); m/z 401 (M, 70%), 386 (89), 310 (94), 255 (89) and 230 (100).

Preparation of the rearranged enones from the thioaldehyde cycloadducts of thebaine.

General method

The cycloadduct (20 mmol) was dissolved in refluxing ethanol (20 ml). 2N Hydrochloric acid (5 ml) was added and the mixture heated under reflux for 5 min. After being allowed to reach room temperature, the reaction mixture was evaporated to low volume and then treated cautiously with 5% aqueous sodium hydrogencarbonate until effervescence ceased and the solution was slightly alkaline. This solution was then extracted with dichloromethane (3 x 40 ml). The combined extracts were washed with water (2 x 30 ml), dried and then evaporated to yield the enones. In this way, the following enones were prepared in yields of 60-70%.

Ethyl (19R)-7,8-didehydro-4-hydroxy-3-methoxy-17-methyl-6-oxo-5β,14β-thiaethanomorphinan-19-carboxylate (86), m.p. 172-174°C (lit.,[59] 173-174°C) (from propan-2-ol or 50% aqueous methanol); δ_H (90 MHz; $CDCl_3$) ($C\underline{H}Cl_3$ signal at δ 7.31) 1.25 (t, J 7 Hz, $OCH_2C\underline{H}_3$), 2.39 (s, NMe), 2.76 (dd, J ca. 18 and 6 Hz, 10α-H), 3.19 (d, J 18 Hz, 10β-H), 3.73 (s, 3-OMe), 4.14 (q, J 7 Hz, $OC\underline{H}_2CH_3$), 4.70 (d, J ca. 1 Hz, 5-H),

5.42 (s, 19-H), 5.96 (dd, J 10 and 2 Hz, 7-H), 6.17 (br s, OH), 6.63 (s, 1- and 2-H) and 6.78 (d, J 10 Hz, 8-H); m/z 415 (M) (42%), 230 (64) and 91 (100).

(19S)-7,8-Didehydro-4-hydroxy-3-methoxy-17-methyl-19-p-nitrophenyl-6-oxo-5β,14β-thiaethanomorphinan (100); δ_H (90 MHz; $CDCl_3$) ($C\underline{H}Cl_3$ signal at δ 7.22) 2.43 (s, NMe), 2.99 (d, J ca. 5 Hz, 9-H), 3.12 (d, J 18 Hz, 10β-H), 3.76 (s, 3-OMe), 4.78 (d, J ca. 2 Hz, 5-H), 4.80 (d, J 10 Hz, 8-H), 5.93 (s, 19-H), 6.02 (dd, J 10 and 2 Hz, 7-H), ca. 5.95 (br s, OH), 6.57 (br s, 1- and 2-H), 7.50 (2H, d, J 9 Hz, 21- and 25-H) and 8.07 (2H, d, J 9 Hz, 22- and 24-H); m/z 464 (M).

(19S)-7,8-Didehydro-4-hydroxy-3-methoxy-17-methyl-6-oxo-19-phenyl-5β,14β-thiaethanomorphinan (138); m.p. 256-258°C (lit.,[61] 260-261°C) (from propan-2-ol); δ_H (90 MHz; $CDCl_3$) (TMS signal at ca. δ -0.03) 1.58 (br d, J ca. 12 Hz, $15_{eq.}$-H), 2.35 (s, NMe), 2.50 (d, J 8 Hz), 2.99 (d, J ca. 5 Hz, 9-H), 3.06 (d, J 18 Hz, 10β-H), 3.65 (s, 3-OMe), 4.67 (d, J ca. 1 Hz, 5-H), 5.78 (d, J 10 Hz, 8-H), 5.79 (s, 19-H), 5.94 (dd, J 10 and ca. 1 Hz, 7-H), 5.94 (br s, OH), 6.58 (s, 1- and 2-H) and 7.0-7.5 (m, Ph).

Preparation of the phenyl enone (138) by sodium ethoxide-induced rearrangement of the thiobenzaldehyde cycloadduct (49c). A variant of McDougall's[61] method was used. Thus, the thiobenzaldehyde cycloadduct (49c) (106 mg, 0.245 mmol), dissolved with heating in dry ethanol (10 ml), was added to a solution of sodium ethoxide prepared from sodium (26 mg, 1.13 mmol) in dry ethanol (20 ml). The resultant mixture was heated under reflux for 3 h, then evaporated to give a viscous residue. This was neutralised with dilute hydrochloric acid then extracted several times with dichloromethane. The combined extracts were washed once with water (20 ml), dried and evaporated to dryness. The residue (26 mg) was found to contain, as judged by ^1H n.m.r. spectroscopy, the desired enone (138) (>80%) and unreacted starting material.

Attempted acid-catalysed hydrolysis of the ethyl ester cycloadduct (49a), at room temperature. The ethyl ester cycloadduct (49a) (50 mg, 0.12 mmol) was dissolved in ethanol (5 ml) and then 2N hydrochloric acid (5 ml) was added. This mixture was stirred at room temperature for 18 h, then evaporated to dryness. Saturated sodium hydrogen-carbonate was added until effervescence ceased and the solution was neutral. This mixture was extracted with chloroform (3 x 15 ml), then the combined organic extracts were dried and evaporated to yield a white residue (27 mg). The ^{1}H n.m.r. spectrum (90 MHz) showed it to be a mixture of the cycloadduct (49a) and the desired enone (86), ratio ca. 3:7.

Preparation of the keto-lactone (179) by acid-catalysed hydrolysis of the ethyl ester 7-thia cycloadduct (49a). The cycloadduct (49a) (150 mg, 0.35 mmol) in ethanol (5 ml) and 2N hydrochloric acid (5 ml) was heated under reflux for 2 h. When the reaction mixture had cooled to room temperature, 5% aqueous sodium hydrogen-carbonate was added until the solution was slightly alkaline. The solution was then extracted with dichloromethane (3 x 25 ml) and the combined extracts were washed with water (2 x 25 ml) and dried. Evaporation of the solvent yielded the keto-lactone (179) (90 mg, 66%) as a brown gum. Recrystallisation from propan-2-ol gave material, m.p. 282-284°C [Found: m/z 387.1132 (100%). $C_{20}H_{21}NO_5S$ requires M, 387.1141]; δ_H [200 MHz; $CDCl_3$ with ca. 0.1 ml $(CD_3)_2SO$] 1.63 (m, $15_{eq.}$-H), 2.02 (dd, J 20.0 and 8.2 Hz, 7α-H), ca. 2.1 (m, $16_{ax.}$-H), 2.33 (s, NMe), 2.45 (m, $15_{ax.}$-H and $16_{eq.}$-H), 2.59 (d, J 20.1 Hz, 7β-H), 2.93 (dd, J 19.2 and 6.5 Hz, 10α-H), 3.22 (d, J 6.6 Hz, 9-H), 3.22 (d, J 19.0 Hz, 10β-H), 3.81 (s, 3-OMe), 4.46 (s, 19-H), 4.51 (d, J 8.0 Hz, 8-H), 4.65 (s, 5-H), 6.07 (s, OH), and 6.71 (s, 1- and 2-H); δ_H [200 MHz; $(CD_3)_2SO$] 1.48 (d, J ca. 12 Hz, $15_{eq.}$-H), ca. 1.9 (m, $16_{ax.}$-H), ca. 1.9 (dd, J ca. 20 and 7.7 Hz, 7α-H), 2.29 (s, NMe), ca. 2.3 (m, $15_{ax.}$-H and $16_{eq.}$-H), 2.38 (d, J 19.8 Hz, 7β-H), 3.72 (s, 3-OMe),

4.31 (s, 19-H), 4.61 (s, 5-H), 4.74 (d, J 7.5 Hz, 8-H), 6.69 (d, J 8.4 Hz, 1-H), 6.84 (d, J 8.4 Hz, 2-H), 8.96 (s, OH); δ_C [50.3 MHz; $CDCl_3$ with ca. 0.1 ml $(CD_3)_2SO$] 24.3 (C-10), 30.6 (C-15), 40.4 (C-7), 43.0 (NMe), 44.9 (C-16), 45.5 (C-5 or -19), 48.0 (C-13 or -14), 55.5 (C-19 or -5), 56.0 (3-OMe), 58.0 (C-13 or -14), 60.1 (C-9), ca. 77 (obscured by $CDCl_3$, C-8), 110.1 (C-2), 119.2 (C-1), 123.1 (C-11), 128.8 (C-12), 142.3 (C-3), 145.0 (C-4), ca. 174 (C-20) and ca. 119 (C-6); δ_C [50.3 MHz; $(CD_3)_2SO$] 23.7 (C-10), 30.2 (C-15), ca. 40 [obscured by $(CD_3)_2SO$, C-7], 42.4 (NMe), 44.6 (C-16), 45.3 (C-5 or -19), 47.7 (C-13 or -14), 54.6 (C-19 or -5), 55.7 (3-OMe), 57.2 (C-13 or -14), 59.9 (C-9), 77.1 (C-8), 111.1 (C-2), 118.5 (C-1), 123.6 (C-11), 129.2 (C-12), 142.7 (C-3), 145.4 (C-4), 174.4 (C-20), and 198.1 (C-6). This keto-lactone was left to stand for several weeks before the n.m.r. data was re-recorded. From this spectra it was apparent that another product was now present. This new product was tentatively identified as the 7,8-didehydro-4-hydroxy-3-methoxy-17-methyl-6-oxo-5β,14β-thiaethanomorphinan-19(R)-carboxylic acid (180); δ_H [200 MHz; $(CD_3)_2SO$] 3.68 (s, 3-OMe), 4.31 (s, 19-H), 4.52 (d, J ca. 2 Hz, 5-H), 5.83 (dd, J ca. 9 and 2 Hz, 7-H), 6.55 (d, J ca. 9 Hz, 8-H), ca. 6.69 (d, J 8.4 Hz, 1-H), 6.84 (d, J 8.4 Hz, 2-H) and 8.64 (s, OH); δ_C [50.3 MHz; $(CD_3)_2SO$] 24.8 (C-10), 29.4 (C-15), ca. 42 (NMe), 45.1 (C), 51.9 (C), 53.0 (C), 53.4 (CH), 55.0 (CH), 55.6 (3-OMe), 58.6 (CH), 109.9 (C-2), 117.4 (C-1), ca. 124 (C-11), 129.4 (C-7), 129.7 (C-12), 143.3 (C-3), 145.2 (C-4), 149.8 (C-8), 170.7 (C-20), and 192.9 (C-6); $\upsilon_{max.}$ (KBr) 3 400, 1 675, 1 490 and 1 280 cm^{-1}.

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