10-oxo-Morphinans as Potential Kappa Selective Analgesics

A Thesis submitted in partial fulfilment

for the Degree of Ph.D.

by

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to my mother

Acknowledgements

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I wish to thank my Wife for the unceasing encouragement and support she has given me.

Contents

Synopsis

Ethylketocyclazocine (EKC), a benzomorphan drug with a 10-oxo group, binds preferentially to κ opiate receptors. The aim of the present research was to introduce a 10-oxo group into known, potent, μ-selective, morphinan analgesics and possibly thereby obtain κ-selectivity. It was hoped that this might cause separation of analgesia from the well documented side effects associated with μ receptors.

The benzylic, 10-oxo group was introduced by making use of an unusual reaction of thebaine. Thebaine was known to react with tetranitromethane, in benzene in the presence of oxygen, to form a bridged peroxide, 8α,10α-epidioxy-8,14-dihydro-14β-nitrothebaine. This readily isomerises in the presence of base to give the 10-oxo alcohol, 8,14-dihydro-8β-hydroxy-14β-nitro-10-oxothebaine. In the present study the yield of the epidioxide was increased from 29% to 72% by conducting the nitration in the presence of ammonia gas to ensure complete reaction of the thebaine. It was further found that the epidioxide rearranged on Grade I alumina to give an isomeric acetal in which a peroxide oxygen had inserted into the C(7)-C(8) bond.

The epidioxide was first deoxygenated with triphenylphosphine to give the known 14β-nitro-8α,10α-epoxide, which was then reduced with zinc and ammonium chloride to yield the corresponding 14β-amino derivative. The aim was to use this new derivative as starting material for the preparation of 10-oxygenated analogues of a known series of potent analgesics, the 14β-acylamino-codeinones and -morphinones.

Accordingly, the 14β-amino-8α,10α-epoxide was converted into a series of 14β-acylamino compounds. The most potent of these, the *N*-3-phenylpropanoyl derivative, underwent ring opening with aqueous or methanolic hydrogen chloride to give 10α-hydroxy-14β-(3-phenylpropanoylamino)codeinone and the corresponding dimethyl acetal, respectively. Oxidation of the former gave the corresponding 10-oxo-codeinone. However, this 10-oxo analogue of 14β-(3-phenylpropanoyl-amino)codeinone was much less potent than the parent 10-methylene compound, and less potent even than normorphine. No κ-selectivity was observed. The only compounds to show any measurable κ activity were the 4-chloro- and 4-methyl-cinnamoyl derivatives of the 14β-amino-8α,10α-epoxide. Thevinols, produced by Grignard reactions of thevinone, the Diels-Alder cycloadduct of thebaine and but-3-en-2-one, are very potent analgesics. It was hoped that 10-oxo derivatives of thevinols might be potent, κ-selective compounds. 10-Oxothebaine, a new derivative of wider synthetic potential, was synthesised in the following way. The epidioxide was converted with sodium ethoxide into the 10-oxo alcohol, described earlier. The 14β-nitro group was removed reductively with tributyltin hydride and the resulting alcohol was dehydrated with phosphorus oxychloride to give 10-oxothebaine. As expected, this diene reacted with but-3-en-2-one to give 10-oxothevinone.

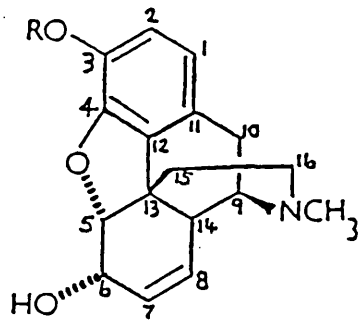
Introduction

Although the analgesic and euphoric properties of opium, the dried sap from the poppy *Papaver somniferum,* have been exploited for millenia, it was not until 1803 that the German pharmacist Freidrich Serturner isolated the main active component morphine (1).[1] The other main components are codeine (2), which is used as a cough suppressant, papaverine (3), which is a muscle relaxant, and thebaine (4) which is too toxic for clinical use.

The structure of morphine was determined by Gulland and Robinson[2] in 1925 and it was first synthesised by Gates and Tschudi in 1956.[3]

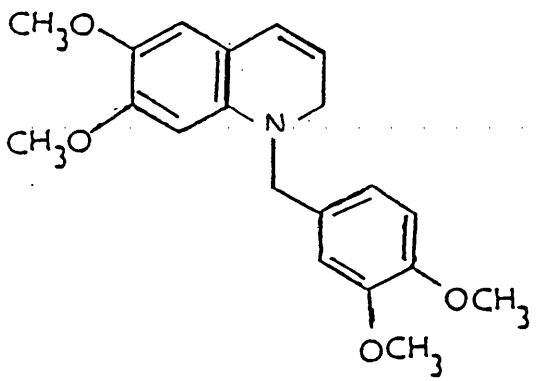
It has been clear from the early days of opium use that opiate analgesics produce a range of physical effects both desirable and undesirable. They produce, as well as analgesia, euphoria and dysphoria, nausea, constipation, respiratory depression and dependence liability,[4] the latter being the most serious side effect.

Heroin (5) was introduced in the 1890's as a safer analgesic, only to be shown later to have a higher dependence liability than the parent morphine. Work has continued for the last century in an attempt to produce non-addictive opiates. A large proportion of the earlier work revolved around the synthesis of simpler fragments of the morphine molecule. It was hoped that this would lead to a separation of the desirable and undesirable effects of morphine. The other driving force behind synthetic opiates was to remove the need for legitimate production of opium. With this removed it was hoped that it would have been easier to control

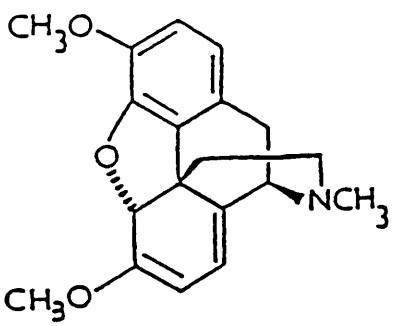


(1) R=H

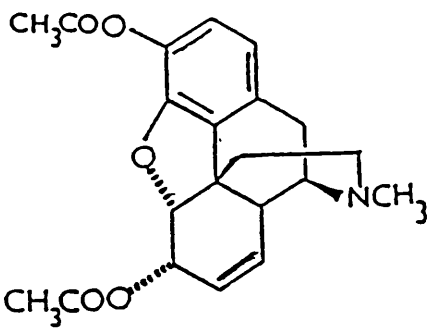
(2) R=CH_3



(3)



(4)



(5)

the abuse of opiates. The pursuit of a purely synthetic alternative to morphine produced many useful analgesics.

The first simplification possible is the removal of the oxygen bridge; this gives rise to morphinans.[5] Levorphanol (6) is a narcotic analgesic showing six to eight times the potency of morphine in man.

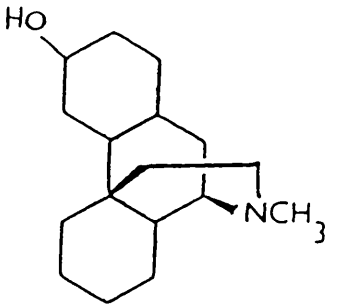
Benzomorphans[6,7,8] of the general structure (7) lack ring C but require alkyl substituents at the 5 and 6 positions for useful analgesic properties. Cyclazocine (8) has analgesic activity in man but also gives rise to a high incidence of hallucinogenic side effects.

The breaking of the ring B gives the 4-phenylpiperidines,[9,10,11] *e.g.* pethidine (9). However, for the most part their abuse and addiction potentials are every bit as great as those of other opiates.

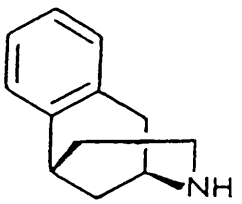
It has not yet been possible to separate the analgesia entirely from the undesirable side effects. In addition to the relief of chronic pain, few analgesics can relieve the same depth of pain as morphine or heroin. For this reason they are still widely used to treat the pain of terminally ill patients.

Bentley[12] suggested that the less complex molecules fit as well or better than morphine to the receptor and thus initiate the same effects. He further suggested that derivatives more complex and rigid than morphine itself would produce a better separation of the various activities. Ring C bridged derivatives of thebaine (4), derived from a Diels-Alder reaction with vinyl ketones and esters followed by further treatment with Grignard or organo-lithium compounds (Scheme 1.1) have been

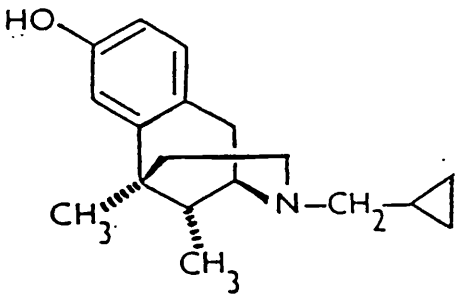
(6) **Levorphanol**



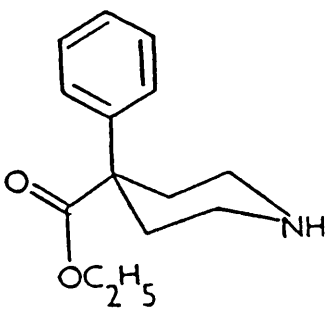
(7) **Benzomorphan**



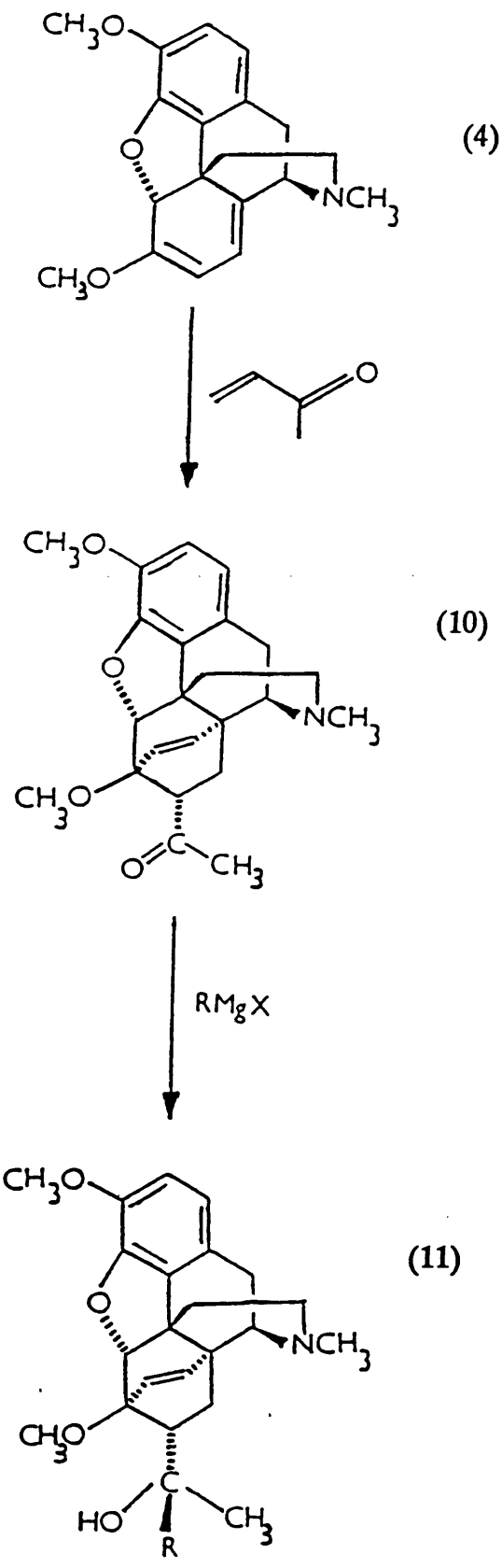
(8) **Cyclazocine**



(9) **Pethidine**



Scheme 1.1


CH3O
O
NCH3
CH3O
(4)
O
CH3O
O
NCH3
CH3O
O
C
CH3
(10)
RMgX
CH3O
O
NCH3
CH3O
C
HO
CH3
R
(11)

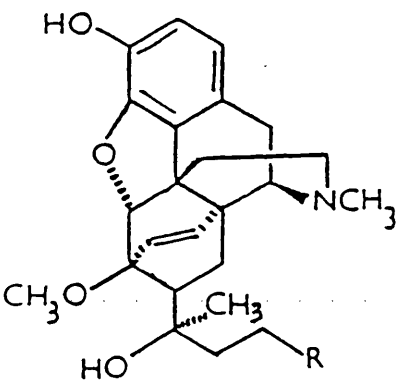
shown to be very potent. For example, etorphine (**12**) is many hundreds of times more potent than morphine.[12,13,14] Bentley and Lewis[15] showed that this introduction of a hydrophobic group [R in (**11**)] by organometallic reactions of thevinone (**10**) greatly increased the potency, with maximum activity being observed with the compound (**13**).

The introduction of a 14β-acylamino group[16] has also been shown to produce very potent analgesics.[17] Allen *et al.*,[16] produced 14β-cinnamoylaminocodeinone (**16**) from thebaine (Scheme 1.2) by first nitrating with tetranitromethane to give (**14a**). Reduction with zinc and ammonium chloride gave the amino-acetal (**14b**), which, after hydrolysis to the 14β-aminocodeinone (**15**), was readily acylated.

Receptors

For many years the only evidence that opiates acted through a receptor mechanism was the specificity of the interaction. Subtle changes in structure could drastically alter the potency of a compound, and usually only one of a pair of enantiomers exhibited strong binding.

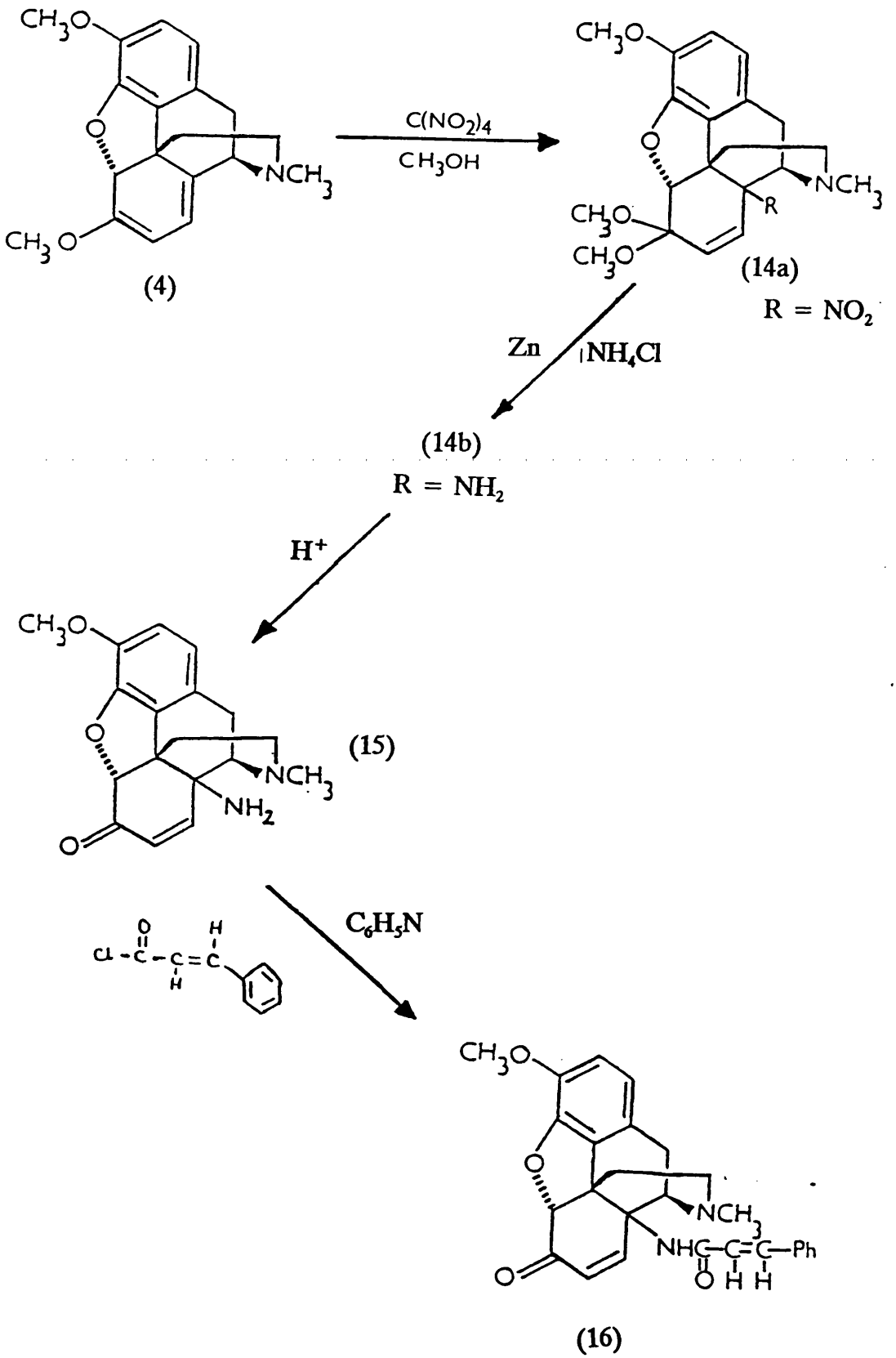
The isolation of methionine and leucine enkephalins (**17**) and (**18**) by Hughes and Kosterlitz in 1975[18] showed that morphine (**1**) and other analgesic alkaloids must act by mimicking the effect of these endogenous opiates. Opiate receptors occur not only in the brain (giving rise to the analgesic effect) but also elsewhere in the body, notably in the gut. The use of isolated tissues led to the development of *in vitro* testing procedures. Examination of the binding of various analgesics on tissues of different origin and selective use of antagonists led to the differentiation of opiate



(12) R=CH_3

(13) R=Ph

Scheme 1.2


CH3O
NCH3
CH3O
(4)
C(NO2)4
CH3OH
CH3O
CH3O
R
NCH3
(14a)
R = NO2
Zn
NH4Cl
(14b)
R = NH2
H+
(15)
NH2
C6H5N
Cl
NHC
C
Ph
(16)

receptors. The following types are now recognised: μ, or morphine-like, with morphine itself being a typical agonist;[19] κ, characterised by ethylketocyclazocine (EKC) (**20**);[19,20] δ, characterised by D-leucine enkephalin (**18**).[19,21]

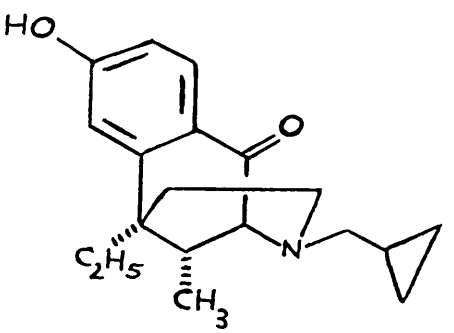
H-Tyr-Gly-Gly-Phe-Met-OH

(17)

H-Tyr-Gly-Gly-Phe-Leu-OH

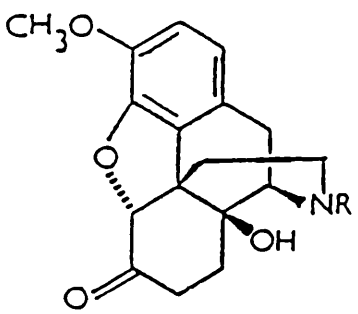
(18)

In most cases, both agonists and antagonists display a spectrum of activity rather than being purely one type. The evidence for a κ receptor is less conclusive than for the other two. EKC (**20**) was found to be poorly antagonised by opiate antagonists in the guinea pig ileum and mouse vas deferens.[22] Ethylketocyclazocine (**20**) differs structurally from cyclazocine (**8**) in having a keto group at C-1 and an ethyl rather than a methyl group at C-6. The κ/μ selectivity of EKC is greater than that of cyclazocine (**8**).[23] Archer *et al.*,[24] prepared 10-ketonaltrexone (**21**) and 10-keto-oxymorphone (**22**) by chromium trioxide-3,5-dimethylpyrazole oxidation of naltrexone 3-methyl ether (**23**) and oxycodone (**24**), respectively (Scheme 1.3). The 10-oxo compounds were found to be far less potent than naltrexone (**25**) and oxymorphone (**26**) at μ sites and had little affinity for κ and δ sites. It was therefore concluded that introduction of the 10-keto group in naltrexone and oxymorphone



(20)

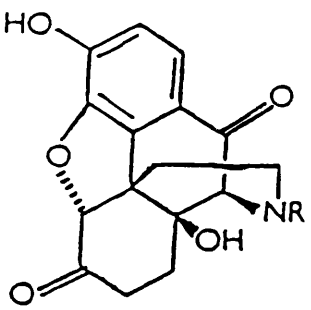
Scheme 1.3



(23) R= 

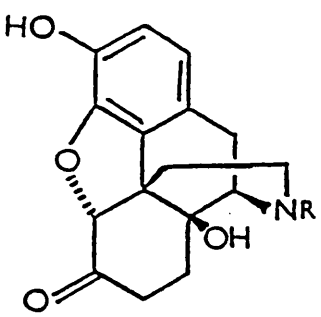
(24) R=CH_3

1. CrO_3-3,5 DMP
2. BBr_3



(21) R= 

(22) R=CH_3



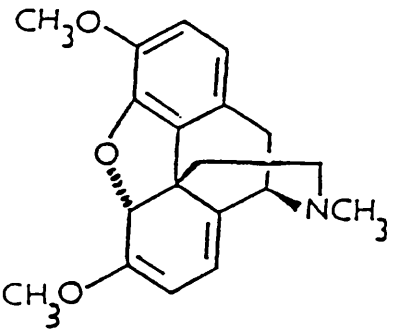
(25) R= 

(26) R=CH_3

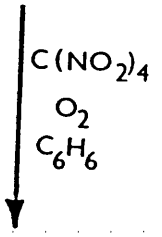
diminished affinity at all binding sites.

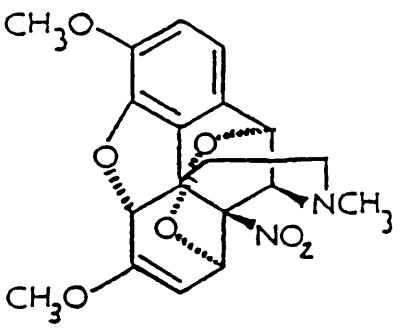
Allen *et al.*,[16] showed that it was possible to introduce a 10-oxo group by nitrating thebaine (**4**) with tetranitromethane in the presence of oxygen and isomerising the resulting epidioxide (**27**) with base (Scheme 1.4). The aim of the present project was to produce 10-oxo-substituted morphinans for evaluation as possible analogues of ethylketocyclazocine (**20**) *i.e.* κ selective analgesics. It was hoped to exploit the reaction of thebaine with tetranitromethane in the presence of oxygen and to use the epidioxide (**27**) as a starting material for a series of 10-oxy-substituted compounds. Since Archer *et al.*,[24] found that a 10-oxo group greatly diminished the potency of simple morphinans, it was desirable that much more potent morphinan nuclei should be used. Both 14β-acylaminomorphinones (**29**) and oripavinol type compounds (**30**) have potencies many hundred times that of morphine. It was therefore hoped that, by introducing a 10-oxo group into these morphinan types, usefully potent compounds would still be produced (Scheme 1.5).

Scheme 1.4

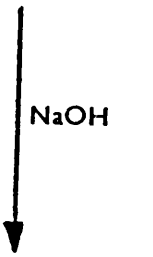


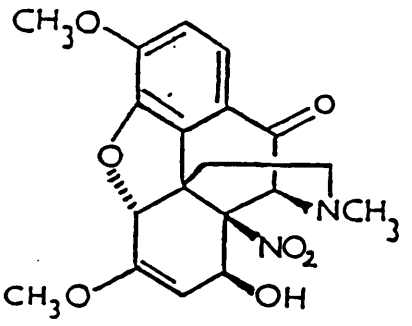
(4)





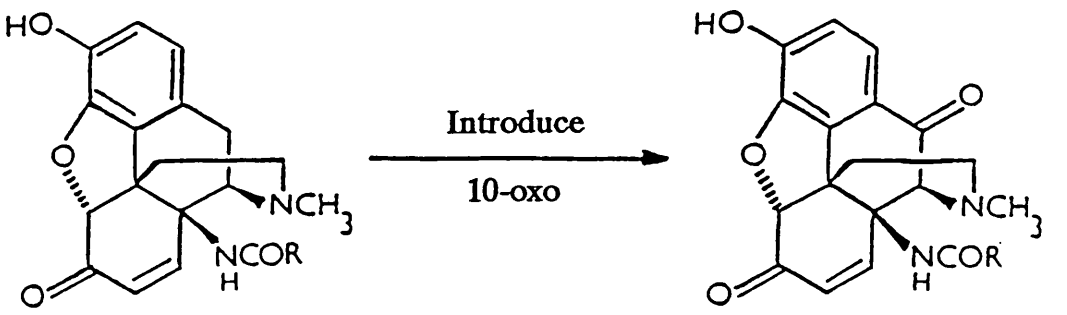
(27)





(28)

Scheme 1.5



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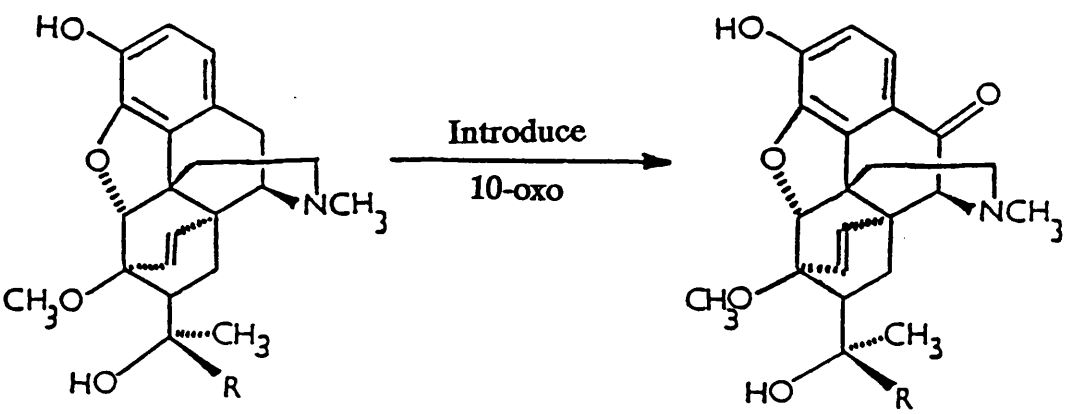


(30)

Discussion

The main aim of the project was to produce 10-oxo-morphinans for pharmacological testing. The starting point of the work was the reaction of thebaine (**4**) with tetranitromethane (Scheme 2.1). This was known to give the epidioxide (**27**) under some conditions. The epidioxide on treatment with base rearranges to give the 8β-hydroxy-10-oxo compound (**28**).

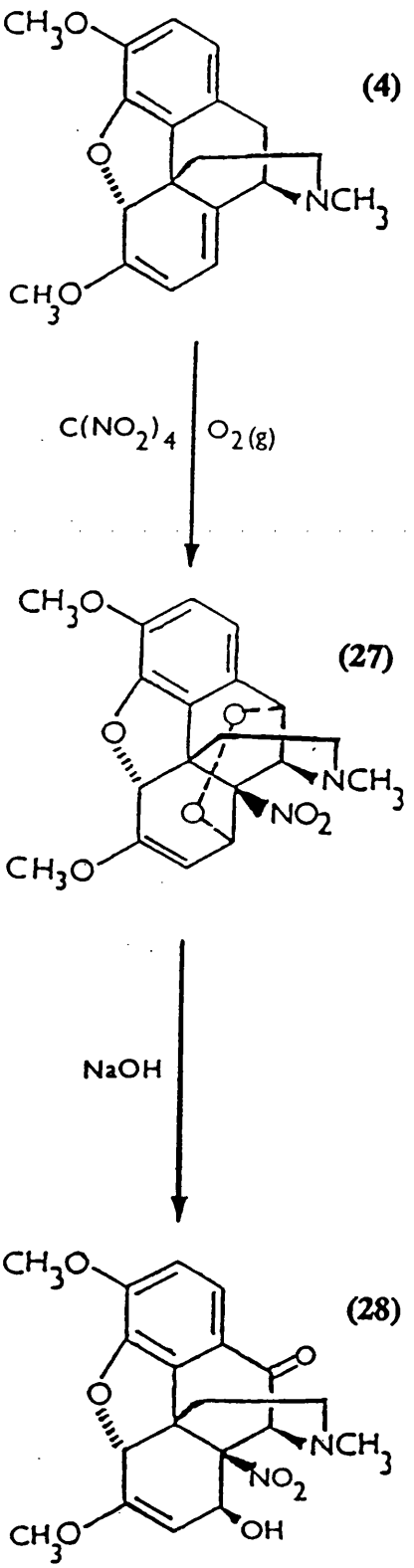
It was intended to prepare a series of 14β-acylamino compounds with a 10-oxo-substituent (**31**). The 14β-acylamino substituent was known to increase the potency of codeinone (**82**) and it was thought that a comparison of the two types would give information about the effect of the 10-oxo substituent on the potency and κ-selectivity.

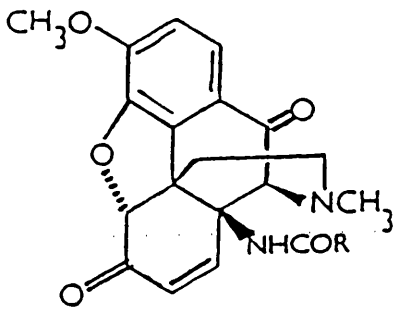
The first priority in the initial stages of the project was to repeat the procedure of Allen *et al.*,[16] to make the epidioxide, and to find ways of improving on the quoted yield of 31%, which was low because *ca.* half of the thebaine was converted into its trinitromethane salt. A large supply of the epidioxide was essential otherwise the synthesis of a series of compounds after several steps would have been impractical.

Nitration of thebaine

The nitration of thebaine with tetranitromethane gives different product ratios according to the solvent used. The reaction in methanol (Scheme 2.2) was found to give the trinitromethane salt (**33**) as a yellow precipitate, accounting for much of

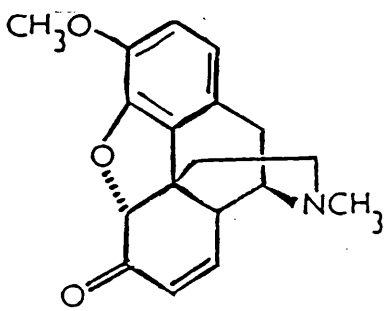
Scheme 2.1


CH3O
O
NCH3
CH3O
(4)
C(NO2)4
O2(g)
CH3O
O
NCH3
NO2
CH3O
(27)
NaOH
CH3O
O
O
NCH3
NO2
CH3O
OH
(28)



(31)

R = various



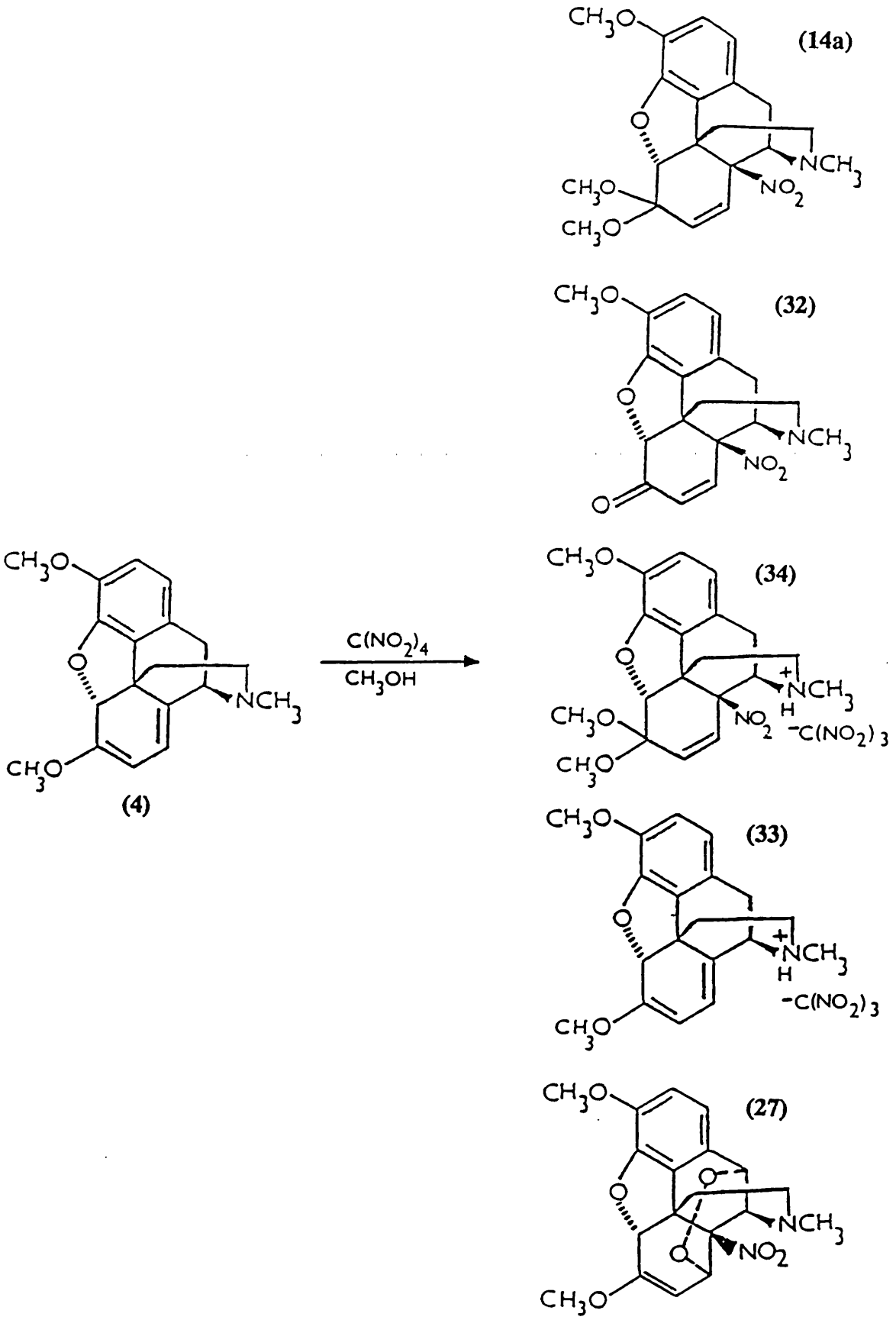
(82)

the thebaine. The 14β-nitrocodeinone dimethyl acetal (**14a**) was the major nitration product and a small amount of 14β-nitrocodeinone (**32**) was also produced. These were the expected products. An unexpected product was isolated by Allen[25] using preparative thin layer chromatography on alumina plates. This was later investigated by McDougall.[26] This compound (**27**) gave a base peak in its mass spectrum with *m/z* 342 along with a set of weak peaks, *m/z* 388, 389 and 390. The weak molecular ion peak frustrated unambiguous identification of the molecular formula.

The infra-red spectrum was similar to that of 14β-nitrocodeinone dimethyl acetal (**14a**). It was only when McDougall followed up the original work that a satisfactory microanalysis was obtained. The problem was that, on crystallisation from ethyl acetate, a non-stoichiometric solvate was formed. This was confirmed by X-ray crystallography, which showed the solvate to be disordered. Evidence for a solvate also comes from the observation that, when crystals of this epidioxide (**27**) are heated to 80°C, a phase change is observed and the clear crystals gradually become opaque as the solvent evaporates. The ^{1}H NMR spectrum showed, apart from signals expected for codeinone derivatives, two pairs of AB quartets at δ 5.42 and 4.22 (J 3.5 Hz) and δ 4.95 and 4.59 (J 6 Hz). These arose from H-10 and -9, and H-8 and -7, respectively. A series of chemical degradations, coupled with spectroscopic observations, eventually established the epidioxide structure (**27**). This was then confirmed by X-ray analysis, a necessary precaution because of the unprecedented structure of the product.

The nitration in methanol was ideal for gaining experience in handling

Scheme 2.2



tetranitromethane. The same mixture of nitration products was observed as reported,[16] but examination of the precipitated trinitromethane salt showed it to be a mixture of thebaine (**33**) and 14β-nitrocodeinone dimethyl acetal (**34**) salts in the approximate ratio of 11 : 1 (by ^{1}H NMR spectroscopy).

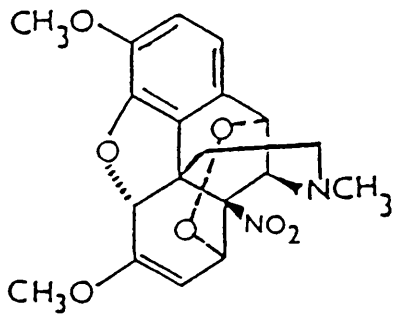
McDougall[26] had found that by conducting the reaction in benzene and passing oxygen in as a steady flow, a yield of 28% of the epidioxide (**27**) could be obtained. Again, about half the thebaine survived nitration as the trinitromethane salt. This reaction was repeated several times to provide enough of the epidioxide for the next step of the sequence. Initially the yield of the epidioxide was disappointing, less than 15%. This steadily increased with experience of the reaction and by the use of freshly prepared tetranitromethane.

In the course of this initial stage, during chromatographic purification of the epidioxide, it was observed to rearrange. Inadvertently, the crude product was applied to a column of grade I, rather than the recommended grade II or III alumina. A series of rearrangement products was observed and the major product, the 'isodioxide' (**35**), was isolated and characterised.

As a first task, it was decided to spend some time attempting to increase the yield of the epidioxide and in building up a suitably sized stock.

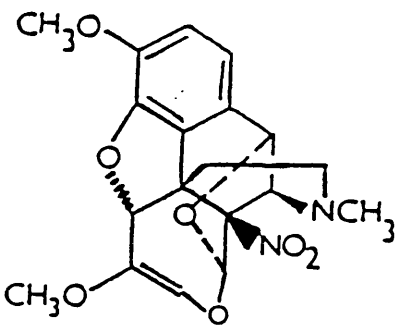
<u>Improving the yield of the epidioxide (27)</u>

The main cause of the low yield is the precipitation of thebaine as its trinitromethane salt (**33**). This was overcome in two different ways, firstly, by performing the reduction as normal then recovering the thebaine from the salt for reuse,



(27)

Al_2O_3 **(grade I)**



(35)

secondly, by introducing another base into the reaction mixture to compete for the trinitromethane. Both were found to work equally well on the basis of the thebaine consumed. The second method was of course preferable because no additional recovery stage was required. However, the first approach appeared, in principle, to be straightforward, while there was no guarantee that an added base would not interfere with the nitration.

Recovery of thebaine

The attempts to recover thebaine from the trinitromethane salt were split into two main types: partition between organic and aqueous phases and chromatographic recovery techniques.

Partition techniques

Partition between an organic solvent and an aqueous base is the classical method of recovering an alkaloid from a salt.[27] The salt was very slow to dissolve in any solvent and could not be made to partition completely when tertiary amines or a weak base, *e.g.* triethylamine or sodium bicarbonate, were used. Stronger bases, *e.g.* sodium hydroxide and ammonium hydroxide, were found to be more efficient. Chloroform is the best solvent for thebaine, but when it was used with strongly alkaline, aqueous phases, emulsions were produced that were difficult to separate. The best overall partition system giving good extraction without producing an emulsion was concentrated aqueous ammonium hydroxide and benzene. In this way thebaine was recovered in 72% yield from its salt. The toxicity of benzene and

doubts about the thermal stability of ammonium trinitromethide made this method unattractive for large scale, industrial use.

Chromatographic techniques

On t.l.c. plates the trinitromethane salt of thebaine gave two spots, corresponding to the salt and the free base. The separation was better on alumina rather than on silica, alumina being more efficient at adsorbing the trinitromethide anion.

The original aim was to find a method of separating the epidioxide and decomposing the trinitromethane salt of the unreacted thebaine on the same column. The discovery that the epidioxide rearranged on activated alumina meant that it was desirable to elute the epidioxide from the column as quickly as possible. For this purpose it was necessary to do a rapid first column which removed the products of nitration, which were purified separately. The remaining material, a mixture of thebaine and trinitromethane salts, was washed off this first column and applied to a second slower column. This second column recovered thebaine for subsequent further reaction. The cost of the solvents alone used for the two columns was in excess of 5 times the cost of the thebaine recovered. However, the following change in the nitration conditions led to virtually complete consumption of the thebaine.

Addition of base (Scheme 2.3)

It was already known that the presence of methanolic ammonia during the nitration of thebaine (4) with tetranitromethane in methanol improved the yield of 14β-nitrocodeinone dimethyl acetal (14a).[17] The by-product, ammonium trinitromethide is thermally unstable[28] and has been shown to be shock-sensitive (explosive). For this reason, it was decided to try the effect of triethylamine, instead of ammonia, on the nitration in benzene. When three equivalents of triethylamine were added to the usual reaction mixture, this produced a slight improvement in the yield of the epidioxide (27). However, it was very difficult to remove the excess of the triethylamine. When the reaction mixture was heated under vacuum it decomposed violently. It was decided therefore to use ammonia. It was thought that the ease with which the excess ammonia could be removed outweighed the lower stability of the ammonia salt.[29]

In the initial experiment, 3 mol equivalents of ammonia were added as a saturated solution in benzene to the benzene solution of thebaine. As before, oxygen was passed through the mixture during the addition of tetranitromethane. This improved the yield of the epidioxide slightly, but it was thought that the flow of oxygen had quickly reduced the concentration of ammonia dissolved in the benzene. Therefore, ammonia gas was passed continuously into the reaction mixture at the same time as the oxygen. The stability of the epidioxide (27) under these conditions was first tested. Both gases were passed through a solution of the epidioxide in benzene for 6 h. At the end of this time, the epidioxide was shown by thin layer

chromatography and ^1H NMR spectroscopy to be unchanged.

Nitration of thebaine with a steady flow of oxygen and ammonia was found to greatly increase the yield of the epidioxide. Although the yield was variable, it was never less than 65%. There was little if any thebaine remaining at the end of the reaction, certainly insufficient to justify recovery.

Not only did the ammonia effect essentially complete nitration of the thebaine, but the ammonium salt of the anion was easily washed out in the work-up and therefore the epidioxide could be chromatographed on silica instead of alumina. In this way the epidioxide could be chromatographed more rapidly and efficiently and without the danger of producing alumina-catalysed rearrangements.

The trinitromethide salt started to collect in the bottom of the reaction flask 20-30 min after addition of the tetranitromethane had been completed. Analysis of the precipitated trinitromethane salt, recovered from the bottom of the flask, by UV-visible spectroscopy showed it to contain less than 5% alkaloid. Most of the remaining trinitromethide anion was removed by washing the decanted benzene solution with saturated sodium hydrogen carbonate solution.

Careful evaporation of the benzene was necessary during work-up of the reaction mixture. The benzene solution still contained small quantities of the trinitromethide anion, therefore excessive heating had to be avoided. It was found that tetranitromethane, which had been used in excess, co-distilled with benzene in a rotary evaporator at temperatures greater than 30°C. The temperature was maintained between 30 and 40°C to ensure that co-distillation of the tetranitro-

methane took place without any decomposition of the trinitromethide salt that remained.

Conditions of reaction

1. *Solvent*

It was already known that the nitration took two distinctly different paths in methanol and in benzene.[16] It was expected that the reaction in toluene would give the same result as that in benzene. When the reaction was repeated in analytical grade toluene under the same conditions used in benzene (oxygen and ammonia gases were continually added and an excess of tetranitromethane was added slowly) the major nitration product was not the epidioxide but the 14β-nitrocodeinone (**32**), which was formed with the epidioxide in a ratio *ca.* 3 : 1. After efficient drying of the toluene, by distilling from sodium and treating the distillate twice with sodium wire, the ratio of the epidioxide to 14β-nitrocodeinone was improved to better than 2 : 1 (the epidioxide crystallised from mixture in ethyl acetate).

The reaction in benzene was nowhere near as sensitive to the purity of the solvent, nor did it produce more than a trace of the 14β-nitrocodeinone. For these reasons, all of the epidioxide was thereafter made using benzene as the solvent, despite the obvious safety considerations.

Oxygen is less soluble (0.128 cm^3 per cm^3 at 20°C and atmospheric pressure) in toluene than benzene (0.219). Also, ammonia is slightly less soluble (3.13 mol % at 20°C and atmospheric pressure) in toluene than in benzene (4.75).[30] These data may explain the observed benefit of benzene as the reaction solvent.

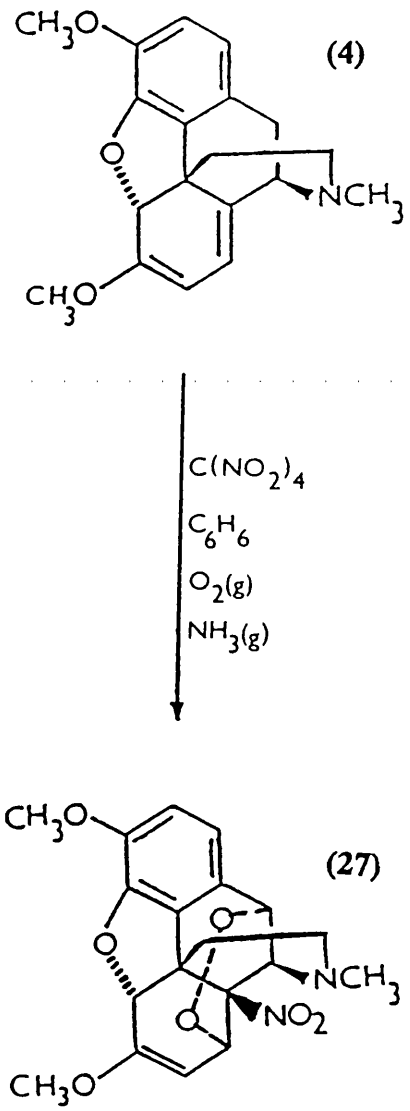
2. *Rate of addition of tetranitromethane*

Varying the rate of addition of tetranitromethane to the reaction mixture was found to have profound effects on the yield of nitration products and product composition. Allen *et al,*[16] specified a period of 12 min for the addition. Using this length of time at the same concentrations as they had used, in the absence of ammonia, was found to give similar results. When ammonia was passed through the reaction mixture continually it was found that the overall yield of nitration products increased dramatically but that the selectivity for the epidioxide was not improved. However, under the conditions used by Allen *et al,* the volume of benzene would have dissolved only 1/15th of a molecular equivalent of oxygen. Therefore, either an increase in the volume of benzene or a longer addition time for the nitrating agent might increase the yield of the epidioxide. This was found to be the case. When the addition time was increased to 20-30 min the yield of epidioxide increased to its maximum of 85%. However, further improvements on the yield were not obtained by addition over even longer times. An addition time of 75 min was found to produce only 51% epidioxide. This may be indirect evidence of a radical pathway to the formation of the epidioxide. Perhaps, at low concentrations of tetranitromethane, nitration by a radical chain mechanism may have been suppressed.

Tetranitromethane

Tetranitromethane is a mild nitrating agent. It is a colourless to pale green liquid (m.p. 13°C, b.p. 126°C), insoluble in water but soluble in most organic solvents. Pure tetranitromethane is stable, but in the presence of metals or organic bases

Scheme 2.3



highly unstable trinitromethane salts may be formed. Tetranitromethane is a strong oxidising agent, forming highly explosive mixtures with hydrocarbons.[28] The toxicity of tetranitromethane has been extensively studied since it was discovered to be a common atmospheric pollutant in trinitrotoluene production.[31]

Tetranitromethane has been prepared in may different ways but the simplest is the method described by Liang,[32] which is essentially that of Chattaway.[33,34] Acetic anhydride is slowly added to fuming nitric acid at 0°C. In this study it was confirmed that the fuming nitric acid had to be freshly distilled from sulphuric acid. When the nitric acid had not been distilled, the yield of tetranitromethane was reduced by at least an order of magnitude.

Initially, commercial tetranitromethane was used with indifferent results. Freshly prepared tetranitromethane was found to give much better and more reproducible results. Using the method outlined above, tetranitromethane (100-150 g) was easily prepared and was stored at 0°C for several weeks without significant loss of reactivity. This was used until a large supply of fresh, commercial tetranitromethane became available. Large batch to batch variations were found in both the freshly prepared and the commercially available material. It was found that the reactivity of a particular batch could be gauged by observing the rate of formation of the charge-transfer complex formed on addition of tetranitromethane to cyclohexa-1,3-diene. If the batch was fresh, a dark red colour was formed instantly and lasted for about a second before fading. If the batch was not fresh, the red colour was slower to appear and much less intense.

The formation of a charge transfer complex was also observed in the reaction with thebaine. Tetranitromethane forms a yellow-green complex with benzene. When this yellow-green solution was added dropwise to a colourless solution of thebaine a dark red thebaine complex was observed for a few seconds before it faded.

^{13}C spectrum of tetranitromethane

The ^{13}C NMR spectrum of tetranitromethane was reported previously[35] as a broad singlet. Carbon disulphide was used both as solvent and internal standard. In order to check the purity of the commercial tetranitromethane and of the sample that had been freshly prepared, both the ^{1}H and ^{13}C NMR spectra were recorded. The ^{13}C NMR spectra were at first obtained in deuteriochloroform alone. A very broad singlet was recorded with difficulty. The symmetrical nature of the molecule gave rise to a very long relaxation time. When the experiment was repeated with the addition of 20% v/v hexadeuteriobenzene to increase the asymmetry of the system, not only was the signal strength enhanced but the spectrum was resolved into the 'binomial' nonet expected from ^{13}C-^{14}N coupling, with relative intensities of 1, 8, 28, 56, 70, 56, 28, 8 and 1.

Effect of alumina on the decomposition of the epidioxide

It was found that, when the crude product from the nitration of thebaine was chromatographed on grade I, column grade basic alumina, a small amount of a compound, tentatively identified by ^{1}H NMR spectroscopy as the 8α-alcohol (**36**), was

produced. When the residence time on the alumina was increased by sealing the column for 2 h the amount of 8α-alcohol did not increase, but two other products were produced. One of these products represented > 95% of the isolated material (Scheme 2.4).

Similar reactions were also observed when grade I, column grade neutral alumina was used. Both the 8α-alcohol and the second minor component, believed to be the 8-oxo compound (**37**), were produced in greater quantities by reaction on basic alumina as compared with neutral alumina (as judged by ^{1}H NMR spectroscopy). The 8α-alcohol was not isolated in sufficient quantities to be fully characterised. A mixture containing the 8α-alcohol was epimerised with base and shown by ^{1}H NMR spectroscopy to be converted into the 8β-alcohol (**28**) (see Figure 2.1). Figure 2.2 shows ^{1}H NMR spectra of the mixtures obtained from basic and neutral grade I, column grade alumina.

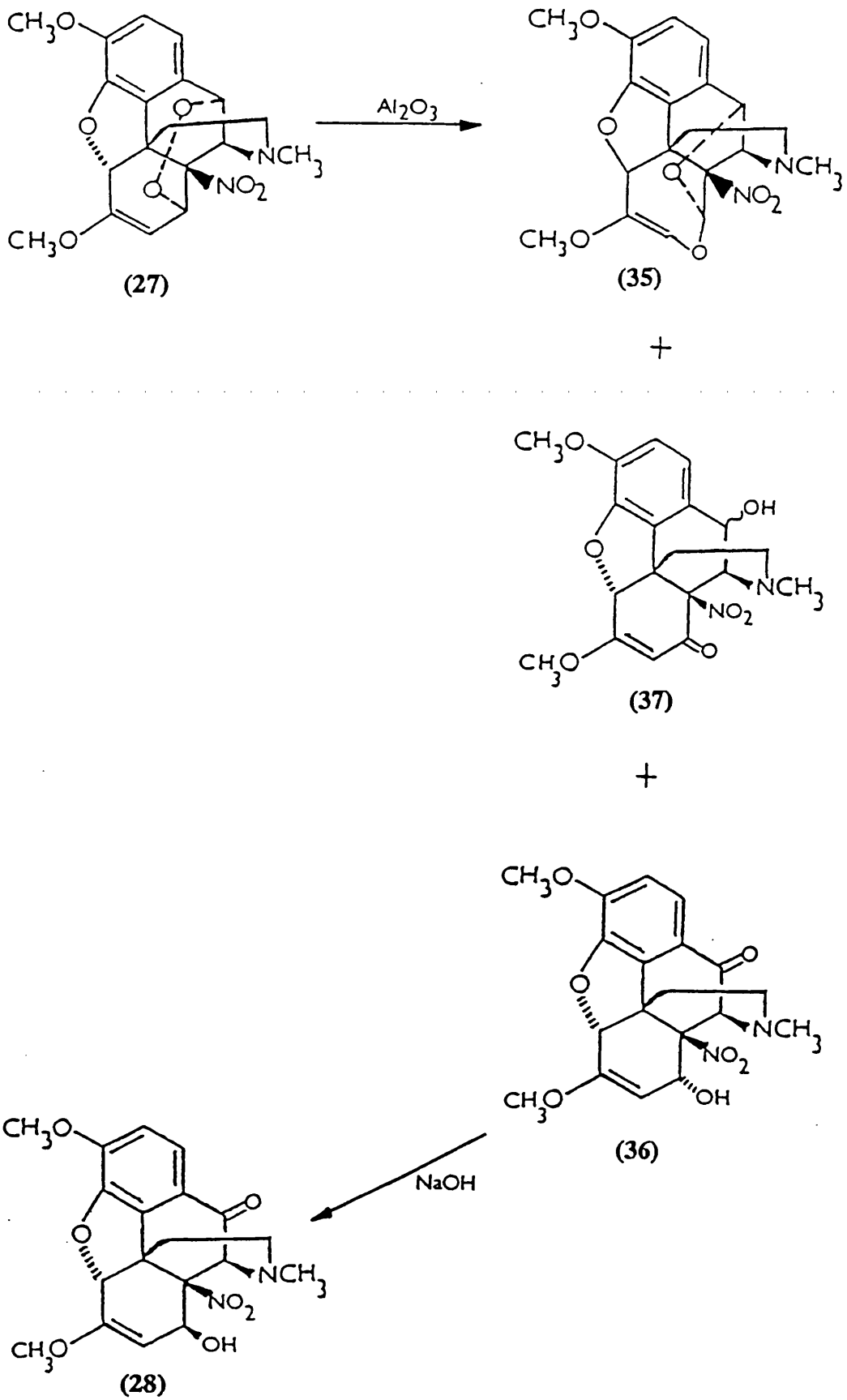
<u>The isodioxide (35)</u>

Microanalysis and mass spectrometry showed that the major product was an isomer of the epidioxide. However, unlike the epidioxide (**27**), the mass spectrum showed an intense molecular ion peak.

Treatment with sodium hydroxide in ethanol, even with heating under reflux, had no effect. It has already been shown[16] that under similar conditions the epidioxide (**27**) was converted to the 8β-alcohol (**28**).

Treatment with triphenylphosphine in refluxing benzene for 24 h, conditions that were known to deoxygenate the epidioxide (**27**), giving the epoxide[16] (**38**) had

Scheme 2.4



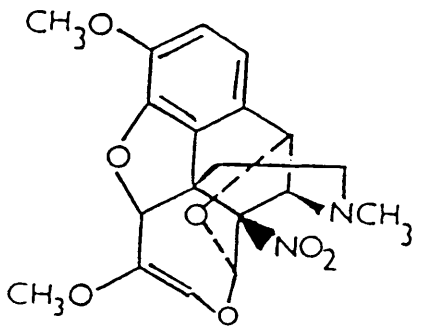
no effect. Similarly, an attempted reduction with sodium iodide in glacial acetic acid at room temperature produced no reaction after 30 h. Under similar conditions the epidioxide (**27**) was converted to the corresponding 8α,10α-diol.

Treatment with ferrous sulphate caused little change, but the ^{1}H NMR spectrum of the product showed two new peaks at δ 4.99 and 6.97. Treatment with D_2O caused the peak at δ 4.99 to disappear, and the peak at 6.97 was enhanced relative to its neighbours. However, if the isodioxide is an acetal (see below) then the ferrous sulphate may have caused partial, acid-catalysed, hydrolysis, rather than reduction.

Both the ^{1}H and ^{13}C NMR spectra indicated the presence of 7 deshielded CH groups, presumably corresponding to 1-, 2-, 5-, 7-, 8-, 9- and 10-CH of the epidioxide (**27**). However, there were substantial chemical shift differences and differences in the ^{1}H coupling constants for 2 pairs of CH groups.

The above evidence was originally thought to show that the isodioxide had the structure (**40**). The NMR spectra could be explained by the presence of an acetal and an amino acetal. Two of the CH groups of the isodioxide were found to resonate at a low field in the ^{13}C NMR spectrum. This reinforced the evidence for the structure (**35**) but could not distinguish it from other possible rearrangement products, for example (**40**). NMR and IR spectra both confirmed the absence of any hydroxy or carbonyl group.

If this product no longer had a peroxide bond (as suggested by its stability to triphenylphosphine and iodide) and had no hydroxy or carbonyl groups, then it must



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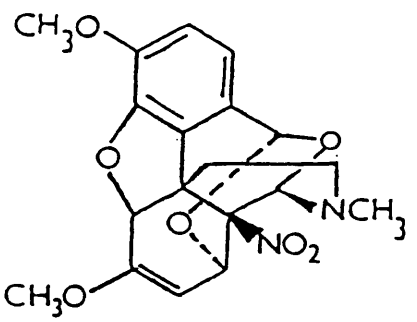


(40)

Table 2.1

Carbon-proton correlations from the n.m.r. spectra (200 MHz, $CDCl_3$) of the isodioxide (35)

Carbon Number	δ_C	δ_H[a], One-bond coupling	δ_H, Long-range coupling
6	154.8		3.4 (6-OMe), 5.2 (5-H), 5.7 (7-H)
3	146.1		3.9 (3-OMe), 6.9 (1-H)
4	145.1		5.2 (5-H), 6.8 (2-H)
12	130.3		2.4 (15β-H), 5.1 (10-H), 5.2 (5-H), 6.8 (1-H)
11	125.9		4.5 (9-H), 6.7 (2-H)
7	120.0	5.73 (d, *J* 1.4 Hz)	5.2 (5-H)
1	119.3	6.86 (d, *J* 7.1 Hz)	
2	113.9	6.75 (d, *J* 7.1 Hz)	
8	105.6	5.37 (s)	5.1 (10-H)
14	95.6		1.8 (15α-H), 4.5 (9-H), 5.1 (10-H)
5	92.7	5.21 (d, *J* 1.4 Hz)	5.7 (7-H)
10	76.6	5.12 (d, *J* 4.4 Hz)	4.5 (9-H), 5.4 (8-H), 6.8 (1-H)
9	71.3	4.47 (d, *J* 4.4 Hz)	2.5 (NMe)
3-OMe	56.3[c]	3.88 (s)	
6-OMe	56.1[c]	3.44 (s)	
13	46.6		1.8 (15α-H), 2.5 (16-H), 4.5 (9-H), 5.2 (5-H)
16	45.8	2.52[b] (m)	2.5 (NMe), 4.5 (9-H)
NMe	43.1	2.52 (s)	2.52 (16-H), 1.9 (15α-H)
15	31.1	1.78 (m) and 2.39 (m)	

a; multiplicity and $J_{H,H}$ from the ^1H spectrum

b; approximate centre of multiplet

c; may need to be reversed

Table 2.2

Carbon-proton correlations from the n.m.r. spectra (200 MHz, $CDCl_3$) of the epoxide (38)

Carbon Number	δ_C	δ_H One-bond coupling	δ_H Long-range coupling
6	156	-	5.33 (5-H), 4.75 (8-H), 3.56 (6-OMe)
3	146	-	6.7, 3.90 (3-OMe)
4	144	-	6.7, 5.35 (5-H)
12	132.5	-	6.7, 5.33 (5-H), 5.05 (10-H)
11	128	-	6.7, 4.68 (9-H)
1	119	6.78 (d, *J* 8 Hz)	6.7, 5.05 (10-H)
2	114.5	6.72 (d, *J* 8 Hz)	6.7
7	97.5	4.80 (d, *J* 5-8 Hz)	5.33 (5-H). 4.75 (8-H)
14	90	-	5.05 (10-H), 4.75 (8-H), 4.68 (9-H), 1.87 ($15_{eq.}$-H)
5	86	5.33 (s)	5.33, 4.80 (7-H)
10	77	5.05 (d, *J* 5.2 Hz)	6.7, 5.05, 4.68 (9-H)
8	76	4.75 (d, *J* 5.8 Hz)	5.05 (10-H), 4.75
9	68	4.68 (d, *J* 5.2 Hz)	2.60 ($16_{eq.}$-H), 4.68
3-OMe	56.5	3.90 (s)	3.90
6-OMe	55	3.56 (s)	3.56
13	46.5	-	4.68 (9-H), 2.55 (NMe or $16_{eq.}$-H)
16	46.5	2.47 (ddd, *J* 11.5,10.9,5.0 Hz, 16_{ax}-H) 2.60 (ddd, *J* 11.5,5.4,2.3 Hz, $16_{eq.}$-H)	4.68 (9-H)
NMe	43	2.55 (s)	2.55 (NMe or $16_{eq.}$-H), 1.87 ($15_{eq.}$-H)
15	28	2.02 (ddd, *J* 13.5,10.9,5.3 Hz, 15_{ax}-H) 1.87 (ddd, *J* 13.5,4.9,2.2 Hz, $15_{eq.}$-H)	2.02 (15_{ax}-H), 1.87 ($15_{eq.}$-H)

Table 2.3

Carbon-proton correlations from the n.m.r. spectra (200 MHz, $CDCl_3$) of the epidioxide (27)

Carbon Number	δ_C	δ_H, One-bond coupling	δ_H, Long-range coupling
6	160.15		5.29 (5-H), 4.98 (8-H), 3.55 (6-OMe)
3	146.2		6.95 (1-H), 3.89 (3-OMe)
4	142.0		6.80 (2-H), 5.29 (5-H)
12	132.7		6.95 (1-H), 5.41 (10-H), 5.29 (5-H), 2.25
11	124.1		6.80 (2-H), 5.41 (10-H), 4.22 (9-H)
1	120.1	6.95 (d, *J* 8.2 Hz)	6.95 (1-H), 5.41 (10-H)
2	114.05	6.80 (d, *J* 8.2 Hz)	6.80
7	90.15	4.57 (d, *J* 5.2 Hz)	5.29 (5-H), 4.98 (8-H), 4.57
14	87.4		5.41 (10-H), 4.57 (7-H), 4.22 (9-H), 1.60
5	86.1	5.29 (s)	5.29, 4.57 (7-H)
8	78.8	4.98 (d, *J* 5.2 Hz)	4.98, 4.57 (7-H)
10	76.3	5.41 (d, *J* 3.4 Hz)	6.95 (1-H), 5.41, 4.22
9	62.2	4.22 (d, *J* 3.4 Hz)	4.22, 2.55, 2.45
3-OMe	56.2	3.89 (s)	3.89
6-OMe	55.3	3.55 (s)	3.55
16	45.25	2.49 (m)	4.22, 2.55, 2.45, 2.25, 1.6
13	44.2		5.29, 4.98, 4.22, 2.45, 2.25, 1.60
NMe	42.3		2.85, 2.55, 2.20
15	28.9	1.60 (m)	2.25, 1.60

Table 2.4

^{13}C N.m.r. spectra (50.4 MHz, $CDCl_3$) of the epidioxide, isodioxide, and oxide

	Epidioxide (27)	Isodioxide (35)	Oxide (38)
1	120.1	119.3	119.0
2	114.0	113.9	114.5
3	146.2	146.1	146.0
4	142.0	145.1	144.0
5	86.1	92.7	86.0
6	160.1	154.8	156.0
7	90.1	120.0	97.5
8	78.8	105.6	76.0
9	62.2	71.3	68.0
10	76.3	76.6	77.0
11	124.1	125.9	128.0
12	132.7	130.3	132.5
13	44.2	46.6	46.5
14	87.4	95.5	90.0
15	28.9	31.1	28.0
16	45.2	45.8	46.5
NMe	42.3	43.1	43.0
3-OMe	56.2	56.3	56.5
6-OMe	55.3	56.1	55.0

a; at 25.2 MHz

Table 2.5

^{1}H N.m.r. spectra (200 MHz, $CDCl_3$) of the epidioxide, isodioxide, and oxide

	Epidioxide (27)	Isodioxide (35)	Oxide (38)
1	6.95 (d, *J* 8.2 Hz)	6.86 (d, *J* 7.1 Hz)	6.78 (d, *J* 8 Hz)
2	6.80 (d, *J* 8.2 Hz)	6.75 (d, *J* 7.1 Hz)	6.72 (d, *J* 8 Hz)
5	5.29 (s)	5.21 (d, *J* 1.4 Hz)	5.33 (s)
7	4.57 (d, *J* 5.2 Hz)	5.73 (d, *J* 1.4 Hz)	4.80 (d, *J* 5.8 Hz)
8	4.98 (d, *J* 5.2 Hz)	5.37 (s)	4.75 (d, *J* 5.8 Hz)
9	4.22 (d, *J* 3.4 Hz)	4.47 (d, *J* 4.4 Hz)	4.68 (d, *J* 5.2 Hz)
10	5.41 (d, *J* 3.4 Hz)	5.12 (d, *J* 4.4 Hz)	5.05 (d, *J* 5.2 Hz)
$15_{eq.}$		1.78 (dt, *J* 13.0 and 2.7 Hz)	
$15_{ax.}$		2.39 (ddd, *J* 13.0, 10.3, and 6.9 Hz)	
16		2.53 (m)	
NMe	2.52 (s)	2.52 (s)	2.55 (s)
3-OMe	3.89 (s)	3.88 (s)	3.90 (s)
6-OMe	3.55 (s)	3.44 (s)	3.56 (s)

contain 2 new C-O bonds. However, on the above evidence it was not possible to confirm either (**35**) or (**40**) as the structure. It was decided to use 2-dimensional NMR techniques to try and prove the structure. Correlation spectra were run for the epidioxide (**27**), the epoxide (**38**) and the isodioxide (**35**). The data for direct and long-range correlations for the three compounds are given in Tables 2.1, 2.2 and 2.3, respectively. These data are correlated, giving ^{1}H and ^{13}C NMR shifts for comparable carbons and protons in Tables 2.4 and 2.5.

Using the signals for the aromatic C-H groups (which are relatively unchanged in all three compounds) as the starting point, it is possible to work around the molecule in stages using direct carbon/proton correlation and long-range (three bond) carbon/proton correlations.

For the isodioxide it was possible to go round the entire molecule in both directions, showing it to have the structure (**35**). The correlations that show the isodioxide has the structure (**35**) with an oxygen inserted between C-8 and C-7 rather than the alternative (**40**), with the oxygen between C-9 and C-10 are:

1. C-11/H-9 (δ ^{13}C 125.9, δ ^{1}H 4.47). This correlation is seen in all the compounds. If the oxygen had been between C-9 and C-10 this would have increased the C-H/H-9 distance by one bond, reducing the possibility of observing a coupling.
2. C-6/H-8. This correlation is missing from the isodioxide (**35**) but is present in both the epidioxide (**27**) (δ ^{13}C 160.15, δ ^{1}H 4.98) and epoxide (**38**) (δ ^{13}C 156.0, δ ^{1}H 4.75).

3. The correlations between C-8/H-10 (δ ^{13}C 105.6, δ ^{1}H 5.1) and between C-10/H-8 (δ ^{13}C 76.7, δ ^{1}H 5.4) are both present in the isodioxide. This clearly shows that only a single oxygen is between C-8 and C-10 rather than two.

The alternative structure is also discounted because of the low shift of C-10 and the high shifts of C-7 and C-8.

Mechanism

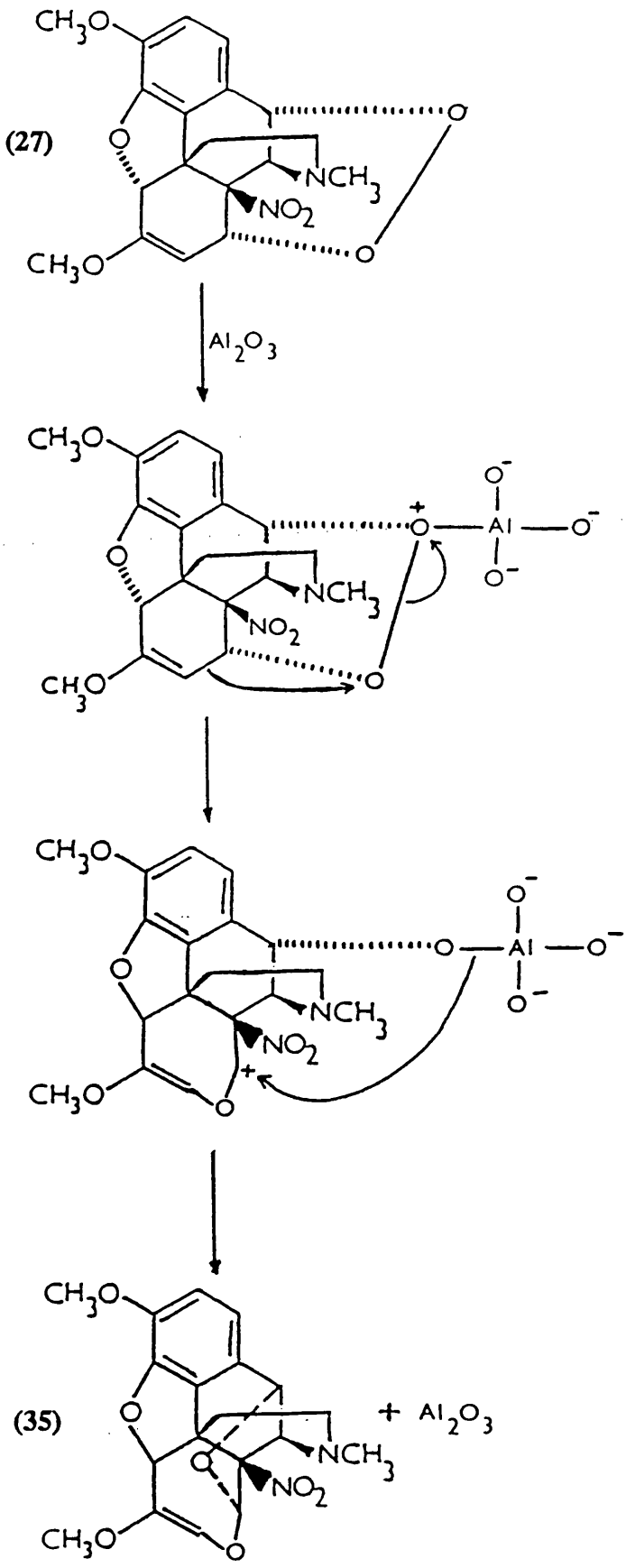
The rearrangement can be viewed as the formal migration of the vinyl group to the electron-deficient oxygen, catalysed by the action of the alumina (Scheme 2.5). This is followed by attack of C-8 by 0-10, leading to the acetal of structure (**35**).

Criegee *et al,*[36,37] studied the decomposition of acylperoxides in the presence of Lewis acids. They showed that the rate of decomposition of peroxy-esters of the type (**83**) to give oxygen bridged bicyclo alkyl esters (**84**) (Scheme 2.6) was proportional to the anionic stability of the parent acid *e.g.* Cl_3CCO- > P-$O_2NC_6H_4CO$-. The reaction was therefore shown to involve heterolytic rather than homolytic cleavage of the O-O bond.

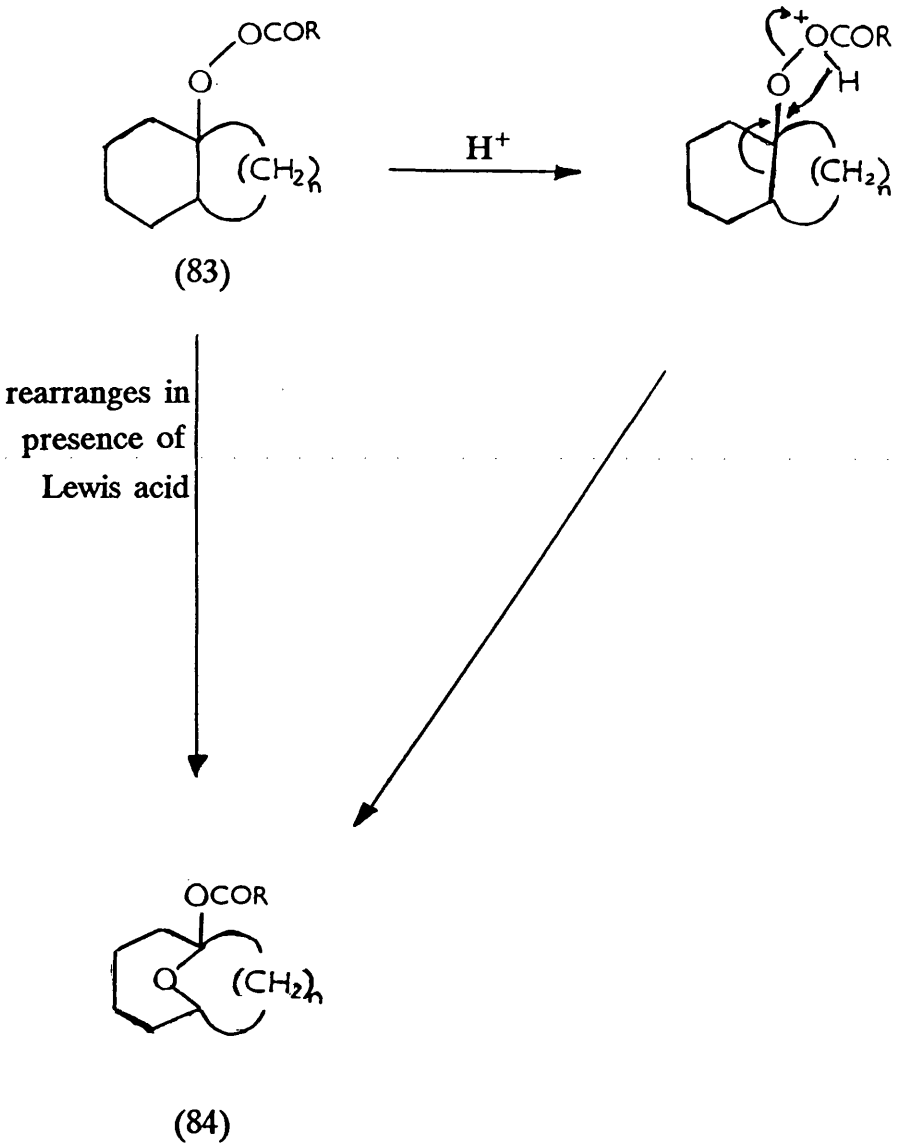
The 8-oxo compound

For the two minor components, the yield of the 8-oxo compound showed the most dependence on the basicity of the alumina (see foregoing comparison of neutral and basic alumina). It was only ever produced in very small quantities (less than 5 mg in total) but was tentatively assigned the enone structure (**37**) on the basis of its ^{1}H NMR spectrum; δ 5.47 (s, 7-H), 5.29 (s, 5-H), 5.10 (br d, J 10 Hz, 10β-H), 4.38

Scheme 2.5



Scheme 2.6


OCOR
O
(CH2)n
H+
+OCOR
O
H
(CH2)n
(83)
rearranges in
presence of
Lewis acid
OCOR
O
(CH2)n
(84)

(s, 9-H), 3.86 (s, 3-OMe), 3.72 (s, 6-OMe), and 2.52 (s, NMe). This structure explains the large shift in the position of the 6-methoxy signal. A similar value, δ 3.77 was reported by Allen *et al.*,[16] for the 8,10-dione, whereas other compounds in the series, lacking an 8-oxy group, give signals within the range δ 3.44-3.56 for the 6-methoxy group.

The 8α-alcohol (36)

As already mentioned, it was the discovery of the presence of the 8α-alcohol (**36**), after chromatography of the epidioxide, that initiated the work on alumina catalysed isomerisation.

As for the 8-oxo compound, the 8α-alcohol was only ever isolated in small quantities and was never produced in sufficient purity to be completely characterised.

The two epimers had very similar I.R. and ^{1}H NMR spectra. The only major difference in the ^{1}H NMR spectra was in the coupling of 7- and 8-H. In the 8α-alcohol the coupling cannot be interpreted at 90 MHz because it is so small, whereas in the 8α-alcohol the protons are no longer approximately parallel to each other and the coupling is increased to 6 Hz.

Synthesis of the epidioxide (42) from *N*-cyclopropylmethyl-*N*-northebaine (41)

The *N*-cyclopropylmethyl (*N*-cpm) group has been shown in many classes of analgesics to confer antagonist or partial agonist properties.[38] There was interest therefore in a synthesis of 10-oxo *N*-cpm derivatives.

An attempt was made to demethylate 10-oxo-14β-(3-phenylpropanoylamino)-

Figure 2.1. ^{1}H NMR of 8α-alcohol.

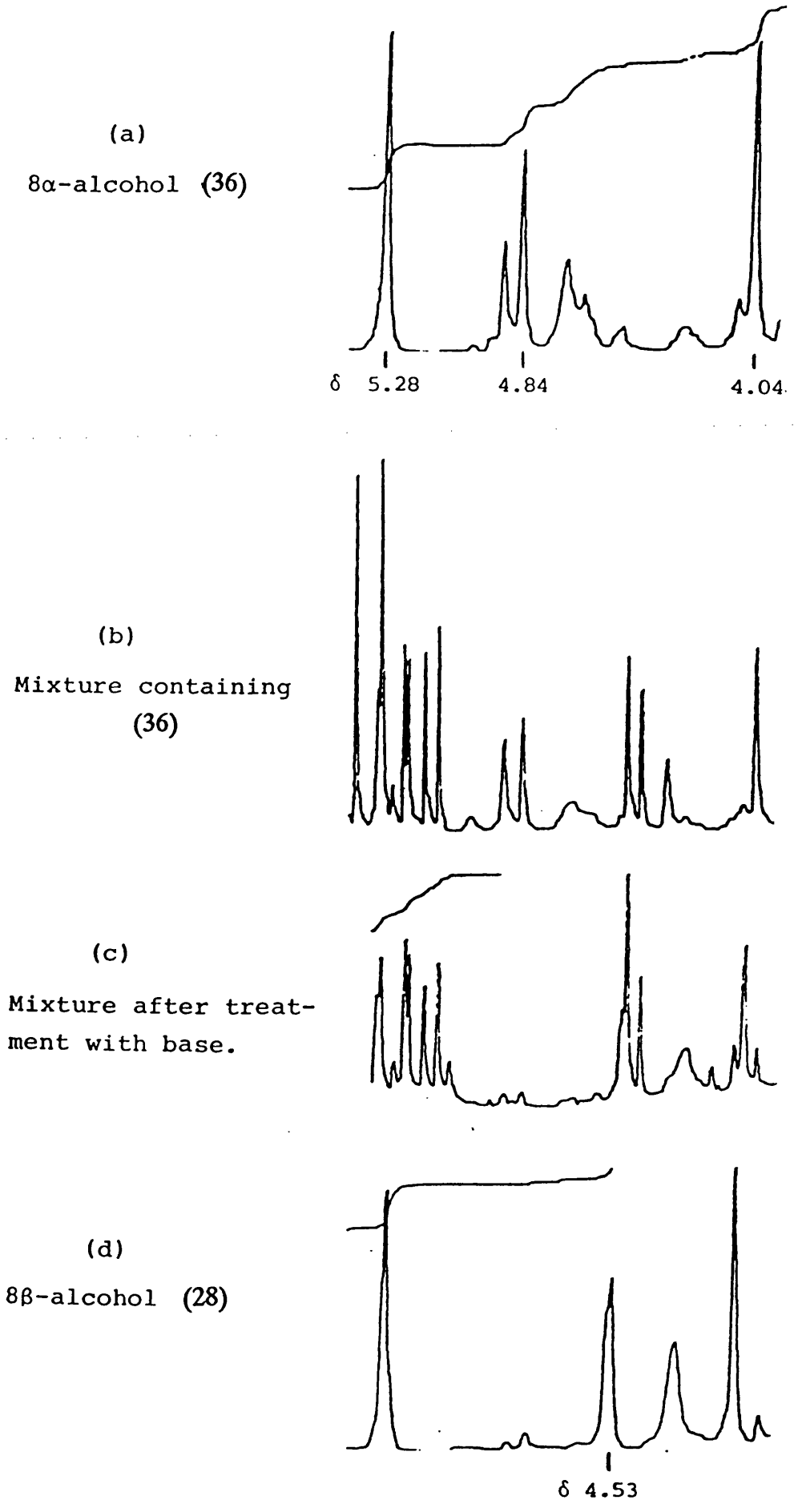
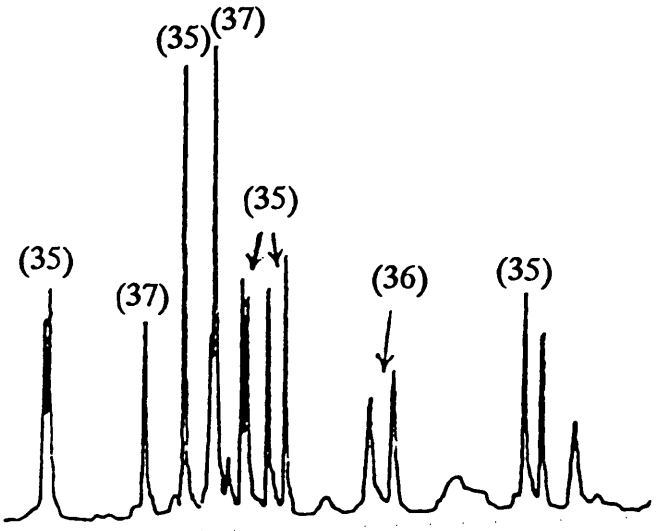
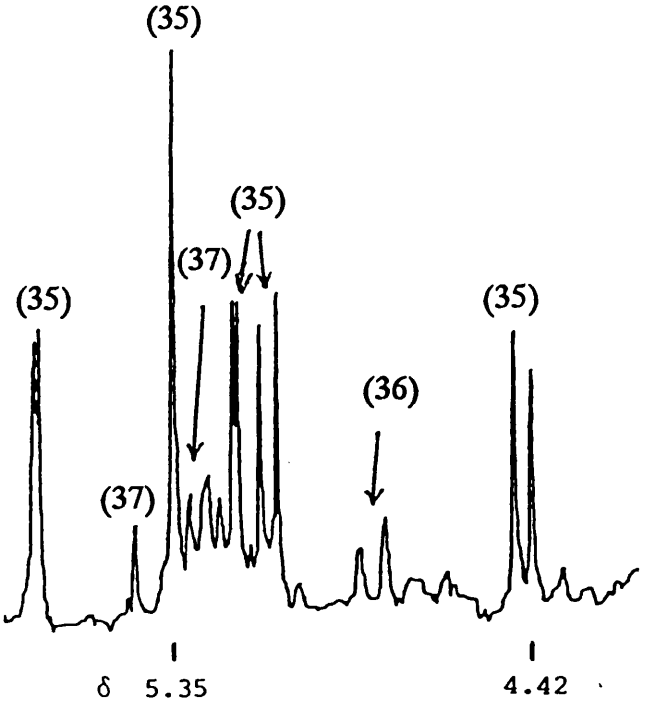


Figure 2.2. Comparison of rearrangement products by ^1H NMR.



(a)

Reaction of epidioxide on basic alumina



(b)

Reaction on neutral alumina

codeinone (**69**) (see page 72) using diethyl azodicarboxylate, followed by hydrolysis. The codeinone (**69**), after treatment with diethyl azodicarboxylate, was found to give a large number of products. This approach was therefore abandoned in favour of nitrating *N*-cpm thebaine (**41**) in the presence of oxygen and to use the derived epidioxide as the starting material for a new series (Scheme 2.7).

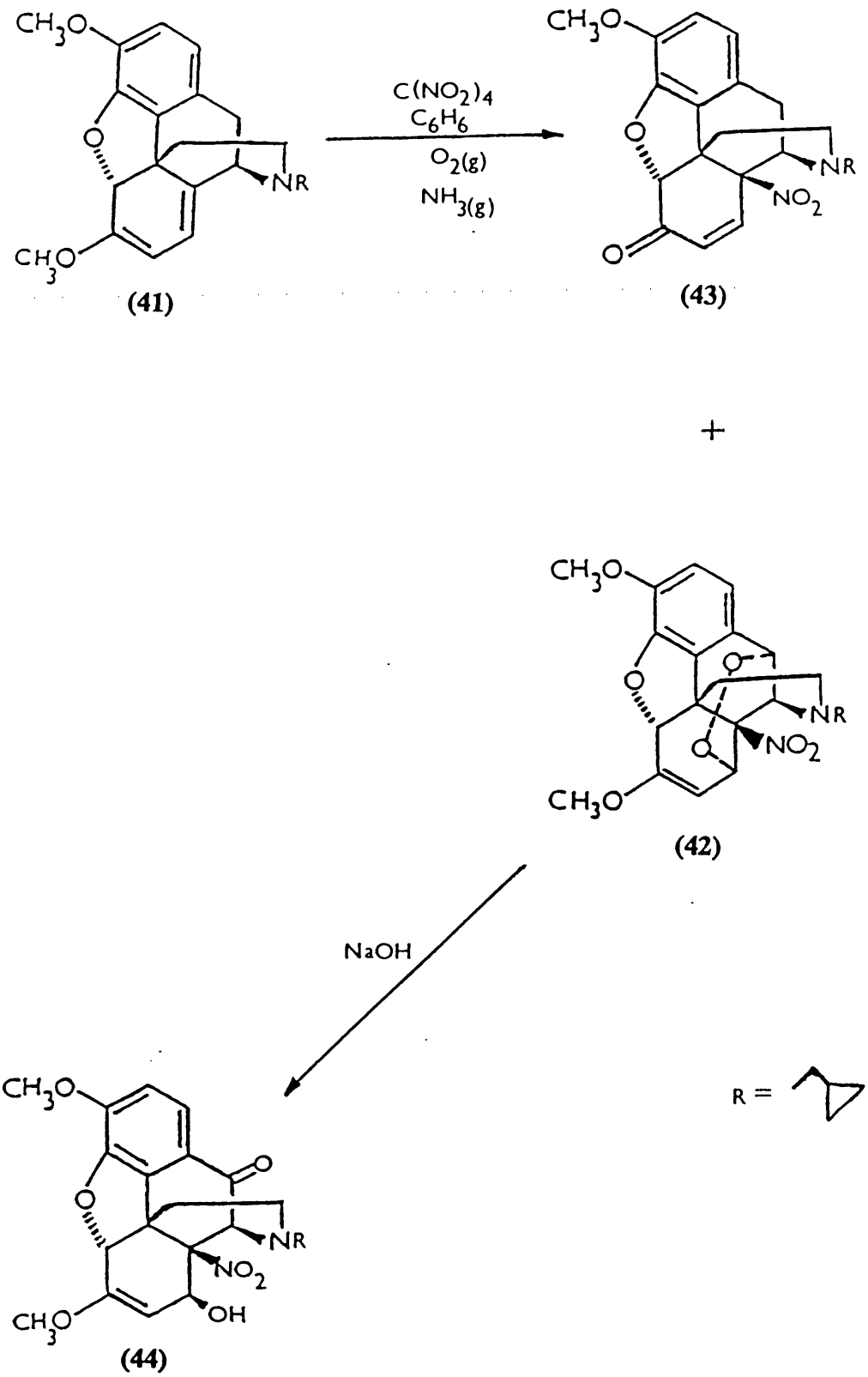
Nitration of *N*-cyclopropylmethyl-*N*-northebaine (41)

N-Cyclopropylmethyl-*N*-northebaine (**41**) was prepared from thebaine,[39] *i.e.* by demethylation with diethyl azodicarboxylate, followed by alkylation with cyclopropylmethyl bromide and sodium iodide in acetone. Nitration of *N*-cpm-*N*-northebaine with tetranitromethane was carried out using the normal conditions worked out for the nitration of thebaine (**4**). When, in a control experiment, ammonia gas was passed into a benzene solution of *N*-cpm-*N*-northebaine a small quantity of the alkaloid was precipitated. Upon evaporation of the mixture, the *N*-cpm-*N*-northebaine was shown by t.l.c. to be unchanged.

The nitration of *N*-cyclopropylmethyl-*N*-northebaine (**41**) with tetranitromethane was found to be less selective than that of thebaine. The nitrated products were the required *N*-cpm-epidioxide (**42**) and *N*-cpm-14β-nitro-*N*-norcodeinone (**43**) in approximately equal amounts, as judged by ^{1}H NMR spectroscopy. The lower yield of the new epidioxide (**42**) than of the old (**27**) and the similar R_f values of the epidioxide (**42**) and *N*-cpm-14β-nitro-*N*-norcodeinone (**43**) made the product mixture more difficult to chromatograph.

The increased flexibility around the nitrogen in a morphinan with an *N*-cyclo-

Scheme 2.7


CH3O
O
NR
CH3O
C(NO2)4
C6H6
O2(g)
NH3(g)
CH3O
O
NR
NO2
O
(41)
(43)
+
CH3O
O
O
NR
NO2
CH3O
(42)
NaOH
CH3O
O
O
NR
NO2
CH3O
OH
(44)
R =

propylmethyl group often makes crystallisation much more difficult. The new epidioxide (**42**) was, as expected, difficult to crystallise. To confirm the peroxy linkage the product was treated with base to give the *N*-cpm-8β-hydroxy-10-oxo compound (**44**). This crystallised readily and its full characterisation confirmed the peroxide. Eventually a small crop of crystals of the *N*-cpm-epidioxide (**42**) was obtained for microanalysis.

First proposed synthetic route to 14β-acylamino-10-oxo morphinans (31)

It had previously been shown that the 14β-nitrocodeinone dimethyl acetal (**14a**) was impossible to reduce without opening the 4,5-oxide bridge.[55]

Treatment of the epidioxide (**27**) with sodium hydroxide was known to give the 8β-hydroxy-10-oxo compound (**28**).[26] It was hoped that treatment of this ketone with methanolic hydrogen chloride would then give the 14β-nitro-10-oxo-codeinone dimethyl acetal (**45**) and that successive reduction and acylation would give the 14β-acylamino-10-oxo-morphinans (**31**) (Scheme 2.8).

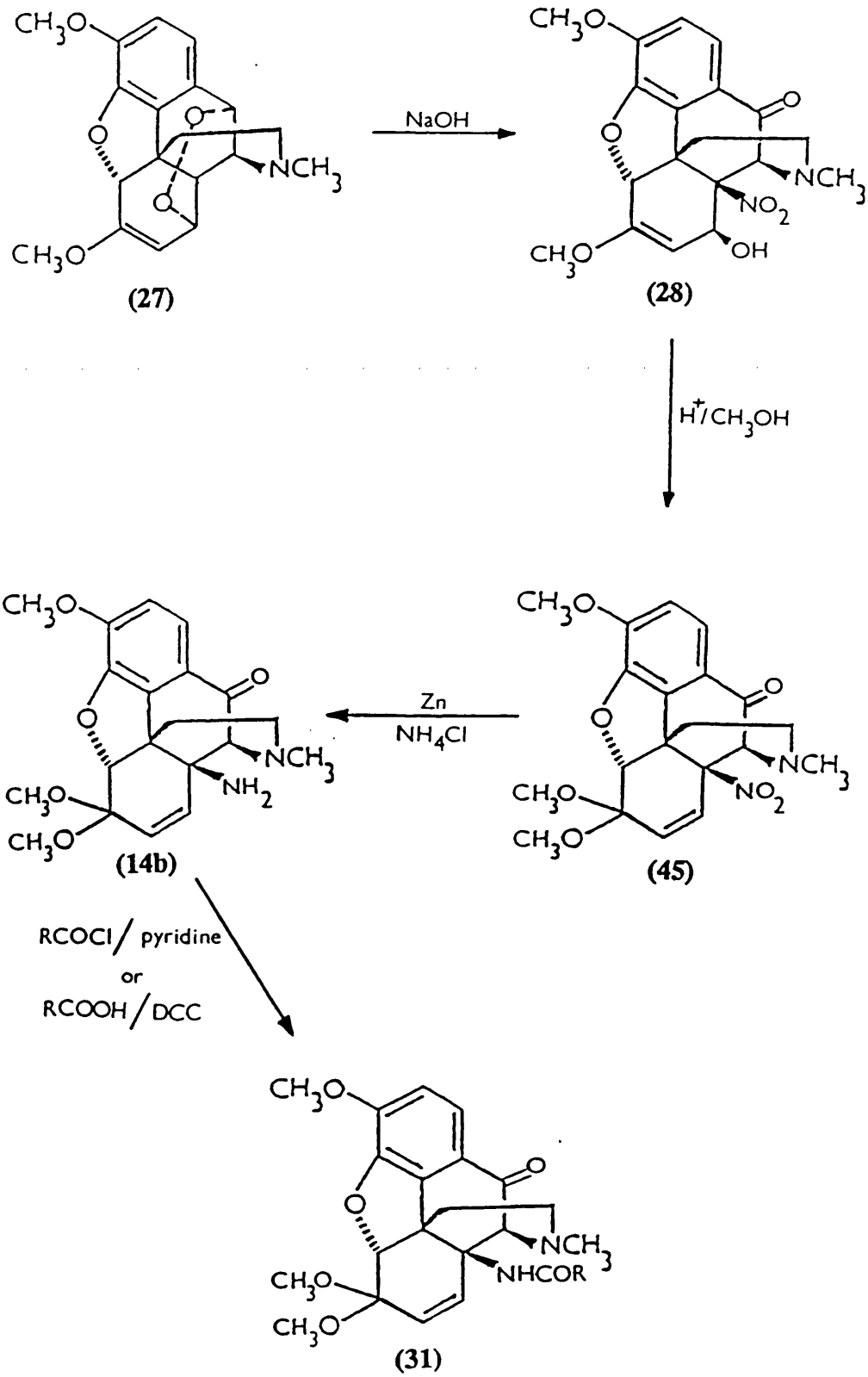
Isomerisation of the epidioxide (27) with base

As explained, the epidioxide (**27**) gave the 8β-hydroxy-14β-nitro-10-oxo compound (**28**) when treated with base. This isomerisation of a peroxide is a widely reported reaction used to confirm a peroxide group.[41] It is interesting to note that the 8β-hydroxy compound is produced rather than the initial 8α-hydroxy isomer. The initially formed alkoxide anion inverts its configuration by ring opening and reclosure. The driving force is formation of the less hindered β-hydroxy group. The 8β-hydroxy group is pseudoaxial and is on the convex face of the morphinan ring system.

The presence of a small amount of the 8α-hydroxy compound (**36**) was observed by ^{1}H NMR spectroscopy of the mother liquors from crystallisation of the major 8β-hydroxy product.

The isomerisation also shows a different type of selectivity. Only the proton at C-10 is abstracted leading to an 8-hydroxy-10-oxo compound (**28**). The other

Scheme 2.8


CH3O
NCH3
(27)
NaOH
NO2
OH
(28)
H+/CH3OH
(45)
Zn
NH4Cl
NH2
(14b)
RCOCl / pyridine
or
RCOOH / DCC
NHCOR
(31)

possible mode of attack, removal of H-8 giving a 10-hydroxy-8-oxo compound (**37**), was not observed with base. However, this type of cleavage was observed to some extent when the epidioxide was treated with neutral alumina.

The lack of reactivity at H-8 is easily understood when a model of the epidioxide is examined. The C(10)-H and O(10)-O(8) bonds are antiperiplanar, the ideal arrangement for a concerted elimination to occur. In contrast, the C(8)-H and O(8)-O(10) bonds are almost at right angles to each other, making a concerted elimination difficult.

Treatment of the 8β-hydroxy-10-oxo compound (28) with methanolic hydrogen chloride

Upon treatment of the 8β-hydroxy-10-oxo compound (**28**) with methanolic hydrogen chloride, even in oven dried glassware and generating hydrogen chloride *in situ* by the addition of acetyl chloride to methanol, mixtures of the codeinone (**32**) and dimethyl acetal (**14a**) were observed. It was clear that the acetal was extremely moisture-sensitive and, as a consequence, was never produced in a pure state. It was therefore decided to abandon the first proposed route.

Second proposed synthetic route to 14β-nitro-10-oxo-morphinans (31)

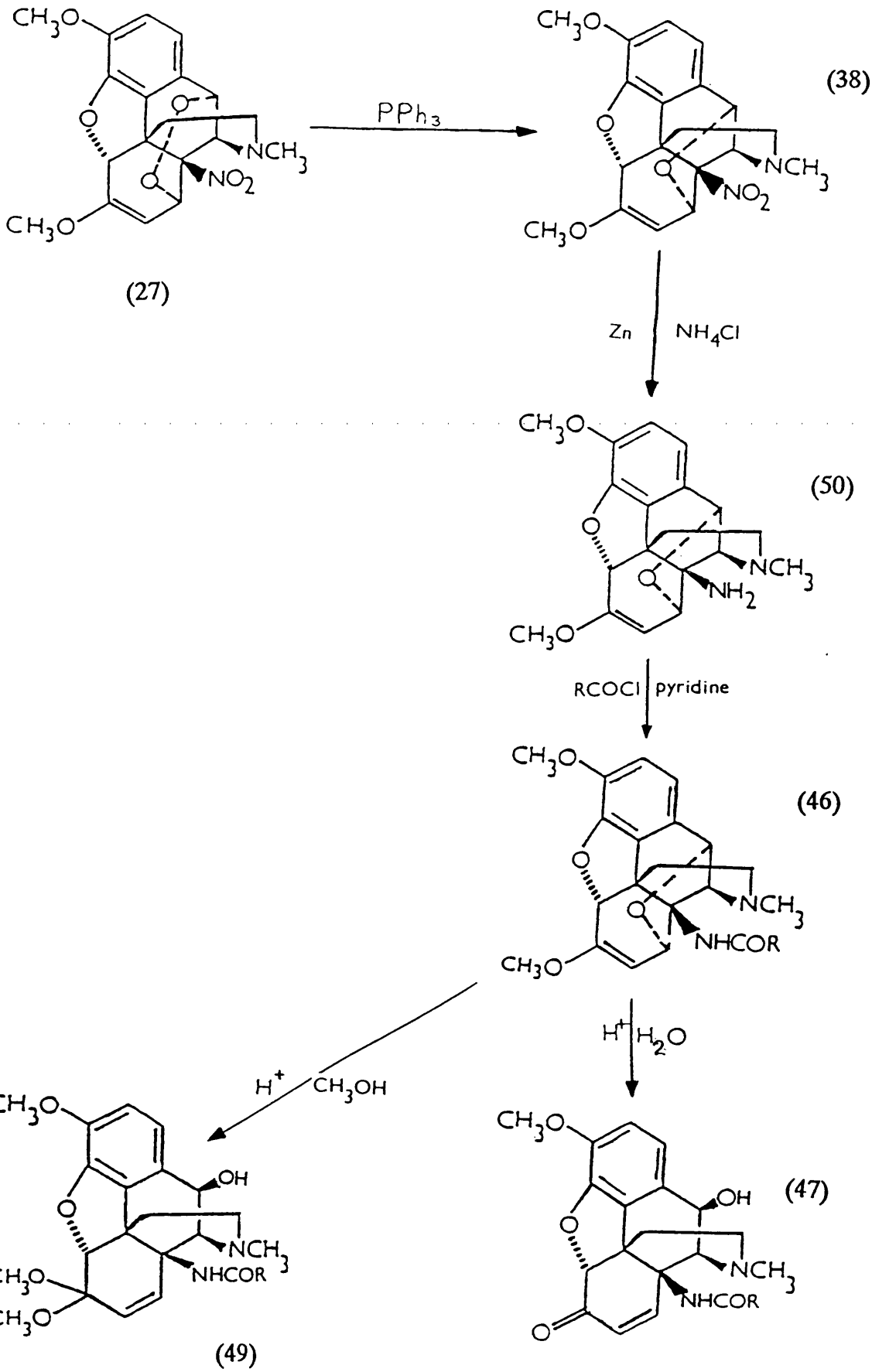
Allen *et al.*,[16] showed that strongly acidic conditions were required to break the epoxy linkage in the 14β-nitro-8α,10α-epoxy compound (**38**). It was hoped therefore to use this compound, obtained by deoxygenation of the epidioxide (**27**) using triphenylphosphine, as a protected form of the enol ether and, as a consequence, prevent the opening of the 4,5-oxide bridge when reducing the nitro

function. In addition to providing an alternative route to 10-oxo morphinans, the second proposed route (Scheme 2.9), it also gave the opportunity to produce an additional two series of compounds: the 14β-acylamino-8α,10α-epoxy series (**46**) and the 10α-hydroxycodeinones (**47**), as well as the same 10-oxo (**31**) and 10β-hydroxy (**48**) series that would have been targets of the first proposed synthetic route. After the reduction and acylation of the 14β-nitro-8α,10α-epoxy compound (**38**) to give the 14β-acylamino-8α,10α-epoxy series (**46**) treatment with acid in either aqueous or alcoholic media would give the 10α-hydroxycodeinones (**47**) or codeinone dimethyl acetals (**49**). Oxidation with manganese dioxide would give the 10-oxo compound (**31**) and subsequent reduction with sodium borohydride the 10β-hydroxy compound (**48**).

Deoxygenation of the epidioxide (27)

Allen *et al.*,[16] showed that the epoxide (**38**) could be produced in good yield by treatment of the epidioxide (**27**) with triphenylphosphine in refluxing benzene overnight. It was found during the course of the present study that an excess of triphenylphosphine was required to ensure the complete reaction of the starting material. Complete reaction of the epidioxide (**27**) was necessary due to the similarity of the R_f values of the starting material and the product. The introduction of an excess of triphenylphosphine further complicated the chromatography. After the reaction was complete the required epoxide was the middle of three bands, lying between the excess of triphenylphosphine and triphenylphosphine oxide. On a large scale, chromatography on three columns of t.l.c. grade silica was often necessary to

Scheme 2.9


CH3O
NCH3
NO2
CH3O
PPh3
(27)
(38)
Zn
NH4Cl
(50)
NH2
RCOCl
pyridine
(46)
NHCOR
H+
H2O
CH3OH
OH
(47)
(49)

produce a pure product.

To reduce the amount of excess triphenylphosphine oxide, it was decided to perform the reaction in toluene instead of benzene. This caused no problem provided that the toluene was freshly distilled.

A more reactive phosphine, tri(dimethylamino)phosphine was also evaluated. Although the reduction was very much quicker than with triphenylphosphine, the R_f values of the phosphine oxide and the epoxide (**38**) were very similar, making chromatography more difficult.

The bulk of the epoxide produced for this project was made using triphenylphosphine in toluene. Chromatography was carried out with a very slow solvent gradient of gradually increasing amounts of chloroform in petroleum ether. In addition, preadsorbing the crude product onto silica and adding this silica to a prepacked column through a head of petroleum ether helped to speed up the elution of triphenylphosphine.

Reduction of the 14β-nitro epoxide (38)

The selective reduction of 14β-nitro group required very mild conditions. It was important to preserve the 8α,10α-epoxy linkage as this both served, with the enol ether, as a masked form of the enone and also enabled the production of another series of compounds, the 8α,10α-epoxy-14β-acylamino series (**46**), for pharmacological testing.

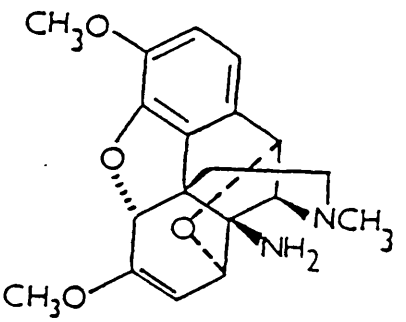
Initially, the conditions employed by Allen *et al.*,[16] for the reduction of 14β-nitrocodeinone dimethyl acetal (**14a**) were used with 3 equivalents of zinc dust and

2 equivalents of ammonium chloride, in methanol under reflux; a pale green oil was obtained. Analysis by t.l.c. and ^{1}H NMR spectroscopy showed it to be a mixture of three products (Scheme 2.10). The desired amine (**50**) was identified in the ^{1}H NMR spectrum of the crude product by the upfield shift of the mid-range proton signals caused by the reduction of the nitro group. Although all these signals were affected, those of 8- and 9-H were affected most, with a 0.5 ppm shift for 8-H and a 1.3 ppm shift for 9-H. This large shift for 9-H from δ 4.70 to 3.44 moved the signal into the methoxyl region of the spectrum and irradiation of the 10-H signal at δ 4.84 was required to give an unambiguous identification.

The second product identified in the crude mixture was the ring-opened, 10α-hydroxyamine (**51**), produced by acid-catalysed hydrolysis. The signals for the ring B and ring C protons were more difficult to identify absolutely. However, the aromatic protons were greatly affected by the production of the benzylic alcohol, with 1-H being shifted downfield, which in turn produced a better separated AB quartet, whereas at 90 MHz, the 14β-amino epoxide (**50**) aromatic protons combined to give a singlet.

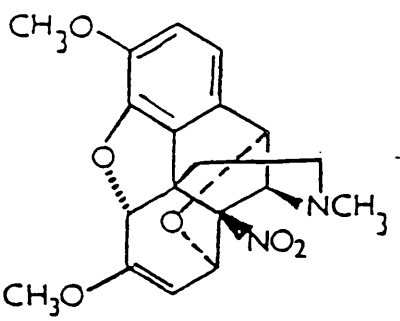
The third product was identified as the 14β-nitroso compound (**52**). This was first observed as a green-blue, non-polar band on a t.l.c. plate while attempts were being made to purify the crude product. When isolated by preparative t.l.c. the nitroso compound had a green-blue colour in solution. Most of this colour disappeared when the solution was evaporated to dryness but was restored when the solvent was replaced. This is the classic behaviour of a tertiary *C*-nitroso compound.

Scheme 2.10

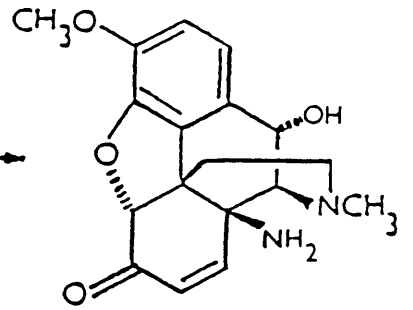


(50)

+

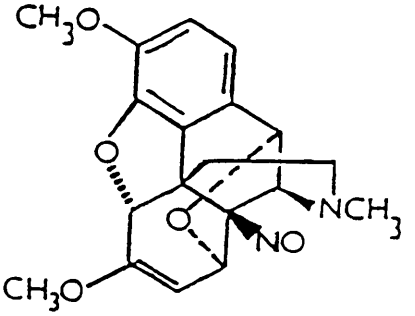


(38)



(51)

+

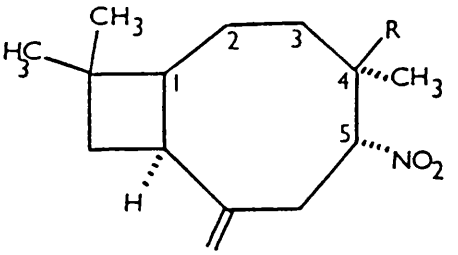


(52)

They are usually observed as colourless dimers in the solid phase and as the highly coloured (usually green or blue) monomers in solution. The mass spectrum indicated a molecular weight of 356, which corresponded to the nitroso monomer (**52**). The anisotropic effect of the nitroso group is evident in the ^{1}H NMR spectrum. Both 8- and 15_{ax}-H are influenced by the shielding and deshielding effects. The effect on 8β-H is to produce a signal at δ 5.96 compared with 4.80 for the nitro compound (**38**) and 4.36 for the 14β-amino epoxide (**50**). Therefore 8-H must be strongly affected by the deshielding cone. A marked difference was noted in the chemical shifts for 15_{ax}-H. The signal for this appears in the nitro compound (**38**) at δ 2.02, in the amine (**50**) at δ 2.14 but is moved upfield in the nitroso compound to δ 1.35. Because of this large upfield shift it was possible to resolve all of the couplings in the ethanamine bridge in a 200 MHz ^{1}H NMR spectrum. In most similar compounds higher-field spectra or 2-dimensional techniques are required to produce this sort of resolution.

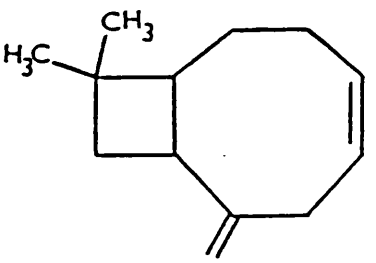
The ^{13}C NMR spectrum of the nitroso compound (**52**) showed the chemical shift for C-14 (δ 104.0) to be greater than that of the 14β-nitro compound (**38**) (δ 90.0). Freer *et al.*,[42] found the signals for C-4 in the nitro (**53**) and nitroso (**54**) derivatives of caryophyllene (**55**) to appear at δ 92.6 and 100.8, respectively. The ^{13}C NMR spectral evidence confirmed that of the ^{1}H n.m.r. spectra, namely that the nitroso group was present and had profound effects on the chemical shifts of C-14 and H-15_{ax}

Of the two impurities, the production of the 14β-nitroso compound is the most



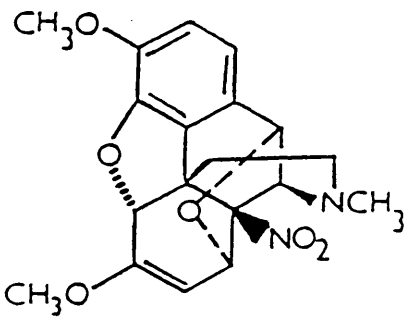
(53) R=NO_2

(54) R=NO



(55)

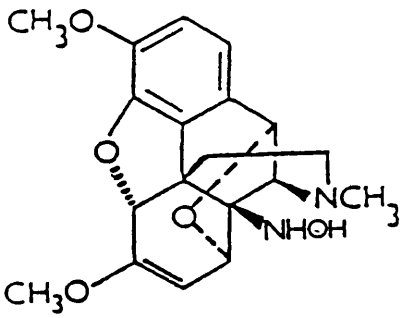
Scheme 2.10a



(38)

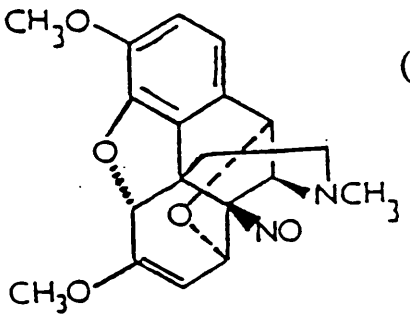
Zn
NH_4Cl

incomplete reduction



(56)

oxidation in air



(52)

surprising. Few reagents are mild enough to stop reduction of a nitro group at the nitroso stage rather than proceeding to the amine. In most cases nitroso compounds are either not formed or react further under the reduction conditions and cannot be isolated.[43] Petersen and Letsinger[44] produced aromatic nitroso compounds by irradiating the corresponding nitro compound in aqueous potassium cyanide with ultra-violet radiation.

Alternatively, the 14β-nitroso compound could have been produced by indirect means. Aromatic hydroxylamines are readily oxidised to give nitroso compounds.[45] In addition, Feuer *et al,*[46] reported that hydroxylamines could be produced by treatment of aromatic nitro compounds with zinc and water under neutral conditions. Therefore incomplete reduction of the 14β-nitro compound (Scheme 2.10a) could have produced the hydroxylamine (**56**). Air oxidation may then have given the nitroso compound (**52**).

Further evidence for incomplete reduction, followed by oxidation, was found when forcing conditions were used. Addition of either zinc chloride (fused) or glacial acetic acid to the reaction mixture, in an attempt to effect complete reduction, only reduced the amount of nitroso compound but did not eliminate it completely.

The dilemma of increased acidity leading to ring opening and reduced acidity producing the nitroso compound, led to a series of experiments involving various methods for activating the zinc dust. A small crystal of iodine was introduced into the reaction mixture before the addition of the nitroepoxide. It was hoped it would increase the reduction rate in the same way that it can increase the rate of Grignard

and Reformatsky reactions. However, there was no improvement in the yield of purity of the amine.

Several methods for purifying zinc dust by washing using alkali, acid, water and organic solvents were tried. These generally were found to reduce the rate of reaction and had no beneficial results.

Erdik[47] has reviewed the activation techniques used to produce organo-zinc reagents. Comparison of several methods showed that zinc chloride, reduced by potassium or lithium in tetrahydrofuran using Rieke's procedure,[48] gave a colloidal zinc which readily forms organo-zinc reagents. Erdik further reviewed the methods used to produce the activated zinc from zinc chloride.[47] On stirring of zinc chloride with lithium in the presence of naphthalene as an electron transfer agent, the reduction is complete in 15 h at room temperature. The use of zinc produced in this way had no beneficial effect on the reduction of the nitroepoxide. When the same mixture of zinc chloride and lithium is exposed to ultrasound at room temperature, reduction to zinc is complete within 40 min. The action of the ultrasonic radiation produces a succession of negative and positive pressure waves. This in turn causes microscopic bubbles to form then disperse. The creation and destruction of these bubbles releases a large amount of energy. This energy causes pitting to occur on the surface of suspended matter, the pits thus formed nucleate the formation of further bubbles, causing an acceleration in the dispersion rates of suspended material. Therefore ultrasonic radiation creates fresh surfaces for reactions to occur and, as a consequence, is ideal for accelerating the rate of

heterogeneous reactions.[49]

The use of colloidal zinc, prepared by the use of ultrasound in the reduction of the 14β-nitro compound had mixed results, ranging from very rapid rates of reaction (also associated with good amine yield) to very slow reaction rates with large quantities of the nitroso compound (**52**) being produced. This variation of results was probably caused by batch to batch variations in the colloidal zinc and its very poor storage ability.

None of the attempts to purify the zinc dust produced reproducible improvements in the reduction of the nitroepoxide (**38**). As a consequence, most of the 14β-amino epoxide was produced using a modified version of the conditions used by Allen *et al.*[16] When 1.1 equivalents of ammonium chloride was used instead of 2 equivalents, the amount of ring opening was greatly reduced. The amount of the nitroso compound, however, was increased. Although this was partially offset by increasing the reaction time, the remainder was carried forward into the acylation reaction. The large R_f value of the nitroso compound made the isolation of this impurity straightforward at this stage.

<u>Acylation of the amine (50)</u>

The 14β-amino epoxide (**50**) was never produced in a pure form. As a consequence, the impurities, the 14β-nitroso (**52**) and 10α-hydroxy (**51**) compounds were always present.

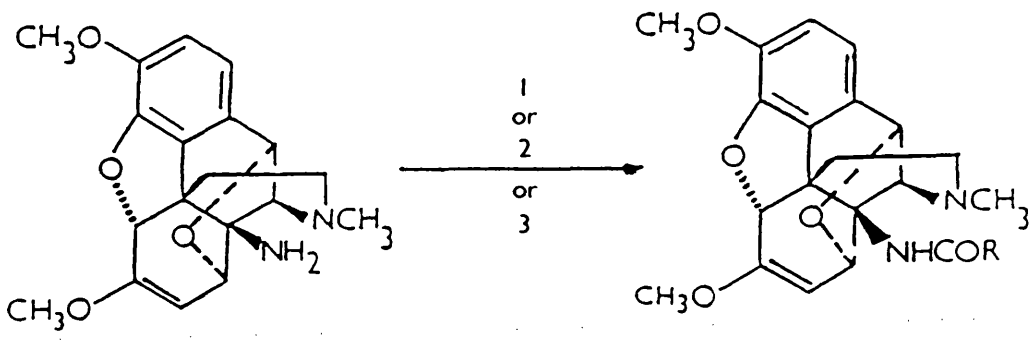
Three methods were used employing (a) the acid anhydride and pyridine, (b) the acid chloride and pyridine and (c) the acid and dicyclohexylcarbodiimide (DCC)

(Scheme 2.11). All three methods gave comparable amounts of the acetylamino compound (**57**), but the DCC method gave a reaction mixture that was far easier to work-up. In the other two methods the reaction mixture gradually became very coloured if all the pyridine was not removed. This removal of pyridine proved to be very difficult. It could only be done by azeotroping the pyridine off with large quantities of toluene. Preparative t.l.c. alone was not sufficient to remove all the pyridine as the R_f value of the acetamide (**57**) was very close to that of pyridine. Silica plates gave the best separation, but the product obtained by chromatography on silica was very coloured and became increasingly so after further chromatography, suggesting that, like the amine (**50**), the acetamide reacted with silica.

The DCC method was far simpler and was adopted for all the amides (**57-65**). After the dicyclohexyl urea had been filtered off, the products were obtained as clear oils, which were purified by chromatography on neutral alumina. The ease with which the product was chromatographed depended upon the purity of the starting amine (**50**). For most of the amides, repeated chromatography was required on neutral alumina t.l.c. plates, the presence of impurities making separation very difficult. It was often necessary to use Draggendorf's reagent[50] to identify the acylamino compound by the distinctive red-orange colour produced.

Attempts to prepare the 14β-(3-phenylpropanoyl)amino compound (**60**) from the acid chloride and pyridine were more successful. This was due to the increased R_f of the product which was therefore more readily separated from residual pyridine.

Scheme 2.11



(50)

(57) R = CH_3
(58) R = C_6H_6
(59) R = phenylacetyl
(60) R = phenylpropanoyl
(61) R = phenylbutanoyl
(62) R = furoyl
(63) R = cinnamoyl
(64) R = 4-chlorocinnamoyl
(65) R = 4-methylcinnamoyl

1. Acid anhydride/pyridine
2. Acid chloride/pyridine
3. Acid/dicyclohexylcarbodiimide

Ring opening of the 14β-(3-phenylpropanoylamino)-8α,10α epoxide (Scheme 2.12)

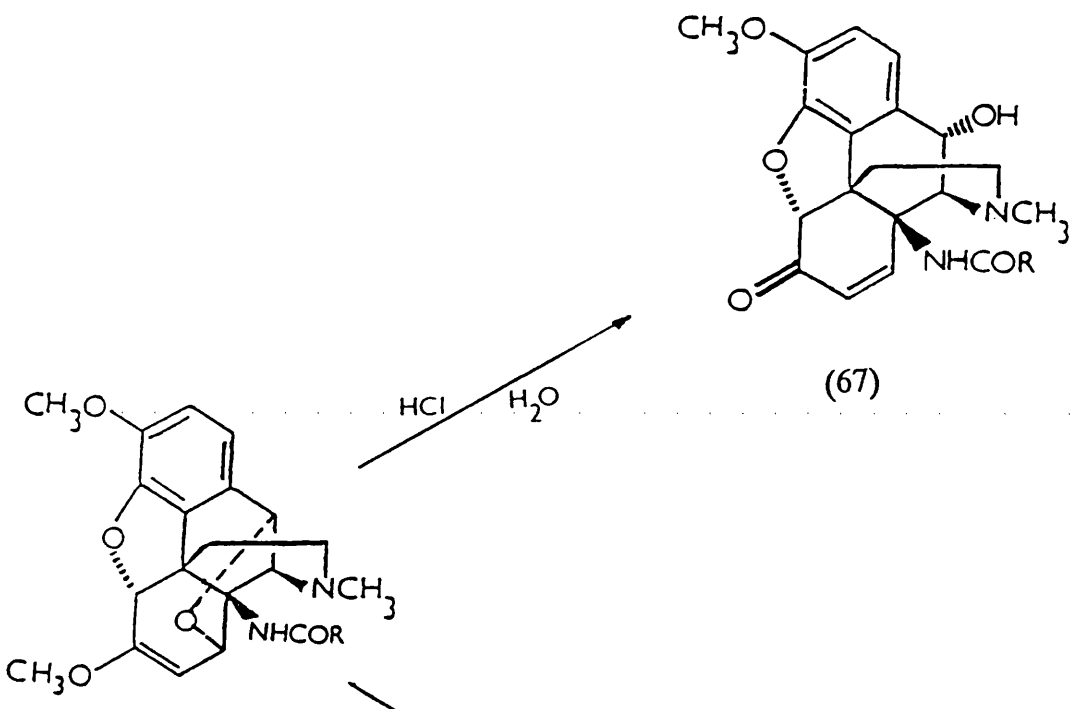
Results of the pharmacological testing showed that the peak of the analgesic activity in the 8α,10α-epoxy series of 14β-acylamino compounds was with two methylene groups: 3-phenylpropanoyl. It was therefore decided to produce the whole series of compounds bearing this substituent as a quick test of Archer's findings that a 10-oxo substituent greatly reduces potency.[24]

It was decided to attempt to ring open the 14β-(3-phenylpropanoylamino)-8α,10α-epoxy compound (**60**) using both aqueous and methanolic media. In this way both codeinone (**67**) and codeinone dimethyl acetal (**66**), analogues of 10α-hydroxy and 10-oxo compounds, could be prepared and evaluated as potential analgesics.

The 10α-hydroxycodeinone (**67**) was prepared by treating the epoxy compound (**60**) with 5 M hydrochloric acid. The appearance of a carbonyl peak in the I.R. spectrum at 1690 cm^{-1} and an AB quartet (δ 6.42 and 6.09) with a coupling of 10 Hz in the NMR spectrum showed the presence of the enone. The presence of the 10α-hydroxy group shifted the signal for 1-H downfield to δ 6.90. This transformed the appearance of the spectrum. In the 8α,10α-epoxy compound 1- and 2-H gave a singlet, δ 6.68, but with the downfield shift of 1-H on ring-opening they gave an AB quartet. The signal for the hydroxy group was not found in the ^{1}H NMR spectrum. The singlet for 10β-H shows the H-C(9)-C(10)-H torsion angle to be *ca.* 90°. The hydroxy group must therefore be in the α-position.

The dimethyl acetal (**66**) was prepared initially by treating the epoxy compound (**60**) as a stirred methanolic suspension with methanolic hydrochloric acid

Scheme 2.12



R = CH_2CH_2Ph

[36% hydrochloric acid (10 ml) made up to 100 ml with Analar methanol] at 0°C. This unexpectedly gave the dimethyl acetal in 83% yield, the remainder being the codeinone. When methanolic hydrochloric acid was used with 1% trimethyl-orthoformate added, only a trace of the codeinone was produced.

In contrast to the ^{1}H NMR spectrum of the codeinone (**67**), which showed no hydroxy signal, the spectrum of the dimethyl acetal (**66**) showed a broader singlet at δ 3.22 for the hydroxy group.

Oxidation of the 10α-hydroxy compounds (Scheme 2.13)

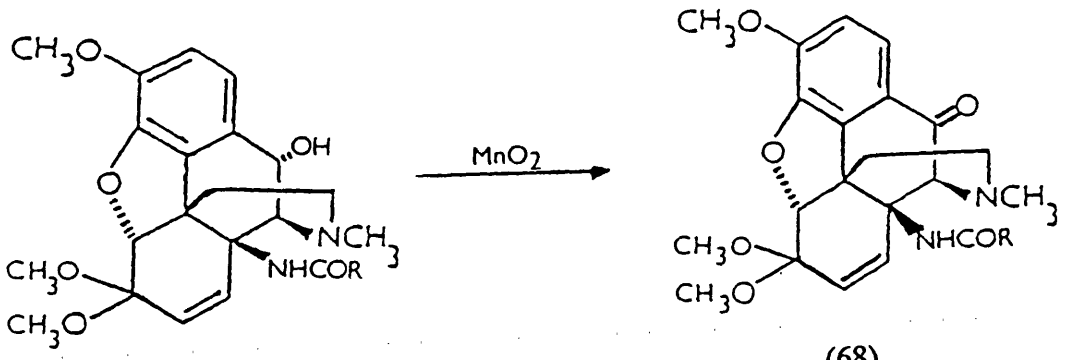
The 10α-hydroxycodeinone (**67**) was readily oxidised with manganese dioxide giving the 10-oxo compound (**69**). The ^{1}H NMR spectrum showed one less mid-range proton signal and the downfield shifts of 1- and 9-H from δ 6.90 and 3.83, to δ 7.31 and 4.25, respectively, showed the formation of a 10-oxo group.

The oxidation of the 10α-hydroxycodeinone dimethyl acetal (**66**) with manganese dioxide was found to produce a series of products. A small yield of the 10-oxo compound (**69**) was however isolated by preparative t.l.c.

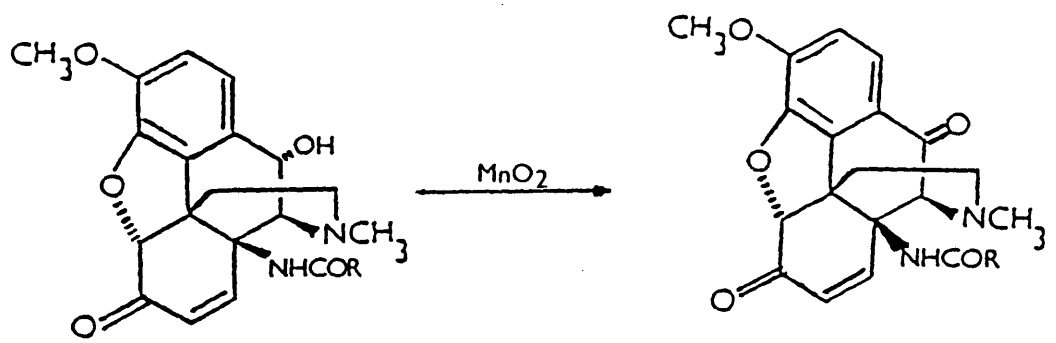
Attempted reduction of the 10-oxo compound (67) (Scheme 2.14)

In order to obtain the 10β-alcohol (**70**) for comparison with the 10-oxo and 10α-hydroxy compounds, the 10-oxo enone (**67**) was treated with sodium borohydride. It was found however that the reduction product was readily oxidised in air back to the parent compound. McDougall[26] found that the product of borohydride reduction of the 8α-hydroxy-10-oxo compound (**28**) was re-oxidised in a similar way and, as a

Scheme 2.13

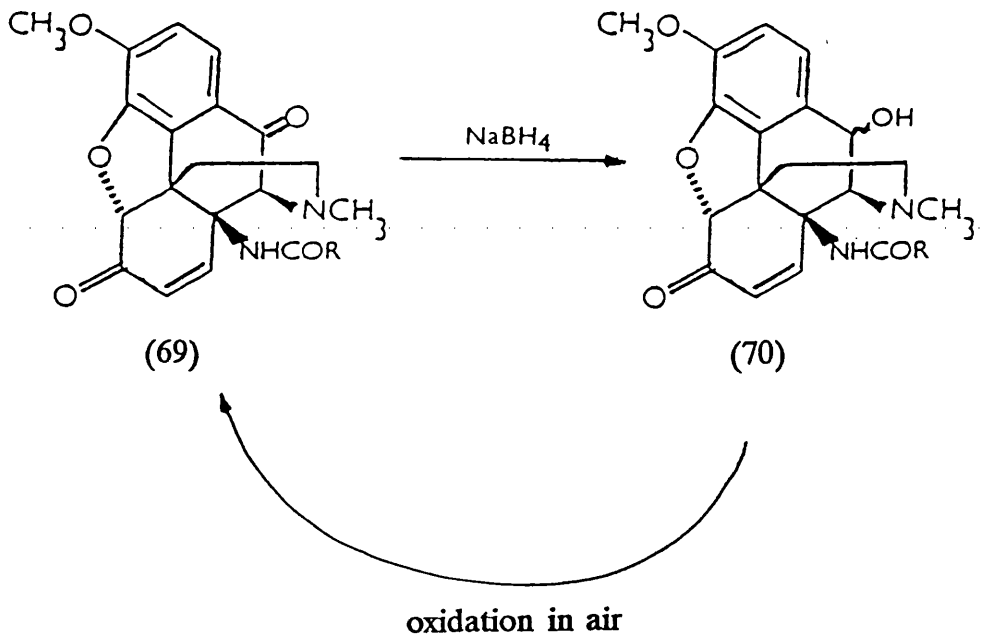


(66) (68)



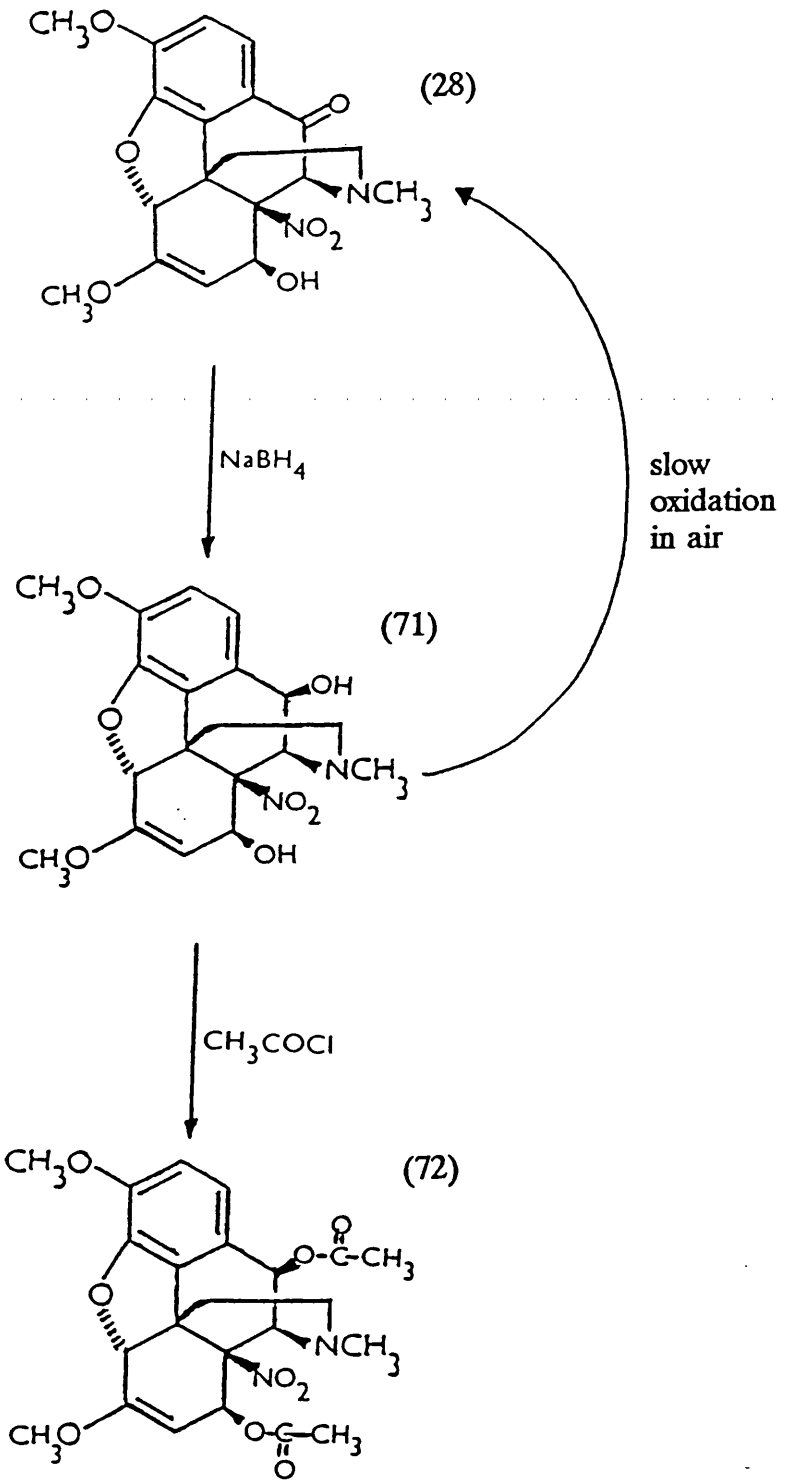
(67) (69)

Scheme 2.14



consequence, was unable to obtain a satisfactory analysis (Scheme 2.15). In the course of this study a satisfactory analysis for this compound was obtained. It was found, however, that the product was indeed air-sensitive and was best stored as the diacetoxy compound (**72**).

Scheme 2.15



10-oxo-Thevinone

Archer *et al.*[24] showed that the incorporation of a 10-oxo group in naltrexone (**23**) and the morphinone (**24**) greatly diminished the potency. It was shown in this study that the potency of the 10-oxo compound (**69**) was less than that of both the 10α-hydroxy (**67**) and the 8α,10α-epoxy (**60**) compounds (Scheme 2.16). It was hoped that, by incorporating a 10-oxo group into an even more potent morphinan, it would be possible to produce a kappa-selective compound that still retained useful analgesic activity.

Bentley and Hardy[12] showed that thebaine formed Diels-Alder adducts with α,β-unsaturated ketones, nitriles and esters. Reaction of the adduct thevinone (**73**) formed between thebaine (**4**) and methyl vinyl ketone with either Grignard or alkyl lithium reagents gave tertiary alcohols, thevinols, of the structure (**74**) (Scheme 2.17). Many of these compounds are potent analgesics with activities of up to several hundred times that of morphine.

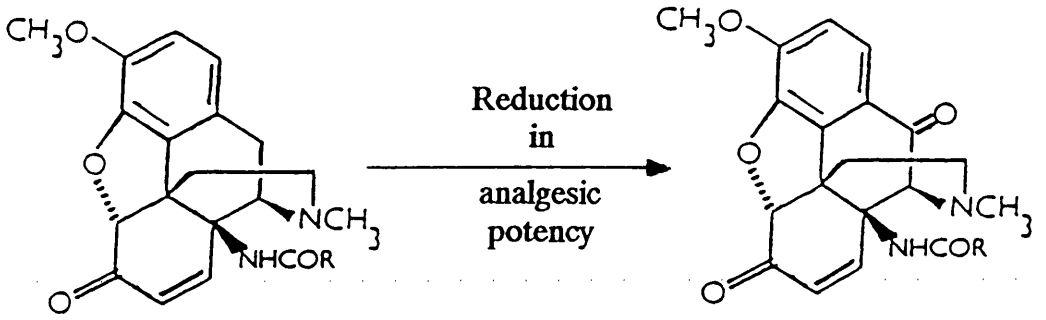
It was hoped that incorporation of a 10-oxo group into thebaine (**4**) would enable the production of a series of 10-oxo-thevinols.

It was hoped that, using a 10-oxy substituted 14β-nitro compound as a starting point, free radical reduction of the nitro group might be followed by conversion to a diene.

First proposed route to 10-oxothebaine (77) (Scheme 2.18)

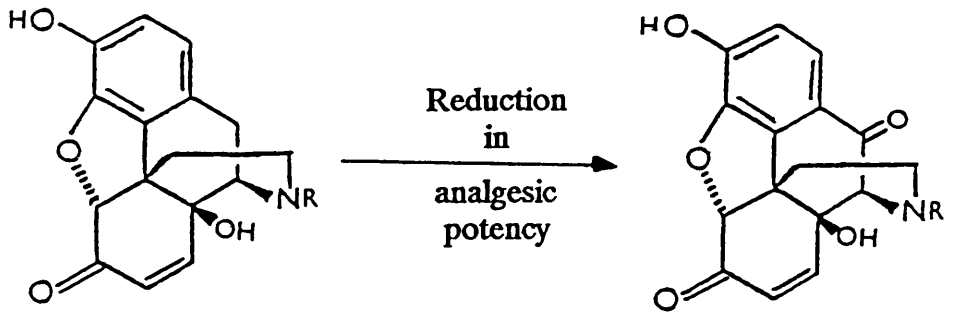
It was envisaged that free radical reduction of the nitro epoxide (**38**), followed by opening of the epoxide ring and subsequent reduction of the resulting oxide

Scheme 2.16



(60) (69

R = CH_2CH_2Ph



(23) R = 

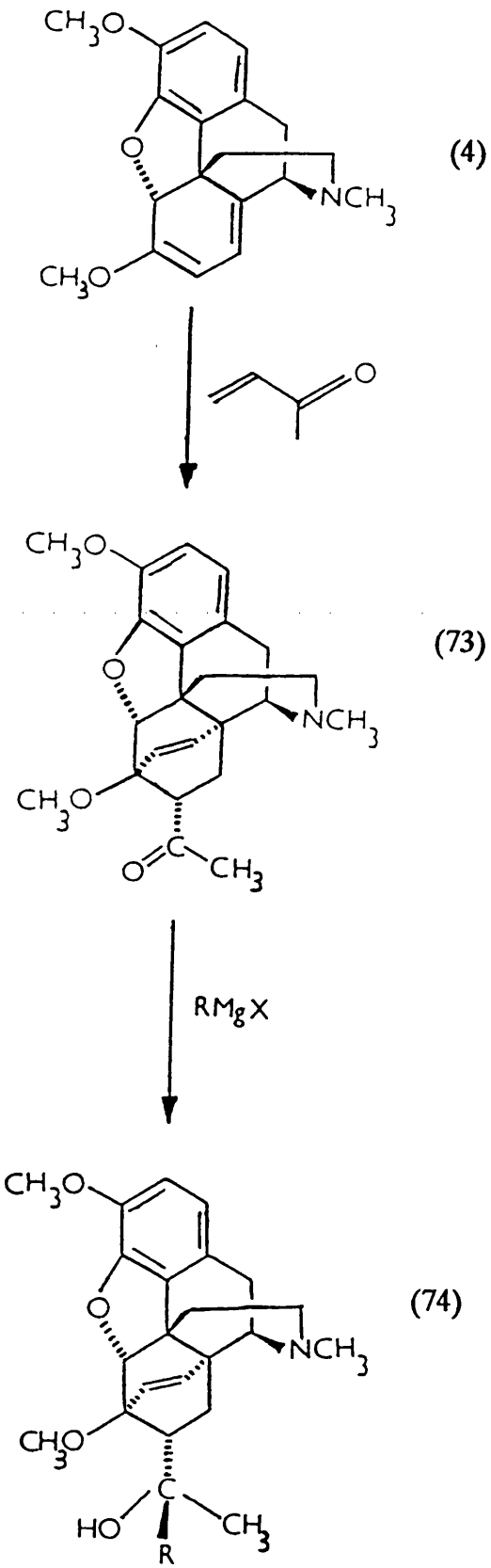
(24) R = CH_3

(21) R = 

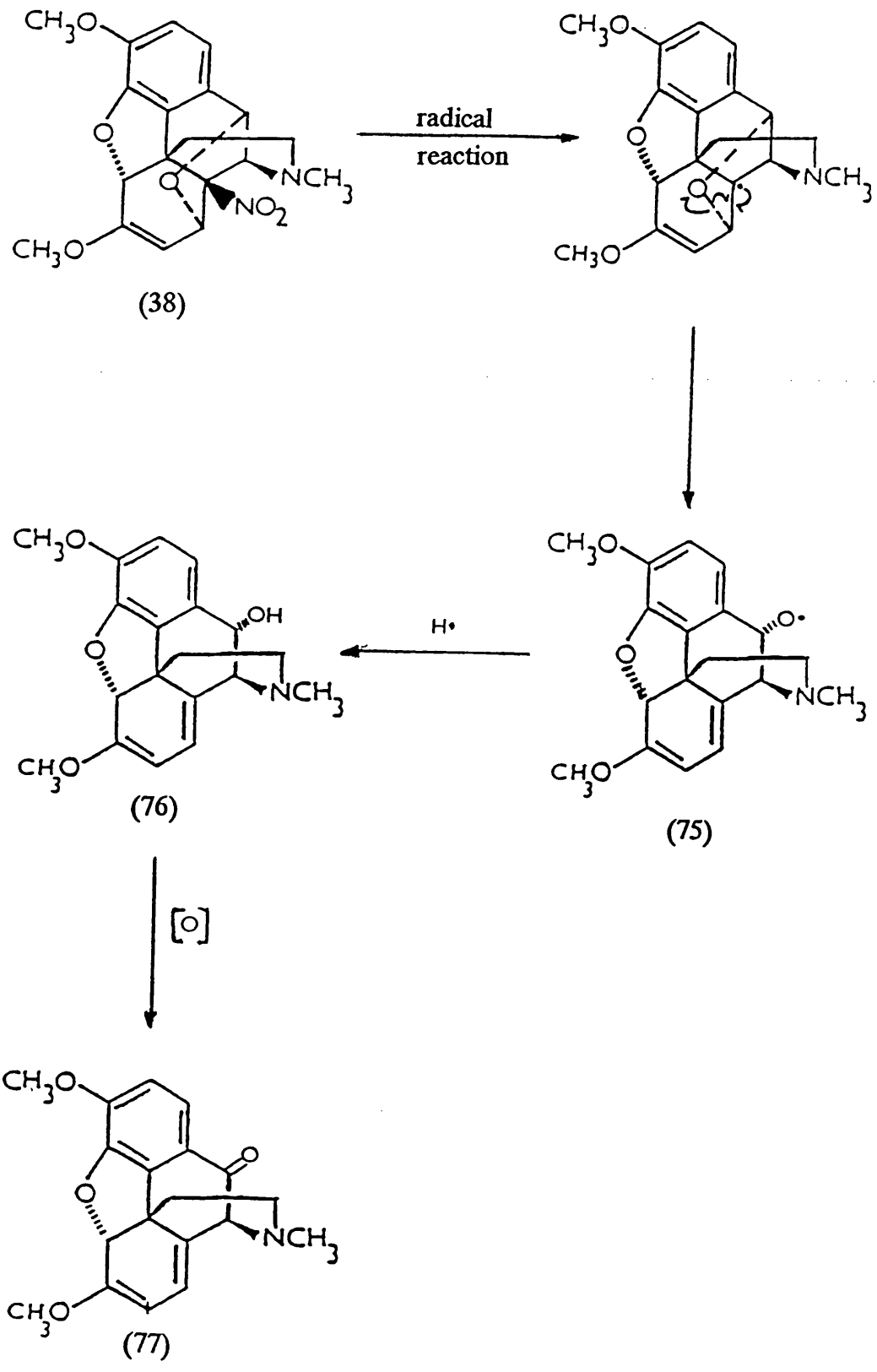
(22) R = CH_3

Introduction of a 10-oxo-substituent was found in the cases of (23) and (24) to greatly reduce the potency.

Scheme 2.17


CH3O
O
NCH3
CH3O
(4)
O
CH3O
O
NCH3
CH3O
O
C
CH3
(73)
RMgX
CH3O
O
NCH3
CH3O
HO
C
CH3
R
(74)

Scheme 2.18



(38) (75) (76) (77)

radical (**75**) might give the 10-hydroxy diene (**76**). Oxidation would then yield 10-oxothebaine (**77**). Kornblum et al.[51] were able to replace a tertiary nitro group in a great many aliphatic compounds using the sodium salt of methane thiol. The methane thiol anion acts as the electron source for the reduction (Scheme 2.19). The decomposition of the radical anion thus produced gives the corresponding alkyl radical. Thereafter, abstraction of a hydrogen atom from another equivalent of methane thiol anion leads to the desired product with the production of thio-formaldehyde. Although Kornblum's work showed that it was possible to replace directly a nitro group by hydrogen, it was thought that a multifunctional opiate might not survive the reaction conditions.

An alternative and more convenient method of generating the alkyl radical is to use tributyltin hydride with azoisobutyronitrile (AIBN) as an initiator. Ono *et al.*[52] used these reagents to replace the nitro group in tertiary nitro compounds by hydrogen (Scheme 2.20). The replacement is selective in that it does not affect keto, ester, cyano or organic sulphur groups.

Initially, the 14β-nitro-8α,10α-epoxy compound (**38**) was treated with a large excess of tributyltin hydride and AIBN (0.25 mol equiv.) in refluxing benzene. Although the starting material was observed by t.l.c. to disappear rapidly, a large number of products were found to be produced. None were identified.

The reduction was later tried on the 8β-hydroxy-10-oxo-14β-nitro compound (**28**). It was hoped that, if the 8β-hydroxy group did not interfere, a cleaner reaction would be observed. In the previous reaction, the 8,10-epoxy linkage might have

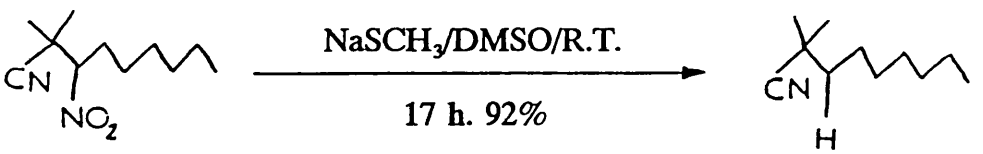
Scheme 2.19

$$R_3C - NO_2 + CH_3S^- \longrightarrow R_3C - \overline{NO_2^{\bullet}} + CH_3S^{\bullet}$$

$$R_3C - \overline{NO_2^{\bullet}} \longrightarrow R_3C^{\bullet} + \overline{NO_2}$$

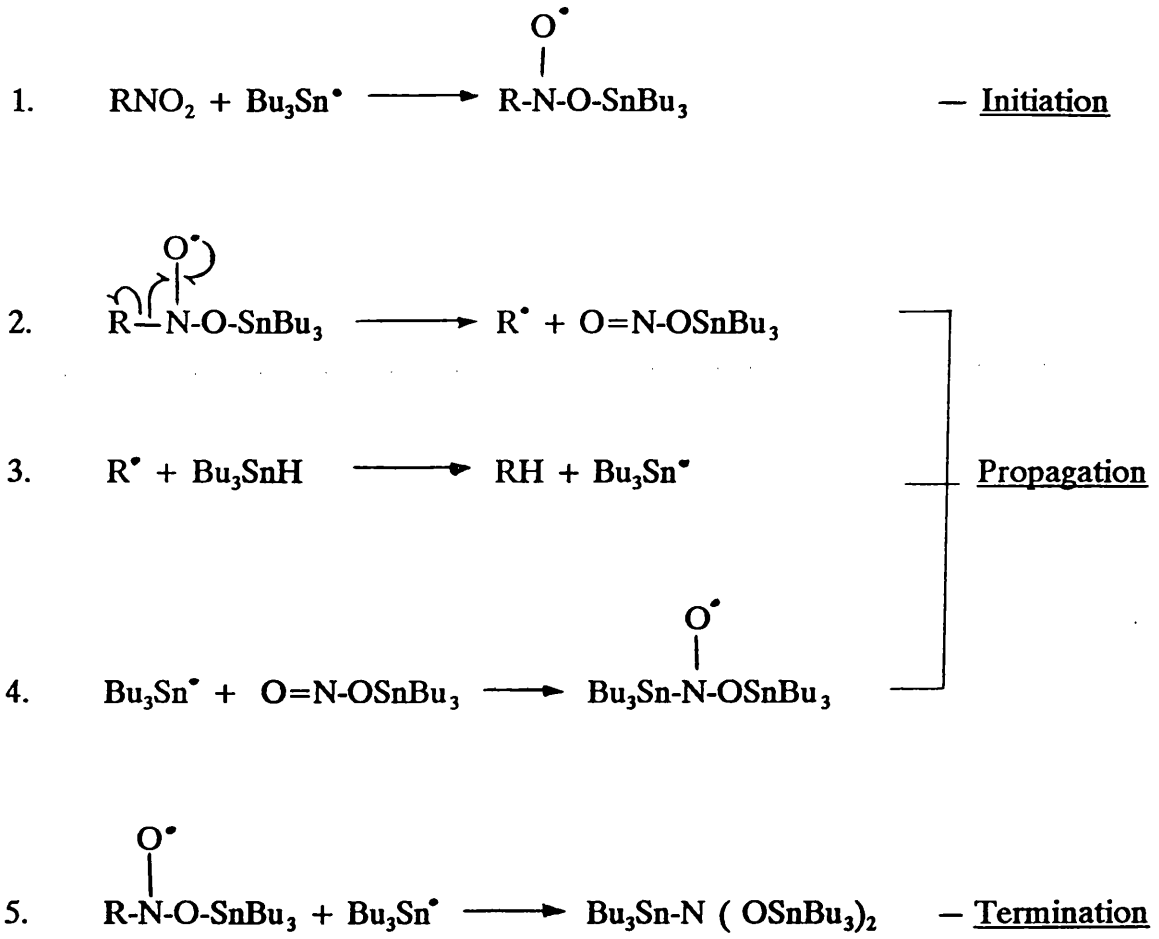
$$R_3C^{\bullet} + H_3C - S^- \longrightarrow R_3C - H + H_2C^{\bullet} - \overline{S}$$

$$H_2C^{\bullet} - \overline{S} + R_3C - NO_2 \longrightarrow H_2C = S \quad R_3C - \overline{NO_2}$$



Scheme 2.20

Reduction of aliphatic nitro compounds with tributyltin hydride



been opened, as hoped, but this might have led to secondary products.

Second proposed route to 10-oxothebaine (77)

As an alternative to trying to produce 10-hydroxythebaine (**76**) by reducing the nitro epoxide (**38**), it was hoped that by reducing the 8β-hydroxy-10-oxo-14β-nitro compound (**28**), using tributyltin hydride to be able to produce the 14β-hydro compound (**78**) which could be dehydrated to give 10-oxothebaine (77) (Scheme 2.21).

Treatment of the 8β-hydroxy-10-oxo-14β-nitro compound (28) with tributyltin hydride

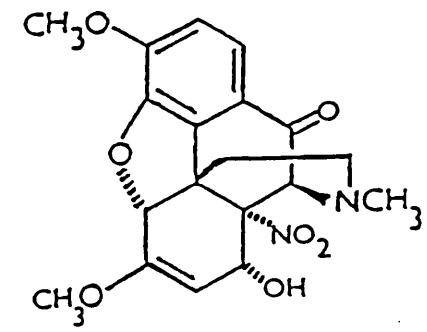
The reduction was found to be dependent on the amount of radical initiator added. When 0.1 equivalents of initiator was used the yield of product was found to be less than 10% (as judged by ^{1}H NMR spectroscopy of reaction mixture after work-up), the balance being unreacted starting material. When a full equivalent of initiator was used an 84% yield of the reduction product was obtained.

The reduction was observed to be very selective, with only the nitro group reacting, even after an extended period of heating. However, the use of an equivalent of radical initiator indicates that the reaction is extremely slow.

Proof of structure

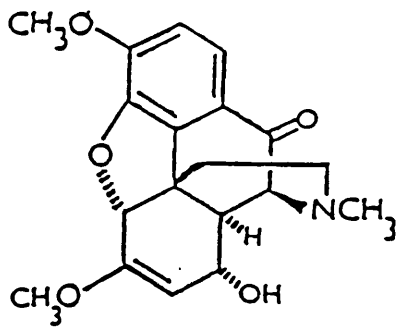
The mass spectrum and microanalysis clearly showed that a nitro group had been replaced by hydrogen. It was difficult however to prove the stereochemistry of the product. The most important signals in the ^{1}H NMR spectrum, those of the newly introduced 14-H, and of the 8β-hydroxyl group could only be assigned with

Scheme 2.21



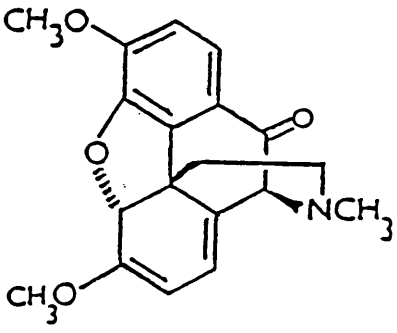
(28)

Bu_3SnH
AIBN
toluene reflux



(78)

dehydration



(77)

confidence after all other signals had been assigned, due to their close proximity to the 15- and 16-H signals. Only after the sample had been cooled was the hydroxyl signal observed as a broad peak (δ 1.72) rather than as an extended drift of the base line. The 6-OMe signal partially obscured the 9-H signal. Direct observation of 14-H, 9-H coupling was therefore not possible. Decoupling of the δ 2.27 (14-H) signal was inconclusive. However, when the 9-H signal was decoupled by irradiation at approximately δ 3.56, the 14-H signal was observed to collapse to a doublet. The large coupling constant, J 9.3 Hz, between 8- and 14-H showed that the stereochemistry at these two centres, 8β-hydroxy and 14β-H, had been retained.

The infra-red spectrum showed only a very weak OH band both for a KBr disc (ν_{max} 3425 cm^{-1}) and for a chloroform solution (ν_{max} 3470 cm^{-1}). However, the starting material itself (**28**) also exhibited only a very weak OH band. In addition, the nitro band clearly seen for the starting material at 1550 cm^{-1} was totally absent in the product.

10-Oxothebaine (77)

The first attempts to produce the diene (**77**) were centred around converting the hydroxy group into a better leaving group to facilitate the dehydration. However, when the alcohol (**78**) was heated with toluene-p-sulphonyl chloride (a slight excess) and 2 mol equivalents of pyridine at 90°C in toluene, neither tosylate formation nor dehydration was observed. The reaction was then repeated at the same temperature but with pyridine as the solvent. After 3 h under these conditions, ^{1}H NMR spectroscopy of the residue after azeotrope distillation of the

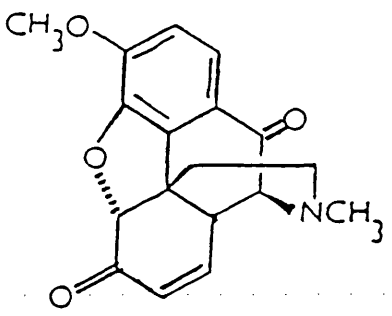
pyridine showed three components. The largest was the starting material. The next largest was 10-oxocodeinone (**79**). The smallest was shown to be 10-oxothebaine (**77**). This was later confirmed by t.l.c. with purified product.

The second method tried was acetylation followed by heating in the presence of a large excess of pyridine. This again yielded a mixture of products, amongst which were identified 10-oxocodeinone (**79**) and 10-oxothebaine (**77**).

Eppenburger *et al.*,[53] had used phosphoryl chloride and pyridine to remove methanol from codeinone dimethyl acetal to give thebaine. The same system is also used traditionally for the dehydration of alcohols.[54] After being heated for 3 h under reflux in dry toluene with phosphoryl chloride and pyridine the alcohol was dehydrated giving 10-oxothebaine (**79**) in 66% yield. The ^{1}H NMR spectrum showed that the signal at δ 3.78 in the starting material, corresponding to 8-H, had completely disappeared. A pair of doublets (J 7.5 Hz) at δ 5.64 and 5.08 corresponding to 8- and 7-H were observed in the product showing that a diene had been produced. Both the coupling constant and chemical shifts were similar to those of thebaine. The ultra-violet spectrum of the 10-oxo product showed an additional peak at 330 nm due to the presence of the C-10 ketone, this value being typical for a 10-oxomorphinan.[16]

<u>10-Oxothevinone (80)</u>

Treatment of 10-oxothebaine (**77**) with methyl vinyl ketone gave rise to the 10-oxo analogue of thevinone (**80**). The product obtained gave a single broad band on a t.l.c. plate. After repeated crystallisation from methanol the product was shown by high field ^{1}H NMR spectroscopy to be a mixture of 10-oxothevinone (**80**) and



(79)

another product which is presumed to be the 7α-isomer (**81**). The mixture of isomers (> 95% of major isomer), exhibited carbonyl bands at 1675 and 1719 cm^{-1} in the infra-red spectrum.

The 10-oxo nature of the compound (**80**) was shown by ^1H NMR spectroscopy. The position of 1-H was shifted 0.76 ppm downfield with respect to the same proton in thevinone to δ 7.30. Identification of the stereochemistry at C-7 was not possible due to the 7β- and 8β-H signals not being identified and were assumed to be obscured by other signals.

Pharmacological Testing

The analgesic potency of several of the compounds prepared was determined by in vitro techniques on Guinea Pig Ileum. The potency for both the μ and κ receptors was determined. The results are given in Table 3.1.

The most potent compound of the 14β-alkarylamino-8α,10α-epoxy compounds was found to be the phenylpropanoyl compound (**60**). The same structure activity relationship was found by Gourlay in the codeinone series.[55]

Ring opening of (**60**) to give the 10α-hydroxy codeinone (**67**) was found to double the potency from 26 to 52 times that of normorphine. The dramatic reduction in potency upon addition of a 10-oxo substituent that Archer *et al.*[24] found was confirmed by the very low figure obtained for the 10-oxo-phenylpropanoyl compound (**69**) (0.5 x normorphine).

Of all the compounds tested only the 4-methyl and 4-chlorocinnamoyl compounds (**65**) and (**64**) gave a measurable κ binding figure. In both compounds it was far less than obtained for μ.

None of the compounds resulting from reactions of 10-oxothebaine were tested although it is hoped that any future work in this field would obtain figures for any possible κ selectivity.

Table 3.1

Results of pharmacological testing

Compound		μ relative to normorphine	κ relative to ethylketo-cyclazocine
14β-acetylamino-8,14-dihydro-8α,10α-epoxythebaine	(57)	0.003	-
14β-benzoylamino-8,14-dihydro-8α,10α-epoxythebaine	(58)	0.41	-
14β-phenylacetylamino-8,14-dihydro-8α,10α-epoxythebaine	(59)	4.5	-
14β-(3-phenylpropanoylamino)-8,14-dihydro-8α,10α-epoxythebaine	(60)	26	-
14β-(4-phenylbutanoylamino)-8,14-dihydro-8α,10α-epoxythebaine	(61)	0.28	-
14β-(2-furoylamino)-8,14-dihydro-8α,10α-epoxythebaine	(62)	0	-
14β-cinnamoylamino-8,14-dihydro-8α,10α-epoxythebaine	(63)	8	-
14β-(4-methylcinnamoylamino)-8,14-dihydro-8α,10α-epoxythebaine	(65)	5.1	0.04
14β-(4-chlorocinnamoylamino)-8,14-dihydro-8α,10α-epoxythebaine	(64)	7.25	0.08
10α-hydroxy-14β-(3-phenylpropanoylamino)codeinone	(67)	52	-
10-oxo-14β-(3-phenylpropanoylamino)codeinone	(69)	0.5	-

Experimental

Tetranitromethane

This was prepared according to a literature procedure.[32,33,34] To obtain satisfactory yields it was necessary to prepare fresh, fuming nitric acid by distilling commercial fuming nitric acid off one third of its volume of concentrated sulphuric acid. Acetic anhydride (100 ml) was added slowly, with cooling in ice, to the distilled fuming nitric acid (100 ml). The mixture was allowed to come to room temperature slowly and was then kept for 7-10 days before being diluted with water (500 ml). The mixture was steam-distilled to give tetranitromethane (15 ml after 7 d, 25 ml after 10 d), which was washed with aqueous sodium carbonate, then water, and was then dried (Na_2SO_4); ν_{max} (CCl_4) 1641, 1620 and 1269 cm^{-1}; δ_C ($CDCl_3$; 50.4 MHz) 119.8 (nonet, $J_{C,N}$ 9.4 Hz). The ^1H and ^{13}C NMR spectra showed the absence of any significant impurities.

8α,10α-Epidioxy-8,14-dihydro-14β-nitrothebaine (27)

1. Using oxygen alone

By essentially the same method as Allen *et al.*,[16] dry oxygen was passed through a solution of thebaine (11.11 g, 28.6 mmol) in benzene (400 ml) at room temperature. Tetranitromethane (7.13 g, 36.4 mmol) in benzene (100 ml) was added dropwise over 40 min, and the flow of oxygen was continued for a further 3 h. The precipitated trinitromethane salt of thebaine was filtered off and the filtrate was evaporated to dryness under reduced pressure, using only moderate heat. The

resultant solid was purified by passing through a short dry column of t.l.c. grade, neutral alumina. Elution with a gradually increasing proportion of chloroform in hexane gave the epidioxide (**27**). Recrystallisation from ethyl acetate gave 8α,10α-*epidioxy*-8,14-*dihydro*-14β-*nitrothebaine* (**27**) (4.02 g, 29%), m.p. 160 °C (lit., 160-161 °C); ν_{max} ($CHCl_3$) 1644 and 1551 cm^{-1}; λ_{max} (EtOH) 283 (ϵ 2100) and 289 nm (ϵ 2130); δ_H ($CDCl_3$; 200 MHz) 6.95 and 6.80 (ABq, *J* 8.2 Hz, 2- and 1-H), 5.41 (d, *J* 3.4 Hz, 10-H), 5.29 (s, 5-H), 4.97 (d, *J* 5.2 Hz, 7-H), 4.57 (d, *J* 5.2 Hz, 8-H), 4.22 (d, *J* 3.4 Hz, 9-H), 3.89 (s, 3-OMe), 3.55 (s, 6-OMe), and 2.52 (s, NMe); δ_C ($CDCl_3$; 50.4 MHz) 160.15 (C-6), 146.2 (C-3), 142.0 (C-4), 132.7 (C-12), 124.1 (C-11), 120.1 (C-1), 114.05 (C-2), 90.15 (C-7), 87.4 (C-14), 86.1 (C-5), 78.8 (C-8), 76.3 (C-10), 62.2 (C-9), 56.2 (3-O<u>C</u>H_3), 55.3 (6-O<u>C</u>H_3), 45.25 (C-16), 44.2 (C-13). 42.3 (N-<u>C</u>H_3) and 28.9 (C-15); *m/z* 388 (M^+), 342, 326, and 176. These data were in reasonable agreement with the literature values.

2. Using ammonia and oxygen

(a) Addition of 1 or 2 equivalents of ammonia

Initial attempts to add ammonia in controlled quantities, 3 equivalents (measured by titration) were found to increase the yield of the epidioxide by measurable quantities. However, the constant flow of oxygen was found to continually reduce the ammonia concentration.

(b) With continuous addition of ammonia (the recommended method)

Dry ammonia gas and dry oxygen were bubbled slowly through a solution of thebaine (18.73 g, 0.60 mmol) in benzene (500 ml) for 30 min at room

temperature. Tetranitromethane (18.87 g, 96 mmol) in benzene (100 ml) was added dropwise during 20 min. The gases were passed through the reaction mixture during addition of tetranitromethane and then for a further 120 min. Soon after the start of the addition of tetranitromethane a red oil was observed on the sides of the flask, which ran slowly down and collected at the bottom. At the end of the reaction, the benzene layer was decanted off leaving the viscous oil, which was washed twice with benzene (2 x 150 ml). The combined benzene solutions were washed with saturated aqueous sodium carbonate (2 x 500 ml) and water (2 x 500 ml). After being dried ($MgSO_4$) and evaporated under reduced pressure the solution gave an oil, which was chromatographed on a column of silica (t.l.c. grade). Elution with a steadily increasing gradient of chloroform in hexane gave the epidioxide (**27**) (16.76 g, 71.7%), m.p. 160°C (from EtOAc).

(c) <u>With addition of triethylamine</u>

Three equivalents of triethylamine were added to the benzene solution of thebaine before the addition of tetranitromethane. ^1H NMR spectroscopy of the crude reaction product showed an improvement in yield of the epidioxide (**27**). It was found to be very difficult to remove the excess triethylamine. Heating of the reaction mixture under vacuum resulted in violent decomposition.

8,14-*Dihydro*-14β-*nitro*-8α,10α-*epoxy*-8a-*homo*-8-*oxathebaine* (35)

This was the major product of the rearrangement of the epidioxide (**27**) with both neutral and basic, grade I, column grade alumina. Thus, the epidioxide (400 mg) isomerised on basic alumina (15 g) to give, after preparative t.l.c. and crystallisation from ethanol the 8,14-*dihydro*-14β-*nitro*-8α,10α-*epoxy*-8a-*homo*-8-*oxathebaine* (**35**) (295 mg, 74%), m.p. 270-271 °C (Found: C, 59.0; H, 5.0; N, 7.1. $C_{19}H_{20}N_2O_7$ requires C, 58.8; H, 5.2; N, 7.2%); ν_{max} ($CHCl_3$) 1549, 1450, 1082, 1285, and 1225 cm^{-1}; δ_H ($CDCl_3$; 360 MHz) 6.87 and 6.75 (ABq, *J* 7.1 Hz, 1- and 2-H), 5.73 (d, *J* 1.4 Hz, 7-H), 5.37 (s, 8a-H), 5.21 (d, *J* 1.4 Hz, 5-H), 5.12 (d, *J* 4.4 Hz, 10-H), 4.47 (d, *J* 4.4 Hz, 9-H), 3.88 (s, 3-OMe), 3.44 (s, 6-OMe), 2.54 (s, NMe), 2.53 (m, 16-CH_2), 2.39 (ddd, *J* 13.0, 10.3 and 6.9 Hz, 15_{ax}-H), and 1.78 (dt, *J* 13.0 and 2.7 Hz, $15_{eq.}$-H). The structure and ^1H and ^{13}C assignments were finally proved using 2-dimensional carbon-proton correlation spectroscopy. Both the direct and long range couplings were determined and, using the aromatic signals as a reference point, the structure was determined in a stepwise fashion using the direct and long range coupling alternately. The direct and long range couplings are given in Table 2.1 and the ^{13}C and ^1H NMR spectra are recorded in Tables 2.4 and 2.5.

8,14-*Dihydro*-8β-*hydroxy*-14β-*nitro*-10-*oxothebaine* (28)

According to the method of Allen *et al.*,[16] the epidioxide (**27**) (600 mg) was suspended in ethanol (75 ml) and treated at room temperature with sodium hydroxide (4 M, 12 drops). After 2 h, the crystals had dissolved. After a further 16 h the resultant green-blue solution was evaporated to dryness under reduced

pressure. The residue was suspended in water, neutralised with 0.1 M hydrochloric acid and extracted with chloroform. The extract was evaporated and the resultant oil crystallised from methanol to give the 8β-alcohol (**28**) (560 mg, 93%), m.p. 220°C (lit., 219 °C) (Found: C, 58.8; H, 5.3; N, 7.1. Calc. for $C_{19}H_{20}N_2O_7$: C, 58.8; H, 5.2; N, 7.2%); ν_{max} ($CHCl_3$) 3585, 1680, 1619, and 1547 cm^{-1}; λ_{max} (EtOH) 243 (ϵ 10750), 289 (ϵ 11000), and 316 nm (ϵ 4940); δ_H ($CDCl_3$; 90 MHz) 7.38 and 6.86 (ABq, *J* 8.6 Hz, 1- and 2-H), 5.25 (s, 5-H), 4.59 (br s, 7-H), 4.38 (br s, 8-H), 4.19 (s, 9-H), 3.97 (s, 3-OMe), 3.56 (s, 6-OMe), and 2.40 (s, NMe); *m/z* 388 and 342. These data were in reasonable agreement with the literature[16] values.

8,14-*Dihydro*-8α,10α-*epoxy*-14β-*nitrothebaine* (38)

1. **Using triphenylphosphine**

   (a) **In benzene**

The method of Allen *et al.*,[16] was used with minor changes. The epidioxide (**27**) (1.167 g, 3.1 mmol) and triphenylphosphine (0.947 g, 3.6 mmol) were heated in benzene (120 ml) under reflux for 32 h. The mixture was evaporated to one third of its original volume and diluted with hexane (*ca.* 10 ml). The precipitate of triphenylphosphine oxide was filtered off using Celite and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in chloroform and adsorbed onto a small quantity of t.l.c. grade silica. The silica was put onto a column of Grade III neutral alumina, which was eluted with hexane-chloroform (4:1). Fractions containing the epoxide (**38**) were then combined.

Further purification was effected on commercial GF_{254} silica t.l.c. plates (10 plates, 20 x 20 cm x 0.25 mm), developed with diethyl ether [the epoxide (**38**) ran faster than the epidioxide (**27**) on silica plates, the reverse of the order on alumina]. Recrystallisation from methanol gave the epoxide (**38**) (0.950 g, 83%) m.p. 131°C (lit.,[16] 131-132°C) (Found: C, 61.1; H, 5.4; N, 7.4. Calc. for $C_{19}H_{20}N_2O_6$: C, 61.3; H, 5.4; N, 7.5%); ν_{max} 1640 and 1551 cm^{-1}; δ_H ($CDCl_3$; 200 MHz) 6.78 and 6.72 (ABq, *J* 8 Hz, 1- and 2-H), 5.33 (s, 5-H), 5.05 (d, *J* 5.2 Hz, 10-H), 4.80 and 4.75 (ABq, *J* 5.8 Hz, 7- and 8-H), 4.68 (d, *J* 5.2 Hz, 9-H), 3.90 (s, 3-OMe), 3.56 (s, 6-OMe), 3.56 (s, 6-OMe), and 2.55 (s, NMe); δ_C ($CDCl_3$; 25.2 MHz) 156 (C-6), 146 (C-3), 144 (C-4), 132.5 (C-12), 128 (C-11), 119 (C-1), 114.5 (C-2), 97.5 (C-7), 90.0 (C-14), 86.0 (C-5), 77.0 (C-10), 76.0 (C-8), 68.0 (C-9), 56.5 (3-O<u>C</u>H_3), 55.0 (6-O<u>C</u>H_3), 46.5 (C-13).

(b) <u>In toluene (the recommended method)</u>

When toluene was used instead of benzene and the reaction mixture was heated under reflux for 24 h under an atmosphere of nitrogen, the product mixture could be purified completely on a t.l.c. grade silica column. The column was eluted with hexane followed by a steadily increasing gradient of chloroform in hexane. The epoxide (**38**) was obtained in 91% yield.

2. <u>Using tri(dimethylamino)phosphine (HMPTA)</u>

The epidioxide (**27**) (300 mg) and HMPTA (160 mg) were heated under reflux in benzene (20 ml) for 2.5 h. After the solvent had been evaporated,

the ^{1}H NMR spectrum of the residue showed that quantitative conversion to the epoxide (**38**) had occurred. However, the very similar R_f values of the epoxide and the tri(dimethylamino)phosphine oxide prevented their separation. It was further found that the deoxygenation took place at room temperature after 48 h, if the reaction was kept under an atmosphere of nitrogen.

Reduction of the Epoxide (38)

1. **Using ammonium chloride and zinc dust**

The epoxide (**38**) (450 mg, 1.21 mmol), ammonium chloride (430 mg, 8.04 mmol) and zinc dust (856 mg, 13.04 mmol) were heated under reflux in dry methanol (125 ml) for 35 min. The reaction mixture was filtered hot through Celite and the filtrate was poured into cold water (450 ml) and extracted with chloroform. The dried ($MgSO_4$) chloroform extracts were evaporated to dryness to give an oil (327 mg, 79%), judged to contain > 90% of the epoxyamine (**50**) by ^{1}H NMR spectroscopy; ν_{max} ($CHCl_3$) 3380, 1638, and 1507 cm^{-1}; δ_H ($CDCl_3$; 200 MHz) 6.71 and 6.65 (ABq, *J* 8.0 Hz, 1- and 2-H), 4.92 (d, *J* 5.9 Hz, 7-H), 4.87 (d, *J* 0.5 Hz, 5-H), 4.84 (d, *J* 4.9 Hz, 10-H), 4.36 (d, *J* 5.9 Hz, 8-H), 3.84 (s, 3-OMe), 3.48 (s, 6-OMe), 3.44 (d, *J* 4.2 Hz, collapses to singlet upon irradiation at δ 4.84, 9-H), 2.65 (m, 16$_{eq.}$-H), 2.54 (s, NMe), 2.40 (m, 16$_{ax.}$-H), 2.14 (m, 15$_{ax.}$-H), 1.70 (m, 15$_{eq.}$-H); *m/z* 342, 326, and 294 (Found: *m/z* 342.1583. $C_{19}H_{22}N_2O_4$ requires *M*, 342.1573). Attempts to purify this amine by chromatography or crystallisation caused partial decomposition.

2. Using finely divided zinc dust

As the purity of the zinc dust was found to have an effect on the course and yield of the reduction of the oxide it was decided to use activated zinc. The finely divided, activated zinc was prepared by the method of Rieke.[47] Zinc chloride was reduced with lithium in tetrahydrofuran (THF) using ultrasound to speed up the reaction.

Zinc chloride (20 g) was suspended in dry THF (300 ml). Argon was bubbled through the suspension to maintain an inert atmosphere. Lithium metal (2.1 g) was added in small pieces while the reaction flask was immersed in an ultrasonic bath. The bath was switched off periodically to allow the flasks to cool. After a total irradiation time of 45 min the flask was allowed to cool to room temperature. The finely divided zinc was collected by centrifugation, the tetrahydrofuran being decanted off. Dry methanol was added and the zinc was washed by centrifugation and decantation 4 times before finally being covered by methanol.

3. Using activated zinc

The epoxide (38) (300 mg), ammonium chloride (295 mg) and activated zinc dust (approx. 590 mg, measured by drying 3 samples of the methanolic suspension of zinc and using the average dry matter value to calculate the required volume of the suspension) were heated under reflux in dry methanol (100 ml, total volume including 5 ml from the suspension) for 35 min. After this time t.l.c. showed that the reaction was only *ca.* 75% complete. More ammonium chloride (100 mg) was then added and the reaction mixture was refluxed for 10 min. T.l.c. then showed

that, although all of the epoxide had been consumed, there were now significant quantities of both the nitroso compound (**52**) and the ring opened product (**51**).

8,14-Dihydro-14β-nitroso-8α,10α-epoxythebaine (**52**)

When the 14β-nitro epoxide (**38**) was reduced to the epoxyamine (**50**) a small amount of another product was observed as a blue band that ran close to the solvent on a t.l.c. plate. After separation by preparative t.l.c. on neutral alumina plates developed with ethyl acetate, the blue band was scraped off the plates and shaken with chloroform. After filtering, this gave a green-blue solution. However, after evaporation under reduced pressure, the resultant foam was a pale green colour. In addition, treatment with activated charcoal did not affect the colour of the solution. This blue-green colour in solution suggested the presence of a *C*-nitroso compound, existing as a dimer in the solid and dissociating to the monomer in solution. Attempts at crystallisation resulted in decomposition (as shown by t.l.c.). The impure product as obtained from the t.l.c. plate was therefore analysed as a foam, obtained by evaporation of diethyl ether under reduced pressure. The yield varied between 5 and 17%. The amorphous nitroso compound (**52**) had ν_{max} ($CHCl_3$) 1635, 1542, and 1508 cm^{-1}; δ_H ($CDCl_3$; 200 MHz) 6.74 (ABq, *J* 8.0 Hz, 1- and 2-H), 5.96 (d, *J* 5.0 Hz, 8-H), 5.19 (d, *J* 4.9 Hz, 7-H), 5.18 (s, 5-H), 4.70 (d, *J* 6.0 Hz, 10-H), 4.53 (d, *J* 6.0 Hz, 9-H), 3.84 (s, 3-OMe), 3.35 (s, 6-OMe), 2.58 (s, NMe), 2.45 (ddd, *J* 11.5, 10.5, and 5.0 Hz, 16_{ax}-H), 2.28 (ddd, *J* 11.5, 5.5, and 3.0 Hz, $16_{eq.}$-H), 1.66 (ddd, *J* 13.3, 5.0, and 3.0 Hz, $15_{eq.}$-H), and 1.35 (ddd, *J* 13.3, 10.5, and 5.5 Hz, $15_{ax.}$-H); δ_C ($CDCl_3$; 50.4 MHz) 159.9 (C-6), 146.3 (C-3), 143.3 (C-4), 133.5 (C-

12), 128.6 (C-11), 118.8 (C-1), 114.0 (C-2), 104.0 (C-14), 96.6 (C-7), 85.15 (C-5), 77.4 (C-10), 69.7 (C-9), 67.8 (C-8), 56.4 (3-OMe), 55.0 (6-OMe), 47.2 (C-16), 45.3 (C-13), 43.6 (NMe), and 26.0 (C-15); λ_{max} (MeOH) 284 (ϵ 2.1 x 10^3), and 696 nm (ϵ 35); *m/z* 356, 326, and 294 (Found: *m/z* 356.1380. $C_{19}H_{20}N_2O_5$ requires *M*, 356.1366).

Acetylation of the Epoxyamine (50)

1. **Using pyridine and acetic anhydride**

The crude amine (**50**) from the reduction of the nitro epoxide (**38**) (82 mg) was dissolved in dichloromethane (4 ml) and dry pyridine (3 drops) was added. Acetic anhydride (59 mg) in dichloromethane (0.5 ml) was added and the reaction mixture was left overnight. The solution, then bright purple, was evaporated to dryness and the residue was dissolved in chloroform and shaken with saturated aqueous sodium carbonate. The chloroform layer was dried ($MgSO_4$) and applied to silica preparative t.l.c. plates, which were developed with ethyl acetate. Three bands were obtained: the uppermost, which was green-blue, contained the nitroso compound (**52**) and the middle band contained the acetamide (**57**) and pyridine; the highly coloured, base-line band was not examined. The acetamide (**57**) was obtained as a bright orange gum and further purification only resulted in decomposition.

2. **Using pyridine and acetyl chloride**

The nitro epoxide (**38**) (363 mg) was dissolved in dry methanol (70 ml), and ammonium chloride (376 mg) and zinc dust (699 mg) were added. The mixture, after being refluxed for 35 min, was filtered to remove the zinc dust, and the filtrate

was poured into cold water (400 ml) and extracted with chloroform. The combined chloroform extracts were dried ($MgSO_4$) and evaporated to give a yellow-green foam. The foam was dissolved in dichloromethane (10 ml); pyridine (79 mg) was added, and the solution was cooled in an ice bath before acetyl chloride (77 mg) was added. The mixture was left in the ice bath for 15 min before being removed and allowed to warm up for a further 15 min. The solution was then evaporated to dryness under reduced pressure but without application of heat. The residue was dissolved in chloroform and shaken with saturated aqueous sodium hydrogen carbonate. The chloroform layer was dried ($MgSO_4$) then applied to preparative, silica t.l.c. plates, which were developed with ethyl acetate. Three bands were observed: the uppermost, green-blue band contained the nitroso compound (**52**), the second band contained the acetamide (**57**) and pyridine, and the bottom, highly coloured band which was not analysed. An attempt was made to remove pyridine from the acetamide (**57**) by co-distillation with toluene, then benzene, then diethyl ether. This procedure removed most of the pyridine but a large mixture of products was observed by ^1H NMR spectroscopy. The product at this point was a bright orange oil which gave five spots on t.l.c.

3. <u>Using dicyclohexylcarbodiimide and acetic acid</u>

The crude amine (**50**) from the reduction of the nitro epoxide (**38**) (400 mg) and glacial acetic acid (74 mg) in dichloromethane (5 ml) were treated with dicyclohexyl-carbodiimide (159 mg) in dichloromethane (2 ml). After 1.5 h at room temperature, the precipitated urea was filtered off and the crude product was

chromatographed on preparative neutral alumina t.l.c. plates, eluted three times with ethyl acetate-diethyl ether (1:3), to give 14β-*acetylamino*-8,14-*dihydro*-8α,10α-*epoxythebaine methanolate* (**57**) (265 mg, 57%), which had m.p. 122-124 °C (from MeOH) (Found: C, 63.4; H, 7.2; N, 6.5. $C_{29}H_{24}N_2O_5$ requires C, 65.6; H, 6.3; N, 7.3%. $C_{21}H_{24}N_2O_5$ MeOH requires C, 63.5; H, 6.8; N, 6.7%. $C_{21}H_{24}N_2O_5$ 2MeOH requires C, 60.3; H, 6.7; N, 6.25%); ν_{max} ($CHCl_3$) 1688, 1641, and 1509 cm^{-1}; δ ($CDCl_3$; 90 MHz) 6.68 (s, 1- and 2-H), 6.13 (s, NH, exch. with D_2O), 4.99 (s, 5-H), 4.93 (d, *J* 5 Hz, 10-H), 4.93 and 4.68 (ABq, *J* 6 Hz, 7- and 8-H), 3.85 (s, 3-OMe), 3.80 (d, *J* 5 Hz, 9-H), 3.48 (s, 6-OMe), 3.39 (s, MeOH), 2.50 (s, NMe), and 2.01 (s, Ac); *m/z* 384, 326, and 294 (Found: *m/z* 384.1688). $C_{21}H_{24}N_2O_5$ requires *M*, 384.1678.

14β-*Benzoylamino*-8,14-*dihydro*-8α,10α-*epoxythebaine* (**58**)

The crude amine (**50**) (305 mg, 0.89 mmol) and benzoic acid (110 mg, 0.90 mmol) in dry dichloromethane (7 ml) were treated with dicyclohexylcarbodiimide (192 mg) in dry dichloromethane (4 ml) at room temperature. After 3 h, the dicyclohexylurea was filtered off and the filtrate was evaporated to dryness. The crude product was chromatographed on preparative alumina (neutral) t.l.c. plates, developed with ethyl acetate. 14β-*Benzoylamino*-8,14-*dihydro*-8α,10α-*epoxythebaine hemihydrate* (**58**) (124 mg, 31%) had m.p. 195-198°C (from methanol) (Found: C, 68.68; H, 5.66; N, 6.10%. $C_{26}H_{26}N_2O_5$ requires C, 67.24; H, 6.03; N, 6.03%. $C_{26}H_{26}N_2O_5$ 0.5.H_2O requires C, 68.57; H, 5.93; N, 6.15%); ν_{max} ($CHCl_3$) 1679 and 1515 cm^{-1}; δ ($CDCl_3$; 200 MHz) 7.82 and 7.49 (2 x m, Ph), 6.73 and 6.72 (ABq, *J* 8.2 Hz, 1- and 2-H), 6.04 (s, NH, exch. with D_2O), 5.10 (d, $J < 1$ Hz, 5-H), 5.04 (d,

J 6 Hz, 7-H), 4.87 (d, *J* 5 Hz, 10-H), 4.79 (d, *J* 6 Hz, 8-H), 3.86 (d, *J* 5 Hz, 9-H, partially obscured by 3-OMe), 3.85 (s, 3-OMe), 3.52 (s, 6-OMe), 2.65 (m, $16_{eq.}$-H), 2.46 (dt, *J* 13 Hz and 4.5 Hz, $15_{ax.}$-H), 2.30 (s, NMe), 2.07 (dt, *J* 13 Hz and 5.5 Hz, $16_{ax.}$-H), 1.79 (m, $15_{eq.}$-H), and 1.59 (br s, H_2O, exch. with D_2O). (The hemi-hydrate composition was confirmed by the 200 MHz ^1H NMR spectrum which showed a dissolved water signal at δ 1.59 with the correct integral for half an equivalent of water. The same NMR spectrum also confirmed that there was no methanol in the sample); *m/z* 446 and 326 (Found: *m/z* 446.4960. $C_{26}H_{26}N_2O_5$ requires *M*, 446.4965).

<u>8,14-*Dihydro*-14β-*phenylacetylamino*-8α,10α-*epoxythebaine* (59)</u>

The crude amine (**50**) (265 mg, 0.77 mmol) and phenylacetic acid (112 mg, 0.82 mmol) in dichloromethane (5 ml) were treated with dicyclohexylcarbodiimide (100 mg) in dichloromethane (3 ml). After 1.5 h at room temperature, the urea was filtered off and the filtrate was evaporated to dryness. The crude product was chromatographed on preparative neutral alumina t.l.c. plates, eluted with ethyl acetate and crystallised with difficulty from methanol to give 8,14-*dihydro*-14β-*phenylacetyl-amino*-8α,10α-*epoxythebaine* (**59**) (189 mg, 53%) which had m.p. 222-225°C (from methanol) (Found: C, 70.55; H, 6.13; N, 5.92. $C_{27}H_{28}N_2O_5$ requires C, 70.41; H, 6.10; N, 6.12%); ν_{max} ($CHCl_3$) 1690 and 1499 cm^{-1}; δ ($CDCl_3$; 90 MHz) 7.30 (m, Ph), 6.66 (s, 1- and 2-H), 6.04 (br s, NH, exch. with D_2O), 4.91 (d, *J* 6 Hz, 7-H), 4.85 (s, 5-H), 4.75 (d, *J* 5 Hz, 10-H), 4.67 (d, *J* 6 Hz, 8-H), 3.82 (s, 3-OMe), 3.76 (d, *J* 5 Hz, 9-H), 3.58 (s, 18-CH_2), 3.47 (s, 6-OMe), and 2.45 (s, NMe); *m/e* 460 and 326 (Found: *m/z* 460.3438. $C_{27}H_{28}N_2O_5$ requires *M*, 460.3444).

8,14-*Dihydro*-14β-(3-*phenylpropanoylamino*)-8α,10α-*epoxythebaine* (60)

The crude amine (**50**) (370 mg) and phenylpropionic acid (177 mg) in dichloro-methane (5 ml) were treated with dicyclohexylcarbodiimide (151 mg) in dichloro-methane (2 ml). After 1.5 h at room temperature, precipitated urea was filtered off and the crude product was chromatographed on preparative alumina t.l.c. plates, eluted with ethyl acetate-petroleum ether (b.p. 40-60°C) (1:1). The *phenylpropanamide* (**60**), (272 mg, 53%) had m.p. 221-225°C (from methanol) (Found: C, 70.6; H, 6.1; N, 5.9. $C_{27}H_{28}N_2O_5$ requires C, 70.4; H, 6.1; N, 6.1%); ν_{max} ($CHCl_3$) 1685, 1643, and 1511 cm^{-1}; δ ($CDCl_3$; 90 MHz) 6.68 (s, 1- and 2-H), 5.87 (br s, NH, exch. with D_2O), 4.92 (d, *J* 5.5. Hz, 7-H), 4.88 (s, 5-H), 4.75 (d, *J* 5 Hz, 10-H), 4.58 (d, *J* 5.5 Hz, 8-H), 3.84 (s, 3-OMe), 3.63 (d, *J* 5 Hz, 9-H), 3.50 (s, 6-OMe), 2.97 (t, *J* 6 Hz, 18-CH_2), 2.46 (s, NMe), and 1.24 (t, *J* 6 Hz, 19-CH_2); *m/z* 474, 326, and 277 (Found: *m/z* 474.2149. $C_{28}H_{30}N_2O_5$ requires 474.2146).

8,14-*Dihydro*-14β-(4-*phenylbutanoylamino*)-8α,10α-*epoxythebaine* (61)

The crude amine (**50**) (297 mg) and 4-phenylbutanoic acid (151 mg) in dichloromethane (5 ml) were treated with dicyclohexylcarbodiimide (183 mg) in dichloromethane (2 ml) at room temperature. After 2 h the dicyclohexylurea was filtered off and the filtrate was evaporated to dryness. The crude product was chromatographed on preparative alumina (neutral) t.l.c. plates, developed with ethyl acetate to give 8,14-*dihydro*-14β-(4-*phenylbutanoylamino*)-8α,10α-*epoxythebaine* (**61**) (130 mg, 31%). The amide (**61**) could not be made to crystallise and was analysed as an amorphous solid foam, produced by the rapid evaporation under reduced

pressure of a solution of (**61**) in diethyl ether (Found: C, 71.11; H, 6.72; N, 5.73. $C_{29}H_{32}N_2O_5$ requires C, 71.29; H, 6.60; N, 5.74%); ν_{max} ($CHCl_3$) 1668 and 1530 cm^{-1}; δ ($CDCl_3$; 90 MHz); 7.20 (m, Ph), 6.56 (s, 1- and 2-H), 6.15 (br s, NH, exch. with D_2O), 5.00 (s, 5-H), 4.95 (d, *J* 6 Hz, 10-H), 4.78 and 4.67 (ABq, *J* 6 Hz, 7- and 8-H), 3.84 (s, 3-OMe), *ca.* 3.80 (d, *J ca.* 6 Hz, partially obscured by 3-OMe, 9-H), 3.50 (s, 6-OMe), and 2.50 (s, NMe); *m/z* 488 and 326 (Found: *m/z* 488.2275. $C_{29}H_{32}N_2O_5$ requires *M* 488.2272).

<u>8,14-*Dihydro*-14β-(2-*furoylamino*)-8α,10α-*epoxythebaine* (62)</u>

The crude amine (**50**) made by the reduction of the oxide (**38**) (401 mg) and 2-furoic acid (121 mg) in dichloromethane (7 ml) were treated with dicyclohexylcarbodiimide (222 mg) in dichloromethane (2 ml) at room temperature. After 2 h, the dicyclohexylurea was filtered off and the filtrate was evaporated to dryness. The crude product was chromatographed on preparative alumina (neutral) t.l.c. plates developed with ethyl acetate to give 8,14-*dihydro*-14β-(2-*furoylamino*)-8α,10α-*epoxythebaine* (**62**) [45 mg, 12% overall yield from the nitro compound (**38**)]. The product was unstable and could not be recrystallised but was analysed as an amorphous, hydrated solid (Found: C, 64.08; H, 5.82; N, 6.15. $C_{24}H_{24}N_2O_6$ requires C, 66.05; H, 5.54; N, 6.42. $C_{24}H_{24}N_2O_6.H_2O$ requires C, 63.42; H, 5.77; N, 6.16. $C_{24}H_{24}N_2O6$ 0.5.H_2O requires C, 64.71; H, 5.65; N, 6.29%); ν_{max} ($CHCl_3$) 1670, 1589, 1512, and 1501 cm^{-1}; δ ($CDCl_3$; 89.55 MHz) 7.49 (m, 3′-H), 7.15 (m, 5′-H), 7.11 (br s, NH, exch. with D_2O), 6.73 (s, 1- and 2-H), 6.51 (m, 4′-H), 5.08 (s, 5-H), 5.00 (d, *J* 5.9 Hz, 7-H), 4.87 (d, *J* 5.0 Hz, collapses to singlet on irradiation at 3.98, 10-H), 4.81 (d, *J* 6.2

Hz, 8-H), 3.98 (d, *J* 5.0 Hz, 9-H), 3.86 (s, 3-OMe), 3.51 (s, 6-OMe), and 2.58 (s, NMe); *m/z* 436, 326, and 294 (Found: 436.1608. $C_{24}H_{24}N_2O_6$ requires *M*, 436.1597).

8,14-*Dihydro*-14β-(*cinnamoylamino*)-8α,10α-*epoxythebaine* (63)

The crude amine (**50**) (315 mg, 0.92 mmol) and *trans*-cinnamic acid (136 mg, 0.92 mmol) in dichloromethane (5 ml) were treated with dicyclohexylcarbodiimide (192 mg, 0.94 mmol) in dichloromethane (2 ml) at room temperature for 3 h. The urea was filtered off and the filtrate was evaporated to dryness. The crude product was chromatographed on preparative alumina (neutral) t.l.c. plates developed with ethyl acetate to give 8,14-*dihydro*-14β-(*cinnamoylamino*)-8α,10α-*epoxythebaine hydrate* (**63**) (74 mg, 17%), m.p. 183°C (from methanol) (Found: C, 66.98; H, 6.10; N, 5.79. $C_{28}H_{28}N_2O_4$ requires C, 71.17; H, 5.97; N, 5.93. $C_{28}H_{28}N_2O_5.H_2O$ requires C, 68.56; H, 6.12; N, 5.71. $C_{28}H_{28}N_2O_5.1.5\ H_2O$ requires C, 67.32; H, 6.20; N, 5.61. $C_{28}H_{28}N_2O_5.2\ H_2O$ requires C, 66.14; H, 6.30; N, 5.51%); ν_{max} 1675 and 1528 cm^{-1}; δ ($CDCl_3$; 89.55 MHz) 7.67 (d, *J* 15 Hz, 18-H), 7.37 (m, Ph), 6.70 (s, 1- and 2-H), 6.52 (d, *J* 15 Hz, 19-H), 6.41 (br s, NH, exch. with D_2O), 5.14 (s, 5-H), 5.01 and 4.81 (ABq, *J* 5.9 Hz, 7- and 8-H), 4.70 and 3.98 (ABq, *J* 5.0 Hz, 10- and 9-H), 3.82 (s, 3-OMe), 3.54 (s, 6-OMe), 2.56 (s, NMe), and 1.65 (br s, H_2O exch. with D_2O). The signal for dissolved water at δ 1.65 confirmed the existence of a hydrate; the ^1H NMR spectrum also confirmed the absence of methanol; *m/z* 472, 326, and 294 (Found: *m/z* 472.1984. $C_{28}H_{28}N_2O_5$ requires *M*, 472.1991).

8,14-*Dihydro*-14β-(4-*chlorocinnamoylamino*)-8α,10α-*epoxythebaine* (64)

The crude amine (**50**) (370 mg, 1.08 mmol) and 4-chlorocinnamic acid (220 mg, 1.20 mmol) in dichloromethane (10 ml) were treated with dicyclohexylcarbodiimide (230 mg, 1.13 mmol) in dichloromethane (5 ml) at room temperature for 6 h. The urea was filtered off and the filtrate was evaporated to dryness. The residue was chromatographed on preparative alumina (neutral) t.l.c. plates developed with ethyl acetate to give 8,14-*dihydro*-14β-(4-*chlorocinnamoylamino*)-8α,10α-*epoxythebaine hydrate* (**64**) (331 mg, 56%), m.p. 189°C (from ethanol) (Found: C, 63.95; H, 5.48; N, 5.28. $C_{28}H_{27}C\ell N_2O_5$ requires C, 66.33; H, 5.37; N, 5.53. $C_{28}H_{27}C\ell N_2O_5.H_2O$ requires C, 64.06; H, 5.57; N, 5.34%); ν_{max} 1681 cm^{-1}; δ ($CDCl_3$; 90 MHz) 7.61 (d, *J* 13.1 Hz, 18-H), 7.25 (4H, m, Ar), 6.79 (s, 1- and 2-H), 6.60 (d, *J* 13.1 Hz, 19-H), 6.45 (br s, NH, exch. with D_2O), 5.05 (s, 5-H), 4.98 and 4.82 (ABq, *J* 5.9 Hz, 7- and 8-H), 4.75 (d, *J* 5.1 Hz, 10-H), 3.97 (s, 3-OMe), 3.89 (d, *J ca.* 5 Hz, 9-H, partially obscured by 3-OMe signal, 3.51 (s, 6-OMe), 2.59 (s, NMe) and 1.72 (br s, H_2O, exch. with D_2O). The signal for water δ 1.72 confirmed the existence of a hydrate; the ^1H NMR spectrum also confirmed the absence of methanol; *m/z* 508 and 506 (M^+) and 326.

8,14-*Dihydro*-14β-(4-*methylcinnamoylamino*)-8α,10α-*epoxythebaine* (65)

The crude amine (**50**) (395 mg, 1.15 mmol) and 4-methylcinnamic acid (205 mg, 1.26 mmol) in dichloromethane (15 ml) were treated with dicyclohexylcarbodiimide (245 mg, 1.20 mmol) in dichloromethane (5 ml) at room temperature for 14 h. The dicyclohexylurea was filtered off and the filtrate evaporated to

dryness. The crude product was chromatographed on preparative alumina (neutral) t.l.c. plates, developed with ethyl acetate. 8,14-*Dihydro*-14β-(4-*methylcinnamoyl-amino*)-8α,10α-*epoxythebaine* (**65**) (360 mg, 61%) had m.p. 163-165°C (from methanol) (Found: C, 69.21; H, 5.99; N, 5.60. $C_{29}H_{36}N_2O_5$ requires C, 71.58; H, 6.21; N, 5.76. $C_{29}H_{30}N_2O_5.0.5\ H_2O$ requires C, 70.28; H, 6.10; N, 5.65. $C_{29}H_{30}N_2O_5.H_2O$ requires C, 69.03; H, 5.99; N, 5.55%); ν_{max} ($CHCl_3$) 1668 and 1520 cm^{-1}; δ ($CDCl_3$; 100 MHz) 7.64 (d, *J* 13.5 Hz, 18-H), 7.50 and 7.19 (ABq, *J* 7.5 Hz, Ar-H), 6.73 (s, 1- and 2-H), 6.60 (d, *J* 13.5 Hz, 19-H), 6.43 (br s, NH, exch. with D_2O), 5.08 (s, 5-H), 4.98 and 4.79 (ABq, *J* 5.4 Hz, 7- and 8-H), 4.63 and 3.98 (ABq, *J* 4.9 Hz, 10- and 9-H), 3.80 (s, 3-OMe), 3.54 (s, 6-OMe), 2.63 (s, NMe), and 2.38 (s, 4′-Me); *m/z* 486 (M^+) and 326.

<u>10α-*Hydroxy*-14β-(3-*phenylpropanoylamino*)*codeinone* (67)</u>

8,14-Dihydro-14β-(3-phenylpropanoylamino)-8α,10α-epoxythebaine (**60**) (322 mg) was dissolved in 5 M hydrochloric acid (50 ml) and methanol (5 ml). After 1 h the solution was neutralised with sodium hydrogen carbonate and extracted with chloroform (5 x 50 ml). The combined chloroform layers were dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The crude reaction mixture was chromatographed on preparative alumina (neutral) t.l.c. plates, developed with ethyl acetate-methanol (10:1). The 10α-*hydroxy*-14β-(3-*phenylpropanoylamino*)*codeinone* (**67**) (144 mg, 47%), had m.p. 199-200°C (decomp.) (from ethanol) (Found: C, 70.40; H, 6.25; N, 6.01. $C_{27}H_{28}N_2O_5$ requires C, 70.42; H, 6.13; N, 6.08%); ν_{max} ($CHCl_3$) 3590 and 1690 cm^{-1}; δ ($CDCl_3$; 89.55 MHz) 7.24 (s, Ph), 6.90 and 6.75 (ABq, *J* 7 Hz,

1- and 2-H), 6.42 (s, NH, exch. with D_2O), 6.42 and 6.09 (ABq, *J* 10 Hz, 7- and 8-H), 5.00 (s, 5-H), 4.88 (s, 10-H), 3.83 (4H, s, 3-OMe and 9-H), and 2.58 (s, NMe); *m/z* 460 and 312.

10α-Hydroxy-14β-(3-phenylpropanoylamino)codeinone dimethyl acetal (66)

8,14-Dihydro-14β-(3-phenylpropanoylamino)-8α,10α-epoxythebaine (**60**) (190 mg) was partially dissolved in methanol (20 ml). The suspension was cooled (in ice) for 30 min before methanolic hydrochloric acid [36% hydrochloric acid (10 ml) made up to 100 ml with Analar methanol, also cooled for 30 min] (3 ml) was added with constant stirring. After 10 min a further amount (3 ml) of the methanolic hydrochloric acid was added. After 15 min, the resulting clear solution was neutralised with saturated aqueous sodium hydrogen carbonate. The heterogeneous mixture was concentrated under reduced pressure at 30°C (heating time 30 min) then extracted with chloroform (5 x 25 ml). The combined chloroform layers were dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was chromatographed on preparative alumina (neutral) t.l.c. plates, developed with ethyl acetate. Three bands were observed. The least polar, which was very luminescent under the u.v. lamp, had an R_f value identical to that of a minor component of the mixture of by-products formed by the incomplete reduction of the 14β-nitro epoxy compound (**38**). The second band, which also was minor, had an R_f value identical to that of the codeinone (**67**). The third, most polar band, which was by far the largest, containing 83% of the recovered products, gave *10α-hydroxy-14β-(3-phenylpropanoylamino)codeinone dimethyl acetal hemihydrate* (**66**) (108 mg, 54%), m.p. 237°C (from methanol) (Found: C, 67.36; H, 6.71; N, 5.59. $C_{29}H_{34}N_2O_6$ requires

C, 68.77; H, 6.72; N, 5.53. $C_{29}H_{34}N_2O_6.H_2O$ requires C, 66.41; H, 6.87; N, 5.34. $C_{29}H_{34}N_2O_6.0.5\ H_2O$ requires C, 67.57; H, 6.79; N, 5.43%); ν_{max} ($CHCl_3$) 3360 and 1680 cm^{-1}; δ ($CDCl_3$; 89.55 MHz) 7.25 (s, Ph), 6.90 and 6.73 (ABq, *J* 8.3 Hz, 1- and 2-H), 6.62 (d, *J* 10.5 Hz, 8-H), 6.26 (s, NH, exch. with D_2O), 5.47 (d, *J* 10.5 Hz, 7-H), 5.00 (s, 5-H), 4.61 (s, 10-H), 4.26 (s, 9-H), 3.85 (s, 3-OMe), 3.40 (s, 6β-OMe), 3.22 (br s, OH, exch. with D_2O), 2.98 (s, 6α-OMe), and 2.48 (s, NMe); *m/z* 506, 326, and 294 (Found: *m/z* 506.2381. $C_{29}H_{34}N_2O_6$ requires *M*, 506.2377).

Alternatively, the epoxy compound (**60**) was treated with anhydrous methanolic hydrogen chloride (prepared by adding acetyl chloride to magnesium-dried methanol at 0°C) containing 1% trimethylorthoformate. Treatment with this solution (0.05 M in HCl) at 0°C for 30 min, followed by neutralisation with powdered sodium hydrogen carbonate gave the acetal (**66**) accompanied by only trace amounts of the corresponding codeinone.

<u>**10-*Oxo*-14β-(3-*phenylpropanoylamino*)*codeinone* (69)**</u>

To 10α-hydroxy-14β-(3-phenylpropanoylamino)codeinone (**67**) (210 mg) in dichloromethane (50 ml) was added activated manganese dioxide prepared by the method of Attenburrow *et al.*[56] (1 g). After stirring for 14 h the suspension was filtered through Celite and evaporated to dryness under reduced pressure. The product was purified by preparative t.l.c. on alumina (neutral) plates, developed with ethyl acetate. The 10-*oxo*-14β-(3-*phenylpropanoylamino*)*codeinone* (**69**) (132 mg, 63.2%) had m.p. 187-189°C (from methanol) (Found: C, 70.69; H, 5.82; N, 6.12. $C_{27}H_{26}N_2O_5$ requires C, 70.72; H, 5.72; N, 6.11%); ν_{max} ($CHCl_3$) 1685 and 1654 cm^{-1}; δ ($CDCl_3$; 89.55 MHz) 7.31 (d, *J* 8.3 Hz, 1-H), 7.20 (s, Ph), 6.78 (d, *J* 8.3 Hz, 2-H),

6.57 (d, *J* 10.1 Hz, 8-H), 6.28 (s, NH, exch. with D_2O), 5.53 (d, *J* 10.1 Hz, 7-H), 5.02 (s, 5-H), 4.25 (s, 9-H), 3.85 (s, 3-OMe) and 2.57 (s, NMe); *m/z* 458 and 310 (Found: *m/z* 458.1926. $C_{27}H_{26}N_2O_5$ requires *M*, 458.1910).

10-Oxo-14β-(3-phenylpropanoylamino)codeinone dimethyl acetal (68)

To 10α-hydroxy-14β-(3-phenylpropanoylamino)codeinone dimethyl acetal (**66**) (350 mg) in dichloromethane (100 ml) was added activated manganese dioxide prepared by the method of Attenburrow *et al.*[56] (1.4 g). After stirring for 14 h the suspension was filtered through Celite and evaporated to dryness under reduced pressure. The product was purified by preparative t.l.c. on alumina (neutral) plates, developed with ethyl acetate. The *10-oxo-14β-(3-phenylpropanoylamino)codeinone dimethyl acetal* (**68**) (105 mg, 30.1%) had m.p. 163-166°C (from methanol) (Found: C, 69.00; H, 6.45; N, 5.53. $C_{29}H_{32}N_2O_6$ requires C, 69.03; H, 6.39; N, 5.55%); ν_{max} ($CHCl_3$) 1672 cm^{-1}; δ ($CDCl_3$; 90 MHz) 7.28 (d, *J* 8.1 Hz, 1-H), 7.12 (s, Ph), 6.76 (d, *J* 8.1 Hz, 2-H), 6.33 (d, *J* 9.7 Hz, 8-H), 6.11 (s, NH, exch. with D_2O), 5.47 (d, *J* 9.7 Hz, 7-H), 5.13 (s, 5-H), 4.43 (s, 9-H), 3.79 (s, 3-OMe), 3.33 (s, 6β-OMe), 3.00 (s, 6α-OMe) and 2.52 (s, NMe); *m/z* 504 (M^+), 356 and 324.

Attempted reduction of 10-oxo-14β-(3-phenylpropanoylamino)codeinone dimethyl acetal (68) using sodium borohydride

Sodium borohydride (10 mg) was added to 10-oxo-14β-(3-phenylpropanoyl-amino)codeinone dimethyl acetal (**68**) (150 mg) in methanol (100 ml). After 3 h at room temperature t.l.c. showed a mixture of starting material and one other product. However, after 16 h when the reaction was worked up by concentration under

reduced pressure, partition between chloroform and water, followed by evaporation of the dried, combined chloroform layers produced only the starting material.

The reaction was repeated under nitrogen to prevent re-oxidation of the product. The ^1H NMR of the product obtained by a similar work-up method, as detailed above, showed a mixture of starting material and a 10-hydroxy product. However, on standing overnight in chloroform solution, only the 10-oxo starting material was evident.

8,14-Dihydro-8α,10α-dihydroxy-14β-nitrothebaine (71)

The keto alcohol (**28**) (100 mg) in methanol (20 ml) was treated with an excess of sodium borohydride in aqueous methanol (15 ml) at room temperature overnight. The reaction mixture was evaporated to dryness under reduced pressure and the residue was shaken with brine and chloroform. The aqueous layer was further extracted with chloroform and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give an off-white solid which crystallised easily from ethanol, to give 8,14-*dihydro*-8α,10α-*dihydroxy*-14β-*nitrothebaine* (**71**) (76 mg, 76%), m.p. 262-263°C (decomp.) (from ethanol) (Found: C, 58.50; H, 5.71; N, 7.00. $C_{19}H_{22}N_2O_7$ requires C, 58.45; H, 5.68; N, 7.18%); ν_{max} (KBr) 3500 and 1543 cm^{-1}; δ (10% CD_3OD in $CDCl_3$; 90 MHz) 7.04 and 6.85 (ABq, *J* 9 Hz, 1- and 2-H), 5.16 (d, *J* 6 Hz, 10-H), 5.13 (s, 5-H), 4.52 (d, $J < 1$ Hz, 7-H), 4.26 (d, *J* 6 Hz, 9-H), 4.21 (s, 8-H), 3.90 (s, 3-OMe), 3.57 (s, 6-OMe), and 2.80 (s, NMe); *m/z* 390, 344, 326, and 294. With the exception of the m.p. (lit.,[26] 237-238°C) these data are in good agreement with the lit.[26] values. This compound was found to be slowly oxidised in

air to reform the 10-oxo compound (**28**), as reported. This inevitably had frustrated earlier attempts.

***8α,10α-Diacetoxy-8,14-dihydro-14β-nitrothebaine* (72)**

The 8α,10α-diol (**71**) (35 mg) in dry pyridine (2 ml) was treated with acetyl chloride (3 drops) at room temperature. After 2 h the excess of acetyl chloride was evaporated under reduced pressure then the pyridine was similarly evaporated as an azeotrope with toluene (4 x 10 ml). The product crystallised easily from methanol giving 8α,10α-*diacetoxy*-8,14-*dihydro*-14β-*nitrothebaine* (**72**) (35 mg, 97%), m.p. 223°C (from methanol) (Found: C, 57.98; H, 5.27; N, 5.71. $C_{23}H_{29}N_2O_9$ requires C, 58.22; H, 5.48; N, 5.90%); δ ($CDCl_3$; 100 MHz) 6.91 (s, 1- and 2-H), 6.54 (d, *J* 5.6 Hz, 10-H), 5.44 (s, 5-H), 5.20 (d, *J* 1 Hz, 8-H), 4.33 (d, *J* 1 Hz, 7-H), 4.18 (d, *J* 5.6 Hz, 9-H), 3.88 (s, 3-OMe), 3.52 (s, 6-OMe), 2.59 (s, NMe), 2.18 (s, COMe), and 2.14 (s, COMe); *m/z* 474, 428, 368, and 326 (Found: *m/z* 474.4592. $C_{23}H_{26}N_2O_9$ requires *M*, 474.4606).

***8,14-Dihydro-8β-hydroxy-10-oxothebaine* (78)**

8,14-Dihydro-9β-hydroxy-14β-nitro-10-oxothebaine (**28**) (2.00 g, 5.15 mmol) and tributyltin hydride (9.00 g, 31 mmol) were heated under reflux in dry toluene (250 ml) under an atmosphere of nitrogen. Azobutyronitrile (AIBN) in dry toluene was added over a period of 2 h using a syringe pump. The solution was refluxed for a further 2 h. Evaporation of the toluene under reduced pressure left a light brown oil. This oil was partitioned between acetonitrile (100 ml) and hexane (100 ml).

The acetonitrile layer was washed repeatedly with hexane (4 x 100 ml) before being evaporated to dryness under reduced pressure to give a yellow-green solid. Chromatography on silica preparative t.l.c. plates developed with ethyl acetate gave two bands. The first, R_f 0.7-0.8, gave a compound (0.27 g, was judged by ^{1}H NMR spectroscopy to be consistent with the starting material (**28**). The second, R_f 0.4-0.5, yielded a product which was crystallised from methanol to give 8,14-dihydro-8α-hydroxy-10-oxothebaine [1.28 g, 84.2% yield, based on the amount of starting material (**28**) that had reacted], m.p. 158-160°C (from methanol) (Found: C, 66.33; H, 6.15; N, 4.02. $C_{19}H_{21}NO_5$ requires C, 66.46; H, 6.16; N, 4.08%); ν_{max} ($CHCl_3$) 3470 and 1630 cm^{-1}; δ ($CDCl_3$; 200 MHz) 7.38 and 6.80 (ABq, *J* 8.4 Hz, 1- and 2-H), 4.95 (d, *J* 1.32 Hz, 5-H), 4.82 (d, *J* 1.84 Hz, 7-H), 3.92 (s, 3-OMe), 3.78 (dd, *J* 9.3 and *ca.* 1.5 Hz, 8-H), *ca.* 3.56 (partially obscured signal, 9-H), 3.55 (s, 6-OMe), 2.72 (ddd, *J* 12.1, 5.0, and 1.8 Hz, $16_{eq.}$-H), 2.44 (s, NMe), 2.37 (td, partially obscured by NMe signal, *J* 12.1 and 4.5 Hz, $16_{ax.}$-H), 2.27 (dd, *J* 9.3 and 2.6 Hz, 14-H), 2.10 (td, *J* 12.3 and 5.0 Hz, $15_{ax.}$-H), 1.95 (ddd, *J* 12.5, 4.3 and 1.8 Hz, $15_{eq.}$-H), 1.72 (br s, OH, exch. with D_2O); *m/z* 343, 325, and 298 (Found: *m/z* 343.1413. $C_{19}H_{21}NO_5$ requires *M*, 343.1419).

It was found that if the amount of initiator was reduced, the amount of the nitro compound reduced was correspondingly diminished even with an extended period of heating.

10-*Oxothebaine*(77)

8,14-Dihydro-8β-hydroxy-10-oxothebaine (**78**) (1.00 g), dry pyridine (4 ml) and freshly distilled phosphorus oxychloride (1 ml) were dissolved in dry toluene (150 ml) and refluxed under an atmosphere of nitrogen for 3 h, by which time a black oil had formed and collected at the bottom of the flask. Toluene was decanted off to leave some solvent (*ca.* 30 ml) covering the oil. Water (30 ml) was added followed by sufficient 4M-sodium hydroxide to make the aqueous layer alkaline (*ca.* pH 11). When the mixture was shaken a thick emulsion was produced which took several hours to separate. The aqueous layer was further extracted with toluene (4 x 40 ml), the foam separating progressively quicker with each extraction. The combined toluene extracts and the solvent (*ca.* 120 ml) initially decanted off were washed with 10% aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and concentrated under reduced pressure. The pyridine was removed by azeotropic distillation with more toluene (4 x 100 ml), followed by benzene (2 x 100 ml), and finally with diethyl ether (3 x 100 ml). The resulting pale yellow-green solid was purified by chromatography on a column of t.l.c. grade silica, eluted initially with chloroform then with an increasing gradient of methanol in chloroform (rising from 1 to 10%). A green oil was obtained which crystallised on standing (0.77 g). Recrystallisation from ethanol gave 10-*oxothebaine* (**77**) (0.69 g, 73%), m.p. 195-198°C (Found: C, 70.29; H, 5.79; N, 4.30. $C_{19}H_{19}NO_4$ requires C, 70.15; H, 5.81; N, 4.31%); ν_{max} ($CHCl_3$) 1680, 1666 and 1607 cm^{-1}; λ_{max} (MeOH) 263 (ε 12900), 285 (ε 10450) and 330 (ε 8470) nm; δ ($CDCl_3$, 100 MHz) 7.45 and 6.76 (ABq, *J* 8 Hz, 1- and 2-H), 5.64 (d, *J* 7.5 Hz, 8-H),

5.38 (s, 5-H), 5.08 (d, *J* 7.5 Hz, 7-H), 3.90 (s, 3-OMe), 3.58 (s, 6-OMe), and 2.46 (s, NMe); *m/z* 325, 310, and 296 (Found: *m/z* 325.1305. $C_{19}H_{19}NO_4$ requires *M*, 325.1314).

10-*Oxothevinone* (80)

This Diels-Alder adduct (**80**) was prepared by the literature method used to prepare thevinone itself.[12,13] 10-Oxothebaine (**77**) (120 mg) was heated under reflux with methyl vinyl ketone (8 ml) for 1.5 h. The excess of the latter ketone was removed by distillation under reduced pressure. The residue was chromatographed on preparative silica t.l.c. plates. The material that was recovered from a very broad band on the plates gave, after repeated crystallisation from methanol, 10-*oxothevinone* (**80**) (126 mg, 86%), m.p. 129-131°C (Found: C, 69.76; H, 6.43; N, 3.50. $C_{23}H_{25}NO_5$ requires C, 69.85; H, 6.37; N, 3.54%); ν_{max} ($CHCl_3$) 1719 and 1675 cm^{-1}; δ ($CDCl_3$; 200 MHz) 7.30 and 6.69 (ABq, *J* 8.4 Hz, 1- and 2-H), 6.02 and 5.58 (ABq, *J* 8.8 Hz, 18- and 17-H), 4.71 (d, *J* 1.2 Hz, 5-H), 3.95 (s, 3-OMe), 3.64 (s, 6-OMe), 3.20 (s, 9-H), 2.51 (s, NMe), 2.23 (s, Ac), 1.42 (dd, *J* 11.4 and 5.4 Hz, 8α-H); *m/z* 395 (M^+), 352 and 325.

8α,10α-*Epidioxy*-8,14-*dihydro*-14β-*nitro*-N-*cyclopropylmethyl*-N-*northebaine* (42)

N-Cyclopropylmethyl-*N*-northebaine (**41**) (2.05 g, 5.8 mmol) was dissolved in benzene (150 ml). The solution was saturated with dry oxygen and ammonia (a slight precipitation of *N*-cyclopropylmethyl-*N*-northebaine was observed on addition of ammonia). Tetranitromethane (1.88 g, 9.6 mmol) in benzene (30 ml) was added

dropwise over a period of 45 min. The flow of gases was maintained for a further 3 h. At the end of this time a red-brown oil had formed and collected at the bottom of the flask. The solvent was decanted off and the oil was washed with benzene (2 x 50 ml). The combined benzene layers were washed with saturated aqueous sodium hydrogen carbonate (3 x 150 ml), then with water (2 x 150 ml). After being dried ($MgSO_4$), the benzene layer was evaporated to dryness under reduced pressure at 30-40°C). More benzene (75 ml) was added and this was evaporated off as before. Diethyl ether (100 ml) was added to the resultant oil. Upon evaporation under reduced pressure a stable foam was obtained. The product was crystallised with difficulty from ethanol giving 8α,10α-*epidioxy*-8,14-*dihydro*-14β-*nitro*-N-*cyclopropylmethyl*-N-*northebaine* (**42**) as yellow rhomboids (1.11 g, 44%), m.p. 133-135°C (Found: C, 61.54; H, 5.60; N, 6.70. $C_{22}H_{24}N_2O_7$ requires C, 61.68; H, 5.61: N, 6.54%); ν_{max} ($CHCl_3$) 1641 and 1550 cm^{-1}; δ ($CDCl_3$; 90 MHz) 6.93 and 6.72 (ABq, *J* 8.2 Hz, 1- and 2-H), 5.35 (d, *J* 3.4 Hz, 10-H), 5.31 (s, 5-H), 5.00 and 4.59 (ABq, *J* 6.2 Hz, 7- and 8-H), 4.52 (d, *J* 3.4 Hz, 9-H), 3.88 (s, 3-OMe), and 3.55 (s, 6-OMe).

8,14-*Dihydro*-8β-*hydroxy*-14β-*nitro*-10-*oxo*-N-*cyclopropylmethyl*-N-*northebaine* (44)

8α,10α-Epidioxy-8,14-dihydro-14β-nitro-*N*-cyclopropylmethyl-*N*-northebaine (**42**) (1.00 g) was dissolved in ethanol (200 ml). Sodium hydroxide solution (4 M, 1 ml) was added and the reaction mixture was left overnight at room temperature. The solution was acidified with dilute hydrochloric acid then neutralised with sodium hydrogen carbonate. The resultant suspension was concentrated under reduced

pressure then partitioned between brine (50 ml) and chloroform (200 ml). The aqueous layer was further extracted with chloroform (2 x 100 ml). The combined chloroform layers were dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow-brown oil. Diethyl ether (100 ml) was added and evaporated off under reduced pressure at room temperature. The oil thus obtained was put on a vacuum line. The resultant foam was crystallised from methanol to give 8,14-*dihydro*-8β-*hydroxy*-14β-*nitro*-10-*oxo*-N-*cyclopropylmethyl*-N-*northebaine* (**44**) (0.86 g, 86%), m.p. 168-171°C (Found: C, 61.59; H, 5.72; N, 6.47. $C_{22}H_{24}N_2O_7$ requires C, 61.68; H, 5.61; N, 6.54%); ν_{max} ($CHCl_3$) 3450, 1680, 1620, and 1548 cm^{-1}; δ ($CDCl_3$; 90 MHz) 7.50 and 6.95 (ABq, *J* 8 Hz, 1- and 2-H), 5.30 (s, 5-H), 4.55 (d, *J ca.* 1 Hz, 7-H), 4.38 (br s, 8-H, gives fine doublet *J ca.* 1 Hz after D_2O exchange), 4.22 (s, 9-H), 3.95 (s, 3-OMe), and 3.61 (s, 6-OMe); *m/z* 428 (M^+) and 382.

References

1. F.A.W. Serturner, *Trommsdorff's Journal der Pharmazie*, 1805. **13**, 234.
2. J.M. Gulland and R. Robinson, Mem. Proc. Manchester Lit. Phil. Soc., 1925, **69**, 79.
3. M. Gates and G. Tschudi, *J. Am. Chem. Soc.*, 1956, **78**, 1380.
4. K. Chang, in 'The Receptors', ed. P.M. Conn, Academic Press, 1984, Chapter 1.
5. G.A. Cordell, in 'Introduction to Alkaloids', Wiley-Interscience, 1981, Chapter 8.
6. N.B. Eddy, *Chem. and Ind.*, 1949, 1462.
7. P.A.J. Jansen, in 'Synthetic Analgesics' Part 1, Pergamon Press, Oxford, 1960.
8. E.L. May *et al.*, *J. Org. Chem.*, 1957, **22**, 1366; 1959, **24**, 1432 and 1435; 1960, **25**, 984; 1962, **27**, 245, 2144 and 2554.
9. A.H. Beckett and A.F. Casey, *Bull. Narcotics*, 1957, **9**, 37.
10. P.A.J. Jansen *et al*, *J. Med. Pharm. Chem.*, 1959, **1**, 105, 281, 299 and 301; 1960, **2**, 271.
11. E.S. Stern *et al*, *J. Chem. Soc.*, 1956, 4088; 1959, 3067; 1960, 2103.
12. K.W. Bentley and D.G. Hardy, *J. Am. Chem. Soc.*, 1967, **89**, 3267.
13. K.W. Bentley, D.G. Hardy and B. Meek, *J. Am. Chem. Soc.*, 1967, **89**, 3273.

14. G.F. Blane and D.S. Robbie in 'Agonist and Antagonist Actions of Narcotic Analgesic Drugs', eds. H.W. Kosterlitz, H.O.S. Collier and J.E. Villarreal, Proceedings of the Symposium of the British Pharmacological Society, Aberdeen, 1971, McMillan Press, London, 1972, p.120.

15. K.W. Bentley and J.W. Lewis, Ref. 14, p.7.

16. R.M. Allen, G.W. Kirby and D.J. McDougall, *J. Chem. Soc., Perkin Trans. 1,* 1981, 1143.

17. R.J. Kobylecki, I.G. Guest, J.W. Lewis and G.W. Kirby, DTOLS 2,812,580/1978 (*Chem. Abs.,* 1979, **90**, 87709?).

18. J. Hughes *et al., Nature*, 1975, **258**, 577.

19. J.A.H. Lord *et al., Nature*, 1977, **267**, 495.

20. W.F. Michne and N.F. Albertson, *J. Med. Chem.*, 1972, **15**, 1278.

21. T. Oka *et al., Eur. J. Pharmacol.,* 1980, **73**, 235.

22. J.H. Hiller and E.J. Simon, *Eur. J. Pharmacol.,* 1979, **66**, 389.

23. J. Magnan *et al., Naunyn Schmiedaberg's Arch. Pharmacol.,* 1982, **319**, 197.

24. S. Archer *et al., J. Med. Chem.,* 1985, **28**, 974.

25. R.M. Allen, Ph.D. Thesis, Loughborough, 1971.

26. D.J. McDougall, Ph.D. Thesis, Glasgow, 1975.

27. H.J.E. Lowenthal in 'Guide for the perplexed organic experimentalist', Heyden and Son, 1978.

28. S. Patai in 'The Chemistry of amino, nitroso and nitro compounds and their derivatives, Parts 1 and 2, Wiley-Interscience, 1970.

29. The Chemistry of amino, nitroso and nitro compounds and their derivatives, Supplement F., Wiley-Interscience, 1982.

30. H. Stephen and T. Stephen in 'Solubility of inorganic and organic compounds', Regan, 1963, Vol. 1, Part 2.

31. Fischer (no initial or first name given), unpublished report, NIOSHTIC Data Base abstract No. 00042741 on Silver Platter CD ROM v. 1.5.

32. P. Liang, in 'Organic Syntheses, Coll. Vol. III, 803.

33. F.D. Chattaway, *J. Chem. Soc.,* 1910, 2099.

34. F.D. Chattaway, *Chem. News*, 1910, **102**, 307.

35. M. Magi *et al.,* Eesti. N.S.V. Tead. Akad. Toim., Keem., Geol., 1971, **20(4)**, 297.

36. R. Criegee, *Chem. Ber.,* 1944, **77**, 722.

37. R. Criegee and R. Kaspar, *Annalen.,* 1948, **560**, 127.

38. F.M. Leslie, *Pharmacol. Rev.,* 1987, **39**, 197.

39. C. Chapleo, Reckitt and Colman, Hull, England, unpublished results.

41. D. Swern, in Organic Peroxides', Wiley, 1970.

42. A.A. Freer *et.al., J. Chem. Soc., Perkin Trans. 2*, 1985, 7, 971.

43. J. March, in Advanced Organic Chemistry, 2nd Ed., McGraw-Hill, 1977.

44. W.C. Petersen and R.L. Letsinger, *Tetrahedron Lett.,* 1971, 2197.

45. S.R. Sandler and W. Karo, in 'Organic Functional Group Preparations, Academic Press, New York, 1986, Vol.2.

46. H. Feuer *et al,J. Org. Chem.,* 1965, **31**, 2880.

47. E. Erdik, *Tetrahedron*, 1987, **43**, 2203.

48. R.D. Rieke, *Acc. Chem. Res.*, 1977, **10**, 301.

49. B. Boudjouck, *J. Chem. Educ.*, 1986, **63**, 427.

50. J.C. Touchster and M.F. Dobbins, in Practice of thin layer chromatography', Wiley 1978.

51. N. Kornblum, S.C. Carlson and R.G. Smith, *J. Chem. Soc.*, 1978, **100**, 289.

52. N. Ono *et al., Tetrahedron Lett.*, 1981, 1705.

53. U. Eppenburger, M.E. Warren and H. Rappaport, *Helv. Chim. Acta.*, 1968, **51**, 381.

54. C.A. Buehler, D.E. Pearson, Survey of Organic Syntheses, Wiley 1977, Vol.2, Ch.2.

55. R.I. Gourlay, Ph.D. Thesis, Glasgow, 1979.

56. J. Attenburrow *et. al., J. Chem. Soc.*, 1952, 1094.