STUDIES IN MORPHINAN CHEMISTRY

A thesis presented in part fulfilment
of the requirements for the degree of
Doctor of Philosophy

by

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To my parents

ACKNOWLEDGEMENTS

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I also wish to thank my laboratory colleagues and the technical staff of the Chemistry Department for their help over the past three years, Reckitt and Colman Ltd. for the pharmacological testing, and the Science and Engineering Research Council for financial support.

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SUMMARY

Synthetic routes from thebaine to 14β-acylaminodeoxydihydrocodeinones were explored. Each route was eventually frustrated by our inability to remove reductively either a 4-phenoxy or a 4-(1-phenyltetrazol-5-yl)oxy group from a number of derivatives.

Routes to the preparation of a thebaine derivative containing a piperidine nitrogen-carbon(14) bridge were investigated. In the *N*-northebaine series no bridged compounds were formed but in the thebaine series two quaternary ammonium chlorides with the desired bridge were prepared.

Treatment of the cycloadduct 6β,14β-(*N*-chloroacetylepoxyimino)-6,14-dihydro-*N*-t-butoxycarbonylnorthebaine with sodium ethoxide in ethanol afforded, unexpectedly, 14β-(2,2-diethoxyethanoylamino)-*N*-t-butoxycarbonylnorcodeinone. Similarly, the cycloadduct 6β,14β-(*N*-phenylacetylepoxyimino)-6,14-dihydrothebaine was found to react with high stereoselectivity with methoxide to give 14β-[(*S*)-2-methoxy-2-phenylethanoylamino]codeinone. Treatment of the hydroxamic acid 14β-(*N*-2-phenylethanoylhydroxyamino)codeinone with toluene-*p*-sulphonyl chloride in pyridine followed by methoxide gave a yellow product which had incorporated one molecule of pyridine. All the foregoing reactions are believed to proceed *via* aziridinone (α-lactam) intermediates. Further studies on model compounds supported the proposed mechanisms. An alternative, high yielding synthesis of the known α-lactam, 1-t-butyl-3-phenylaziridin-2-one, has been achieved by treating the appropriate hydroxamic acid with trifluoromethanesulphonic anhydride and triethylamine at 70°C.

The reaction of the hydroxamic acid 14β-(*N*-chloroacetylhydroxyamino)-*N*-t-butoxycarbonylnorcodeinone ethylene acetal with ethoxide gave the 14β-aminonorcodeinone derivative. A similar treatment of

the corresponding hydroxamic acid derived from thebaine and also of model compounds yielded ester products. These reactions are rationalised in terms of oxazetidinone intermediates.

CONTENTS

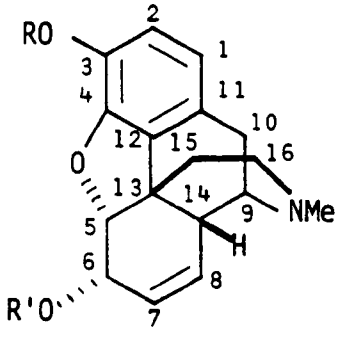
CHAPTER 1

INTRODUCTION

"And Helen, daughter of Zeus, poured into the wine they were drinking a drug nepenthes which gave forgetfulness of evil."

Homer in The Odyssey.

For centuries, nepenthes and other preparations of opium, the dried latex of the poppy plant *Papaver somniferum*, have been used to alleviate pain and produce euphoria. The principal active constituent morphine (1; R = R' = H) was first isolated by Sertürner[1] in 1805 and its structure was established 120 years later by Gulland and Robinson.[2] In the intervening period various minor alkaloids were discovered, of which codeine (1; R = Me, R' = H) a well-known cough remedy, and thebaine (2) a non-narcotic and strychnine-like poison, bear particularly strong resemblance to morphine. In 1956 Gates and Tschudi[3] reported the first total synthesis of morphine thereby providing confirmatory proof of its structure.



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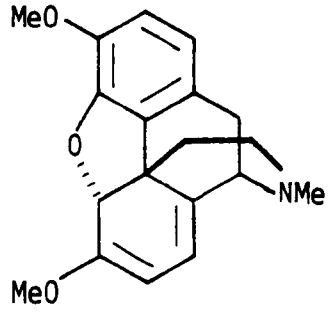

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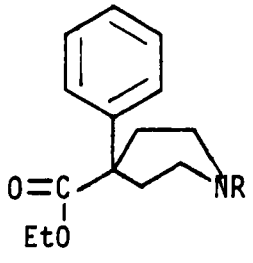
Due to side reactions, *viz.* spastic constipation, depression of the respiratory centre, sedation, euphoria and addiction, morphine is not the ideal analgesic. In the search for a potent analgesic with no adverse effects, chemists have made modifications to the morphine nucleus and synthesised new types of skeleton. The synthetic compounds have nuclei akin to that of morphine, *viz.* 4-phenylpiperidines (3), morphinans (4) and 6,7-benzomorphans (5), with side chains whose nature and location were suggested by results in the morphine field. For example pethidine (3; R = Me), levorphanol (4; R = Me) and metazocine (5; R = Me) are all analgesics but have similar disadvantages to morphine.[4]



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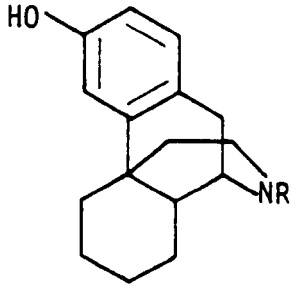

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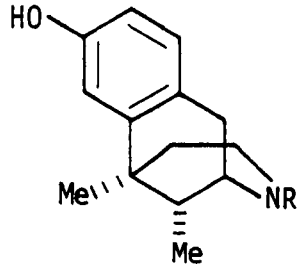

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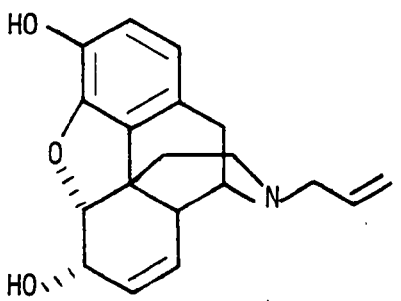
Before the detailed structures of the morphine alkaloids were known, minor modifications had already yielded derivatives with increased activity. The most notable of these was heroin (1; R = R' = Ac), and in 1898, on the basis of pharmacological reports, it was marketed (misleadingly!) in Germany as a non-addictive analgesic. More recently, morphine derivatives with a hydroxy or amino group at the 14-position have been prepared and some of these show analgesic activity in excess of that of morphine.[5,6]

N-Allylnormorphine (6), rediscovered more than 25 years after its original preparation by Pohl in 1915,[7] was recognised as the first

of the antagonists, a group of compounds which later included *N*-propyl and *N*-cyclopropylmethyl derivatives. A pure antagonist produces none of the pharmacological actions characteristic of morphine but can block the effects of it and other agonists. Naloxone (7) and nalorphine (6) are two such examples and are used as antidotes in cases of narcotic overdose.



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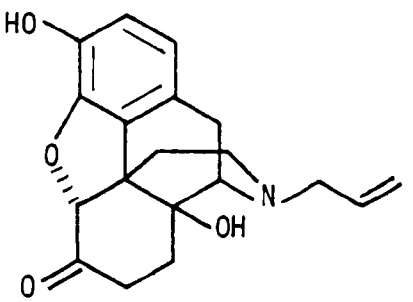

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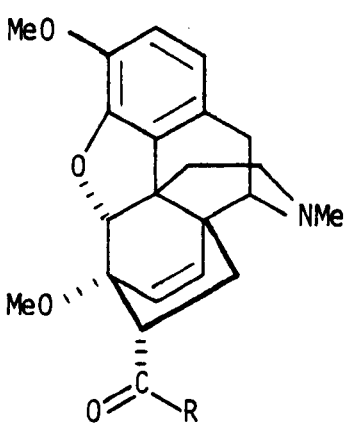
Generally most antagonists, for example pentazocine (5; R = $CH_2CH{=}CMe_2$) and cyclazocine (5; R = cyclopropylmethyl), have a degree of agonist activity, *i.e.* they are partial agonists, and since they are less open to abuse they make clinically valuable analgesics.

A novel series of potent agonists were discovered by Bentley *et al.*[8] in the following way. The conjugated diene system of thebaine reacted with α,β-unsaturated ketones to give high yields of Diels-Alder adducts with the general structure (8; R = alkyl).



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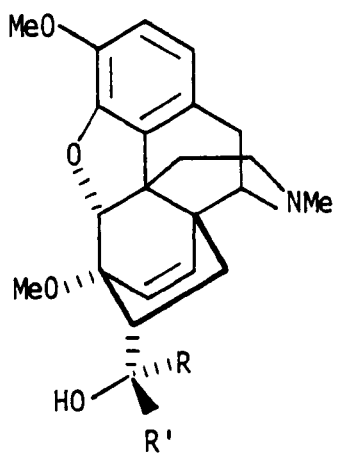
Although, in principle, a number of adducts are possible, only the isomer with the stereochemistry shown was formed. This outcome resulted from dienophile addition occurring readily only to the exposed β face of the diene, and under electronic control due to the 14-position of thebaine being electron rich. Several of the adducts were found to be more potent analgesics than morphine.

Treatment of the ketones with Grignard reagents gave the related series of tertiary alcohols (9; R,R' = alkyl). A high degree of



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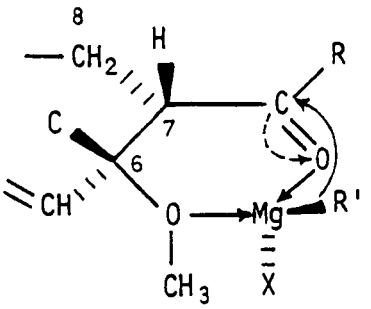

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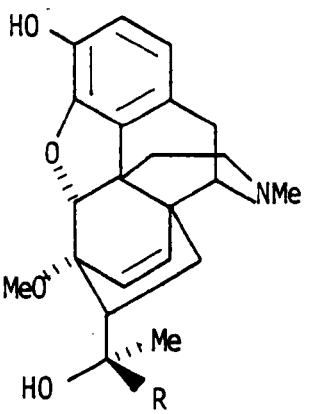
stereoselectivity was observed in these reactions due to the reagent participating in a six-membered cyclic intermediate (10) in which attack on the carbonyl group from above is less hindered than attack from below. The most extensive series of alcohols studied was that obtainable from the ketone (8; R = Me). Structure-activity relationships[9] have shown in this series, *i.e.* (9; R = Me, R' = alkyl), as the length of the hydrophobic group R' increased to a size equivalent to a three to five carbon chain, potency increased. Peak activity (500 x morphine) was attained in the phenethyl derivative (9; R = Me,

R' = CH_2CH_2Ph) and further lengthening of the chain resulted in a steady decrease in activity. Further, demethylation of the C-3 methoxy group of these alcohols yielded a series of very highly potent analgesics (*cf.* morphine and codeine). For example, the phenol etorphine (11; R = Pr^i) has analgesic activity 12,000 times



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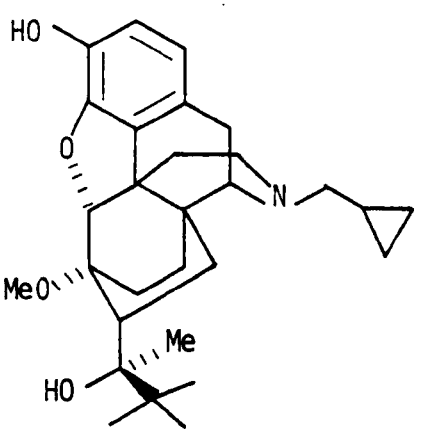
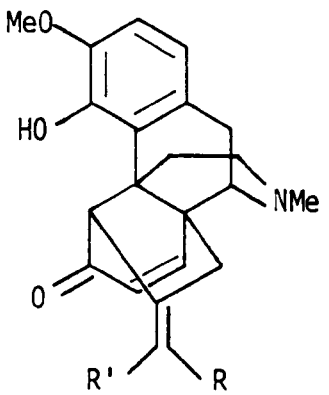


(12)

that of morphine and is widely used for the immobilization of wild animals for game conservation and veterinary purposes. As mentioned on p. 3, substitution of the *N*-methyl group of morphine by, *inter alia*, *N*-cyclopropylmethyl produced antagonists. Incorporation of this feature into the alcohols yielded mixed agonists-antagonists, for example, buprenorphine (12). Although reduction of the 7,8-double bond marginally increased the potency, more importantly, it conferred greater stability on the derivative. Prior to this modification the alcohols had been sensitive to dehydration and rearrangement to (13) in acidic media.



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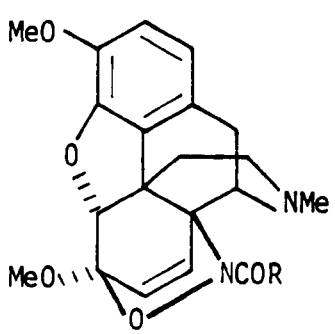
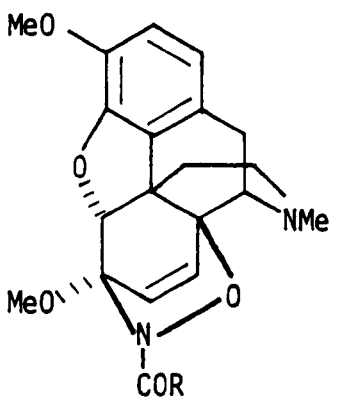
α,β-Unsaturated ketones are not the only dienophiles to undergo Diels-Alder reactions with thebaine; hydroxamic acids (RCONHOH) when oxidised *in situ* give short-lived nitrosocarbonyl compounds (RCONO) which behave likewise. Nitrosocarbonyl compounds were first postulated as transient intermediates in the pyrolysis of a mixture of nitrite esters and aldehydes[10] and in the oxidative cleavage of hydroxamic acids[11] but the isolated products all involved cleavage of the CO-N bond. However in the presence of conjugated diene systems such as thebaine, intact nitrosocarbonyl compounds were trapped as the Diels-Alder adducts (14; R = alkyl).[12,13,14]



(14)

The stereochemistry of the cycloadducts was reasoned to be as illustrated by analogy with the Bentley compounds and verified in subsequent reactions. Thus, with the 14-position of thebaine being electron rich and the nitrosocarbonyl compound being slightly electron deficient on the nitrogen atom due to the electron withdrawing effect of the neighbouring oxygen and carbonyl groups, dienophile addition to the exposed β face of the diene afforded the adduct (14) and not the isomeric species (15).



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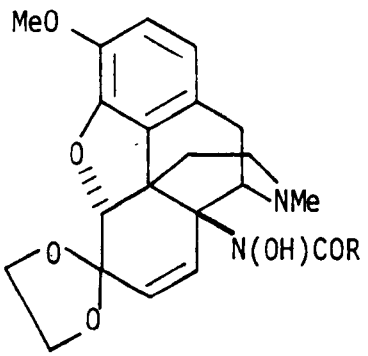
Treatment of the cycloadducts with anhydrous hydrogen chloride in ethylene glycol afforded the ethylene acetals (16; R = alkyl) in quantitative yield. These compounds gave a positive reaction with ferric chloride solution, the qualitative test for hydroxamic acids. Thus, the presence of a hydroxamic acid group at the 14-position in these derivatives proved the original structure of the cycloadducts. In basic solution, if not protected as acetals, the hydroxamic acids rearrange to the phenols (17).



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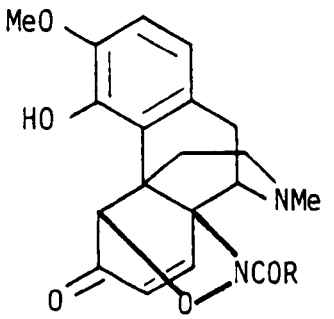
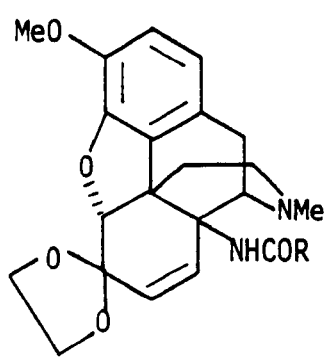


(17)

The reduction of the hydroxamic acids to the corresponding amides (18; R = alkyl) has been extensively investigated by R. I. Gourlay[14] who concluded that the most successful reagent for the conversion was sulphur dioxide in pyridine. These conditions are also used for the reduction of aromatic *N*-oxides.[15] Finally, hydrolysis of the ethylene acetals afforded the 14-acylaminocodeinones (19; R = alkyl) in *ca.* 60% yield from thebaine.



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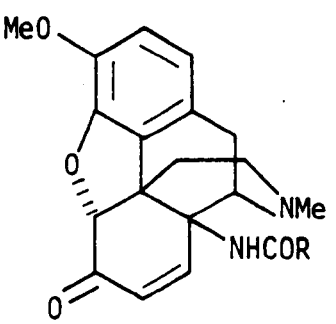


(19)

Compounds of this series, *i.e.* (19; R = alkyl), originally prepared from 14-nitrocodeinone dimethyl acetal,[16,17] like the Bentley compounds, show high analgesic potency with suitable hydrophobic side chains. For example, the 3-phenylpropanoyl derivative (19; R = CH_2CH_2Ph)

has analgesic activity 125 times that of morphine.

Opiates act on the central nervous system through receptor sites on the surface of nerve membranes in the brain and spinal chord. The mechanism of action is not clear but it is believed that agonists and antagonists stereospecifically bind to different, interconvertible, forms of the receptor. Pure antagonists, which have no intrinsic agonist activity, can thus prevent attachment and response of the agonist. Moreover, molecules able to bind strongly to the receptor and which possess high lipid solubility are the most potent drugs.

The existence of opiate receptors suggested that there may be naturally occurring, morphine-like substances. In 1975 Hughes and Kosterlitz[19] isolated, from homogenised pig brain, methionine-enkephalin (20) and leucine-enkephalin (21) in the ratio, 3:1.

H-Tyr-Gly-Gly-Phe-Met-OH (20)

H-Tyr-Gly-Gly-Phe-Leu-OH (21)

These peptides behaved like morphine in tests with isolated tissue preparations and their effects were reversed by antagonists like naloxone.

The structural relationship between methionine-enkephalin and the potent 6,14-bridged phenol (11; R = CH_2CH_2Ph) is not immediately apparent. However, the enkephalin may be folded (at least in models) so that the tyrosyl end group corresponds to the phenol ring and nitrogen atom of the morphine nucleus, and the phenyl group of the phenylalanine residue corresponds to the hydrophobic group R. It is assumed that the enkephalins adopt this type of conformation when bound to the receptor.

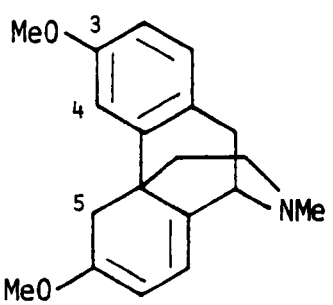
The enkephalins are rapidly hydrolysed in organisms and are

themselves not effective drugs. However, a large number of more stable analogues have been reported with analgesic activity in excess of that of morphine.[20,21]

CHAPTER 2

ATTEMPTED ROUTES TO 14-ACYLAMINODEOXYDIHYDROCODEINONES

As mentioned in the introduction, compounds based on the morphinan ring system (4), particularly those with a 3-hydroxyl group, are useful analgesics. Thus, removal of the ether bridge between C-4 and C-5 in thebaine to form deoxy-β-dihydrothebaine (22) is of considerable interest. The total synthesis of this compound has not been reported, but its analogue (23) has been prepared[22] in 14 steps and in < 1% yield from 7-methoxy-2-tetralone (24). Further, modification



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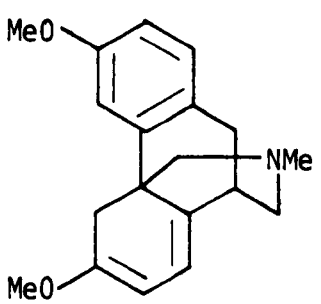

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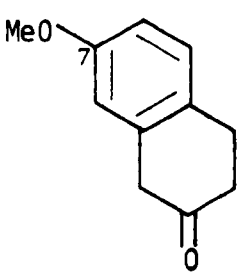

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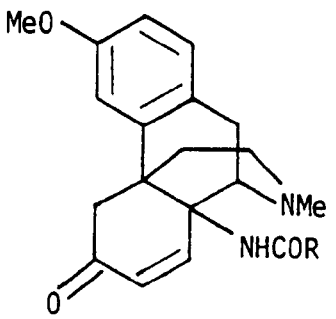
of the lower ring by Diels-Alder addition of dienophiles may lead to more stable and/or more active analgesics. The original aim of this project was to form the aforesaid deoxy-β-dihydrothebaine (22), prepare a series of 14-acylaminodeoxydihydrocodeinones (25; R = alkyl or aralkyl) and to compare their analgesic activity with the corresponding codeinone derivatives.



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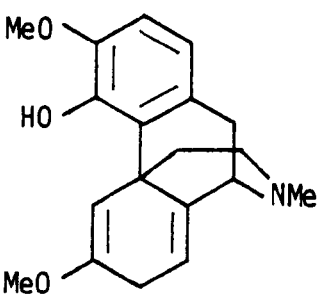
2.1 By Reduction of a 4-*O*-Phenyl Ether

Bentley *et al.*[23] discovered that Birch reduction of thebaine efficiently cleaved the ether bridge and the product dihydrothebaine-ϕ (26) was isolated in high yield. The isomeric diene, β-dihydrothebaine (27), has until recently, only been available through an unsatisfactory



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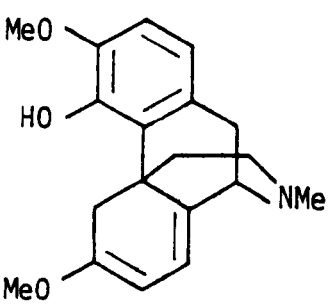
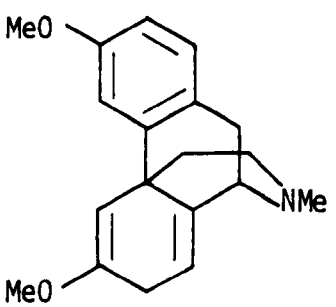


(27)

lithium aluminium hydride reduction of thebaine.[24] The new preparation of this diene, reported by Razdan *et al.*,[25] involved carrying out the Birch reduction of thebaine in the presence of potassamide. Potassamide conjugated the diene system of (26) to (27) and similar reaction

conditions to these have been employed by Birch[26] to promote conjugation in simpler methoxydienes. Although an equilibrium 1:1 mixture of the isomeric dienes (26) and (27) was isolated, fractional crystallisation afforded pure β-dihydrothebaine (27) in 34% yield. Razdan also reported that in the presence of sodamide the reduction yielded only dihydrothebaine-ϕ (26). However, R. I. Gourlay[14] found that sodamide was an effective conjugation reagent, and also that slightly enriched mixtures of (27) were obtained by equilibrating the reduction products with base for several hours.

Further, removal of the hydroxy group in dihydrothebaine-ϕ, leading to deoxydihydrothebaine-ϕ (28) was accomplished in two steps by Sawa *et al.*[27] By a similar process these workers have also successfully eliminated the 4-hydroxy group on the alkaloid sinomenine (29) and some of its derivatives.[28] The phenol (26) was converted into its phenyl ether (30) by an Ullmann reaction with bromobenzene



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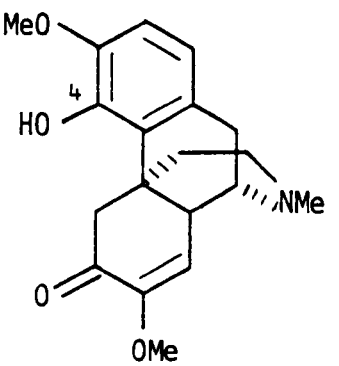

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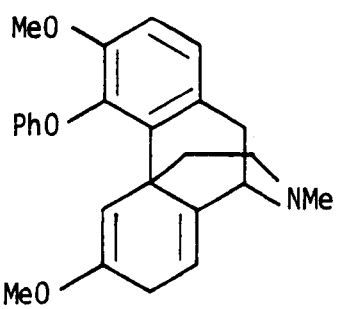
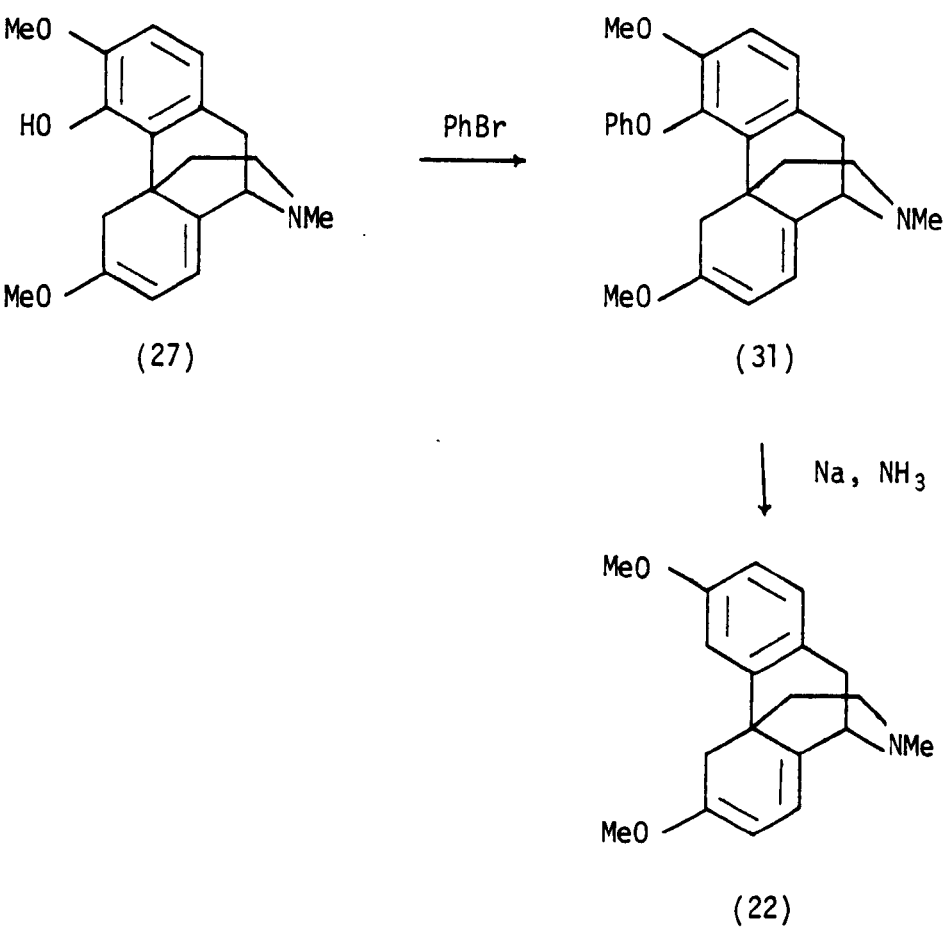


(30)

in pyridine in the presence of potassium carbonate and copper. Sodium in liquid ammonia reduction of this phenyl ether gave the desired deoxy compound (28) in high yield.

The proposed route to deoxy-β-dihydrothebaine (22) (Scheme I) was analogous to that used for the preparation of deoxydihydrothebaine-ϕ (28).



(27) (31) (22)

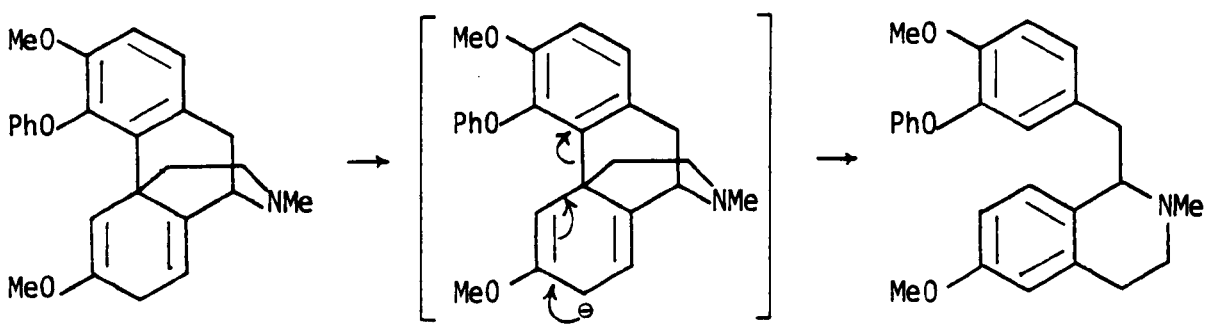
SCHEME I

β-Dihydrothebaine (27) was prepared by the method of Gourlay (see earlier) and, after fractional crystallisation, was 80% pure, the impurity being dihydrothebaine-ϕ (26). Treatment with bromobenzene in an Ullmann reaction converted the phenol to the 4-phenyl ether and

the product (31) was isolated after alumina chromatography as a dark viscous oil. The n.m.r. spectrum of this ether indicated that a small amount of the isomeric compound (30) was present.

Birch and Dastur[29] have observed that catalytic amounts of, *inter alia*, dichloromaleic anhydride conjugate 1-methoxycyclohexa-1,4-dienes to their 1,3-isomers. Thus, in an alternative approach to the desired ether (31), the unconjugated ether (30) was refluxed with dichloromaleic anhydride, prepared by the method of Försch and Roedig[30] in toluene and xylene. In each case only starting material was isolated.

Attempts at sodium in liquid ammonia cleavage of the phenoxy group on compound (31) yielded a complex mixture of products. While this work was in progress, Razdan *et al.*[31] published a communication describing the results of a related study. Reaction of the unconjugated ether (30) with potassamide in liquid ammonia afforded the benzyl-isoquinoline (32). Possibly, a similar type of cleavage was causing the problems encountered in our reduction.



(30) (32)

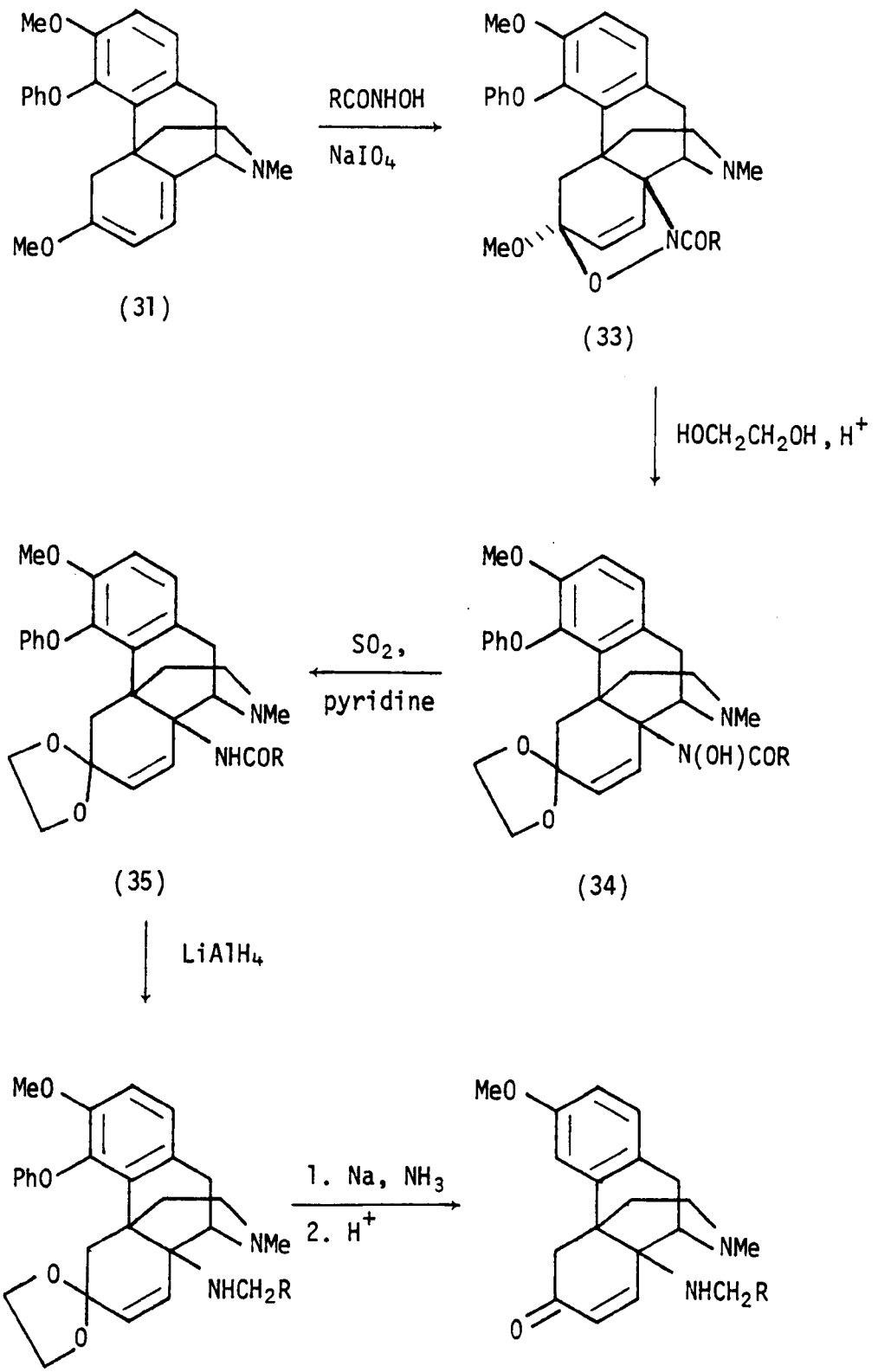
With this unexpected failure, an alternative route to the synthesis of deoxy-β-dihydrothebaine was considered, namely, isomerisation of deoxydihydrothebaine-φ. Two sets of conditions were applied, sodamide

in liquid ammonia and dichloromaleic anhydride in toluene. This latter reaction, as expected (see above), gave starting material. The sodamide experiments did not give reproducible results, but in the more promising cases the n.m.r. spectrum of the reaction products showed that all the starting material had reacted, and the appearance of two doublets at δ4.27 (7-H?) and δ6.32 (8-H?) suggested that isomerisation may have taken place. In the hope that a crystalline adduct could be formed and isolated these reaction mixtures were treated with nitroso-carbonylbenzene, generated from benzohydroxamic acid and periodate, in an attempted Diels-Alder reaction. Further complex mixtures ensued which were not investigated further.

Owing to the unavailability of deoxy-β-dihydrothebaine it was decided to leave the phenoxy group on C-4 until a later stage when further attempts at removal would be made. The revised route to the 14-aminodeoxydihydrocodeinones now envisaged is outlined in Scheme II.

Since the diene system of β-dihydrothebaine phenyl ether (31) is essentially the same as that of thebaine it too should undergo Diels-Alder reaction with nitrosocarbonyl compounds. Accordingly, dihydro-cinnamohydroxamic acid was oxidised with sodium periodate in the presence of (31) and the expected cycloadduct (33; R = CH_2CH_2Ph) was isolated in 47% yield. The above hydroxamic acid was chosen to establish the feasibility of the route since in the 14-acylamino-codeinone series the 3-phenylpropanoyl derivative was the most active analgesic. By analogy with the thebaine adducts (see introduction) and on the basis of later experiments (see below), the cycloadduct was reasoned to have the structure shown.

The adduct was treated with anhydrous hydrogen chloride in ethylene glycol to afford a 1:1 mixture of the protected (34; R = CH_2CH_2Ph) and unprotected (36) (see later) forms of the thebainone. Both of these

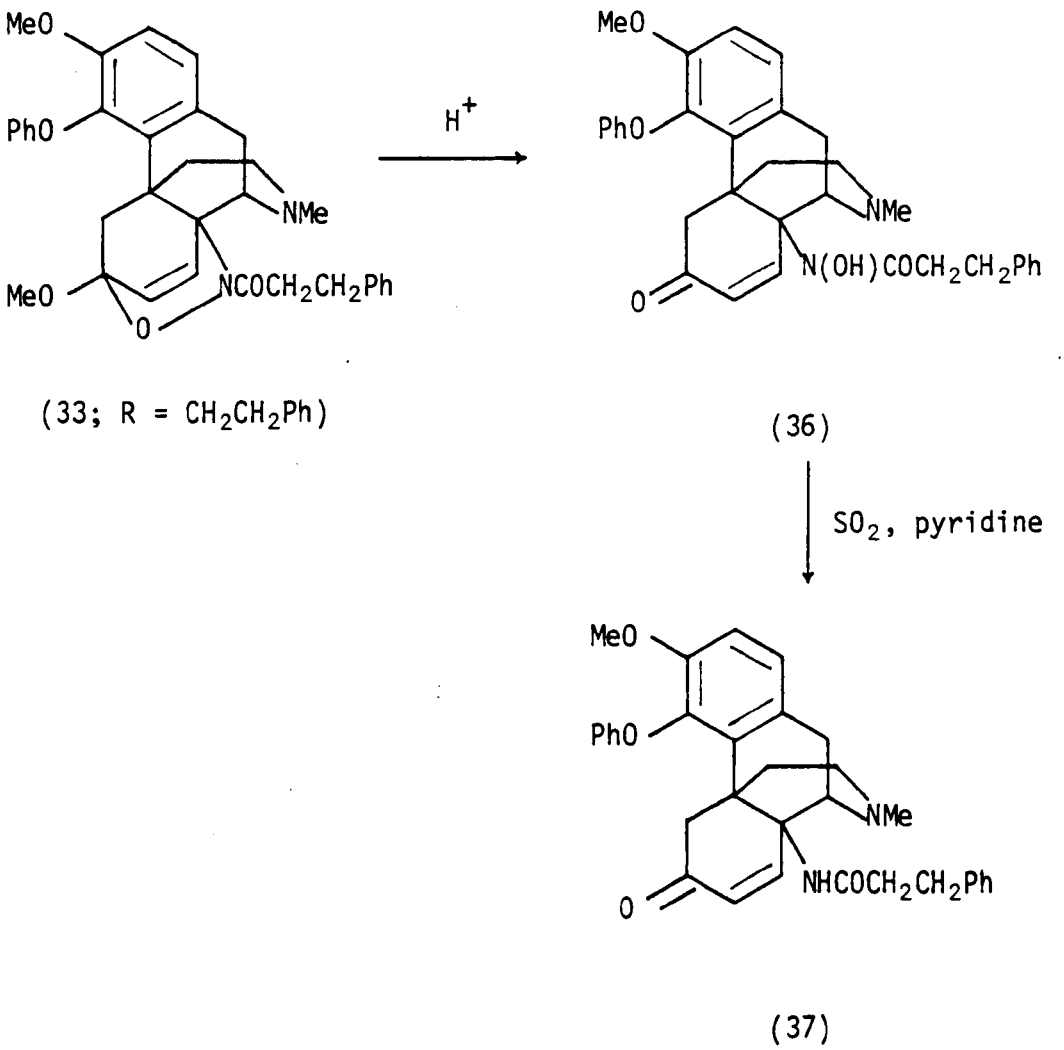

MeO
PhO
NMe
MeO
RCONHOH
NaIO4
(31)
(33)
NCOR
HOCH2CH2OH, H+
SO2,
pyridine
NHCOR
N(OH)COR
(35)
(34)
LiAlH4
1. Na, NH3
2. H+
NHCH2R
O

SCHEME II

derivatives gave a positive reaction with ferric chloride, *i.e.* they were hydroxamic acids, and hence the structure of the cycloadduct was established. Fortunately, the unprotected thebainone, utilized in later reactions (Scheme III), proved insoluble in the common solvents, unlike its ethylene acetal, and so separation was readily achieved. Sulphur dioxide in pyridine reduced the hydroxamic acid (34; R = CH CH Ph) to the corresponding amide (35; R = CH_2CH_2Ph), but neither of these compounds was obtained crystalline.

The next step proposed involved lithium aluminium hydride reduction of the amide carbonyl group in (35; R = CH_2CH_2Ph). The i.r. spectrum of the reaction product after workup showed a significant adsorption at 1 670 cm^{-1}, identical to that in the starting material. As repetition yielded similar results no further work related to Scheme II was carried out.

A parallel series of experiments (Scheme III) leading to the thebainone (37) was also successfully implemented. Thus the cycloadduct (33; R = CH_2CH_2Ph) was hydrolysed to the hydroxamic acid [(36), *cf.* p. 16] which was reduced as before to the amide (37). A sample of this amide was tested for pharmacological activity but it was found to be inactive, probably due to the presence of the phenoxy group at C-4.



(33; R = CH_2CH_2Ph)

(36)

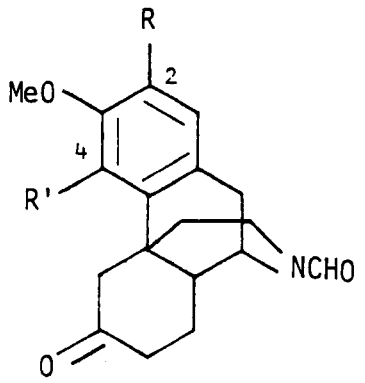
(37)

SCHEME III

2.2 By Reduction of a 4-*O*-(1-Phenyltetrazol-5-yl) Ether

Beyerman *et al.* have observed that the phenolic hydroxy group at C-2 in the synthetic morphinans (38; R = OH, R' = H)[32] and (38; R = R' = OH)[33] can be removed by hydrogenolysis of the 1-phenyl-tetrazol-5-yl ethers. The corresponding 4-ethers were not prepared but it seemed reasonable that these too might be hydrogenolysed.

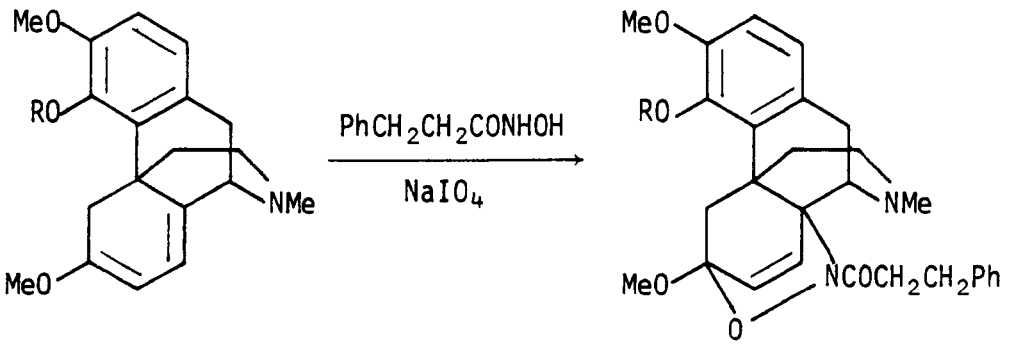
Alkylation of β-dihydrothebaine (27) with 5-chloro-1-phenyl-tetrazole proceeded slowly but in acceptable yield to give the ether (39). A series of derivatives analogous to those in section 2.1 was



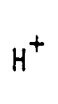
(38)

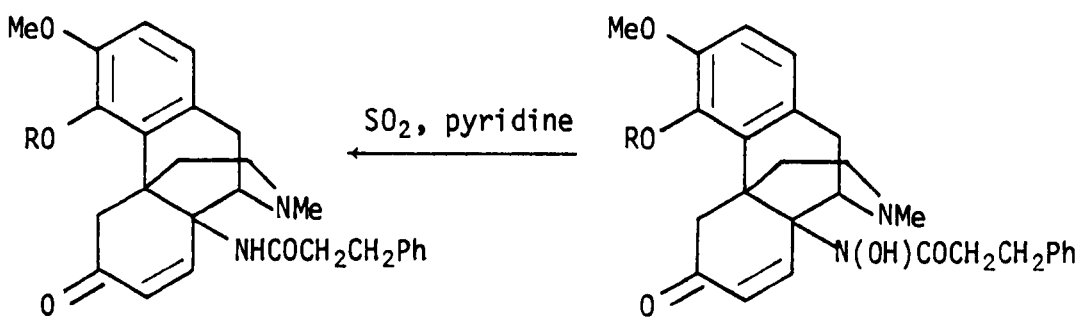
then prepared (Scheme IV). Various attempts (see Experimental) were made to hydrogenolyse off the phenyltetrazolyloxy group from the cycloadduct (40) and the thebainones (41) and (42). All met with failure and starting material was recovered.

Due to the difficulties encountered, this procedure for the preparation of 14-acylaminodeoxydihydrocodeinones was abandoned and with it the original aim of the project.

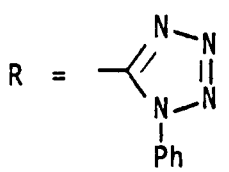


(39) (40)





(42) (41)



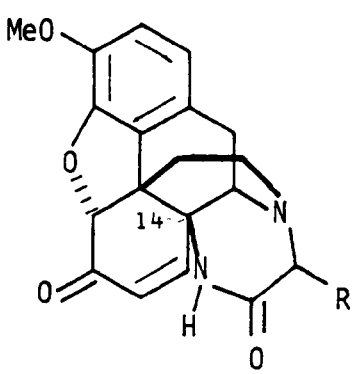
SCHEME IV

CHAPTER 3

ATTEMPTED ROUTES TO A N-C(14)-BRIDGED CODEINONE DERIVATIVE

The pharmacological importance of the substituent on the piperidine nitrogen has already been noted. In morphine, X-ray studies have shown that this methyl group occupies an equatorial position on the piperidine ring,[34] but on binding to the receptor the conformation of the molecule may be altered. In the antagonists, where the piperidine nitrogen alkyl group is considerably more flexible, no details are known about the conformation adopted either in the crystalline state or bound to the receptor. Moreover, it is possible that the *N*-alkyl group adopts different (axial or equatorial) conformations in agonists and antagonists when the drugs are so bound.

Our aim was to prepare a codeinone derivative, for example (43; R = H), in which the piperidine nitrogen substituent was linked

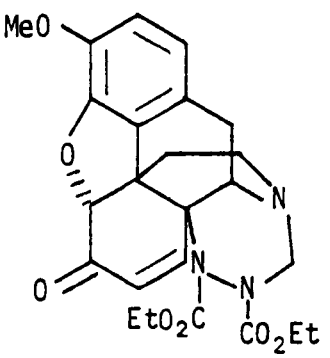


(43)

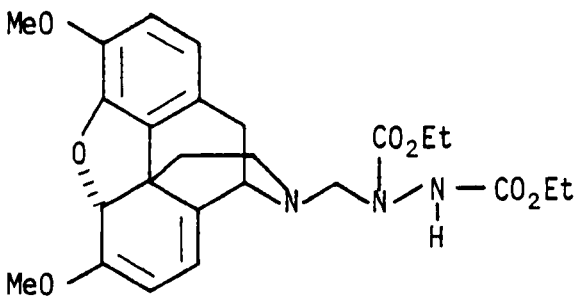
to the 14-position to form a rigid structure of known stereochemistry. Further modifications, reduction of the amide carbonyl group and the introduction of alkyl side chains (R) would lead to a new series of compounds in which the piperidine nitrogen substituent is unambiguously

axial. The structure-activity relationships for such a series may give some insight into the receptor site and how the morphine derivatives are bound.

To date, only one example of a piperidine-N-C(14) bridge has been reported. Merz and Pook[35] discovered that when thebaine was treated with two equivalents of ethyl azodicarboxylate and the reaction mixture hydrolysed with acid, the hexacyclic derivative (44) was obtained. Equimolar quantities of thebaine and ethyl azodicarboxylate gave *N*-(1,2-diethoxycarbonylhydrazinomethyl)northebaine (45),

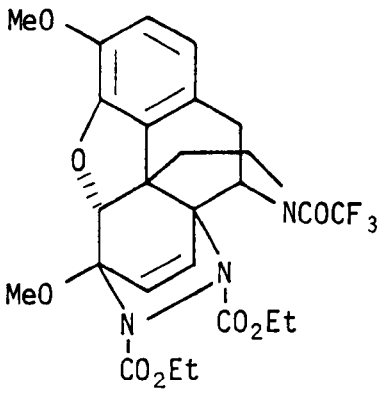


(44)

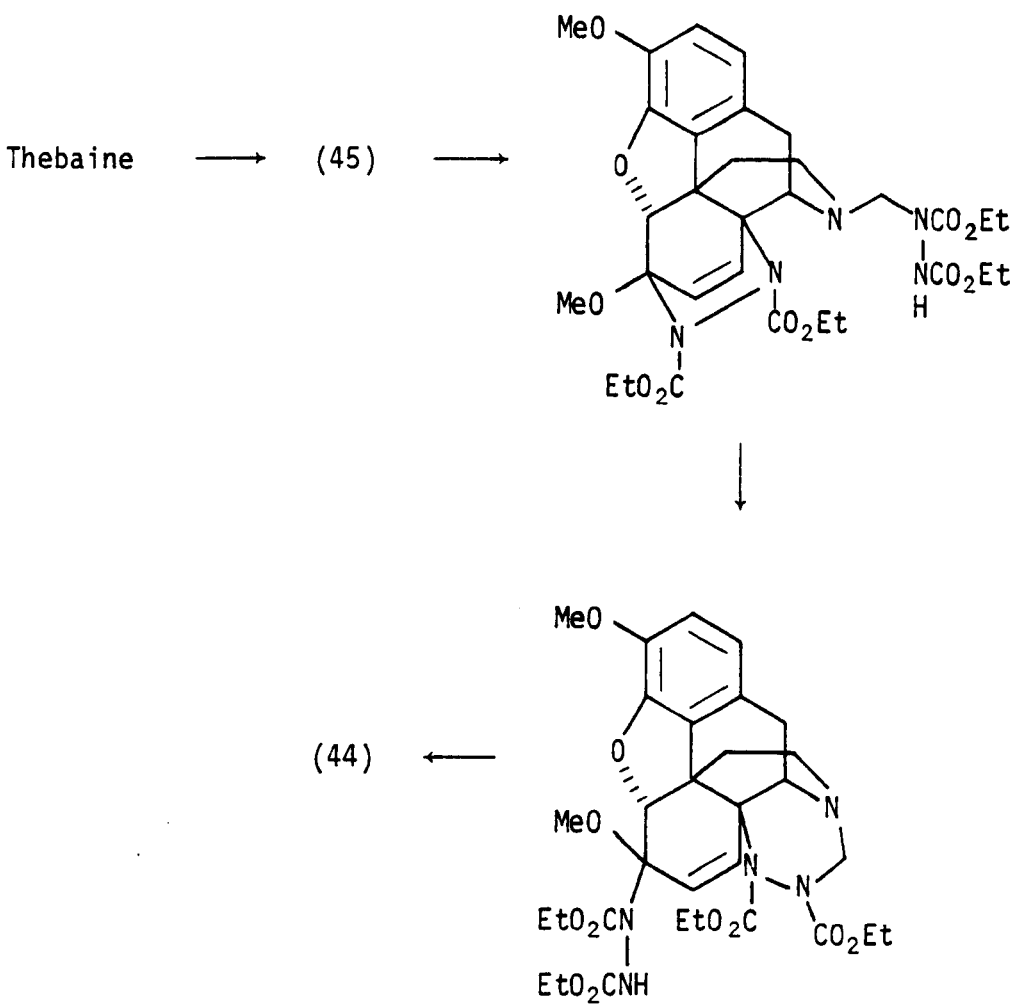


(45)

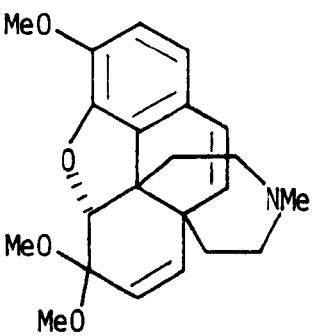
an intermediate in the preparation of northebaine (see section 3.1). The mechanism of formation of (44) was partially deduced from the reaction of *N*-trifluoroacetylnorthebaine (2; $NCOCF_3$ for NMe) with ethyl azodicarboxylate which yielded the normal Diels-Alder adduct (46) and which could be transformed into (44) by a three step sequence. The mechanism proposed for the formation of (44) involved formation of the Diels-Alder adduct which rearranged and hydrolysed.


MeO
O
NCOCF3
MeO
N
CO2Et
N
CO2Et

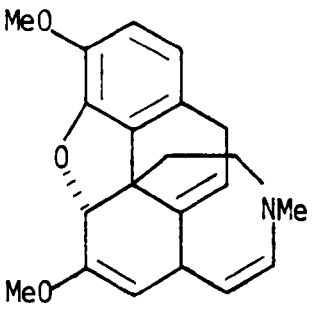
(46)


Thebaine
(45)
MeO
O
N
NCO2Et
NCO2Et
H
MeO
N
CO2Et
N
EtO2C
(44)
MeO
O
N
MeO
N
N
EtO2CN
EtO2C
CO2Et
EtO2CNH

The tertiary base (47), recently reported by Fleischhacker and Richter,[36] contains a N-C(14) bridge but the integrity of the morphine skeleton has been destroyed. Cleavage of the N-C(9) bond also features in the preparation, by two groups of workers,[37,38] of the enol ether (48).



(47)



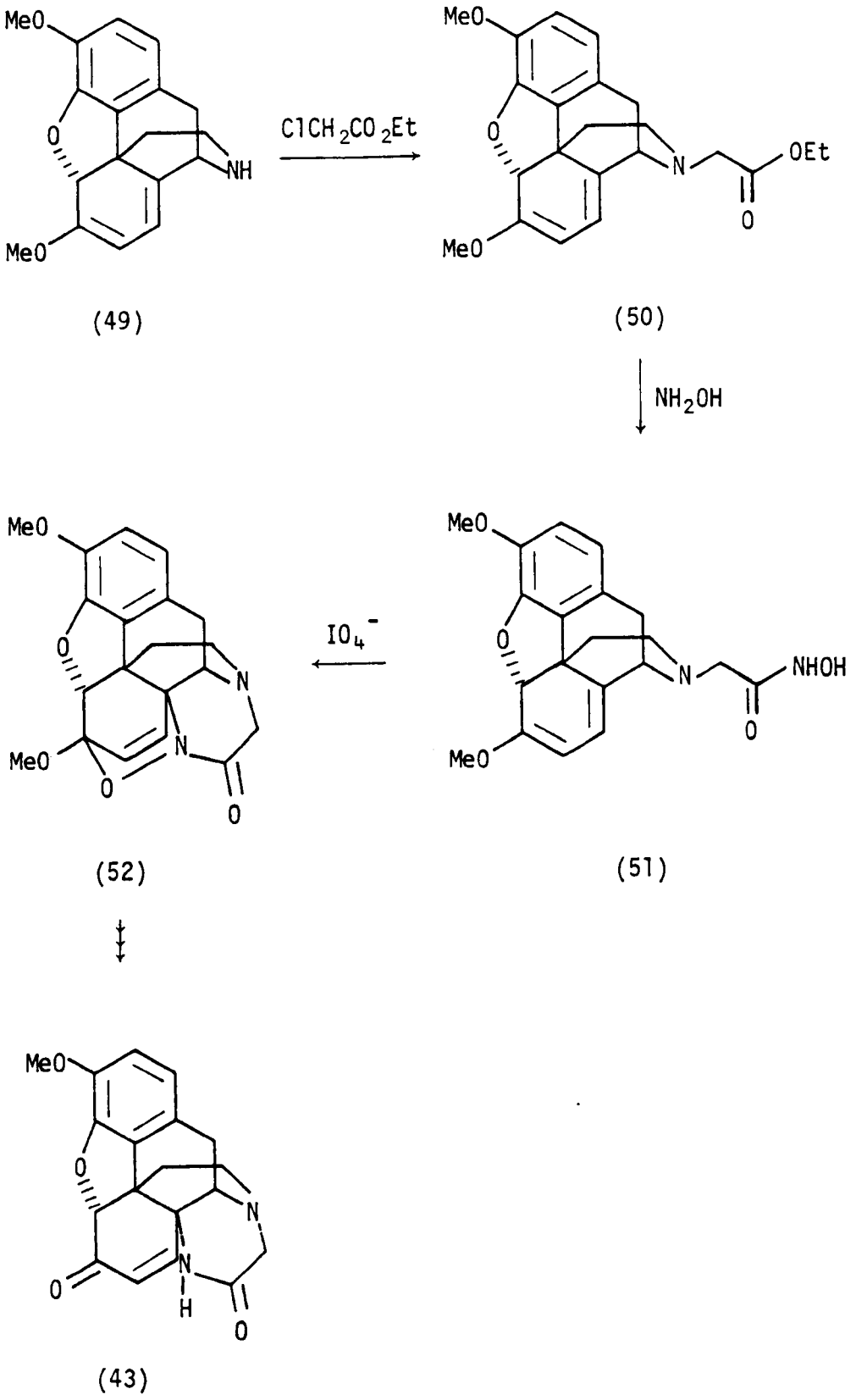
(48)

3.1 By an Intramolecular Diels-Alder Reaction

In the first route considered (Scheme V) the prospective bridge atoms were in the form of a hydroxamic acid group on the piperidine nitrogen. Cyclisation should thus be accomplished by an intramolecular Diels-Alder reaction of the related nitrosocarbonyl compound. By a series of similar reactions to those discussed in Chapter 2, *viz.* ring opening, reduction and hydrolysis, this adduct should be transformed into the bridged codeinone (43).

Northebaine (49) was prepared by the method of Eli Lilley and Co.[39] although there are other preparations available.[40] Thebaine was treated with one equivalent of ethyl azodicarboxylate to give the intermediate (45) which was hydrolysed with ammonium hydroxide to northebaine (49).

Bentley *et al.*[8c] have prepared a large number of *N*-alkyl-,


MeO
O
NH
MeO
ClCH2CO2Et
MeO
O
N
OEt
O
MeO
(49)
(50)
NH2OH
MeO
O
N
N
MeO
O
O
IO4-
MeO
O
N
NHOH
O
MeO
(52)
(51)
MeO
O
N
N
H
O
O
(43)

SCHEME V

N-alkenyl- and *N*-alkynyl-norbases but no ester derivatives were synthesised. Nevertheless, the general experimental procedure was followed and an overnight reflux in anhydrous acetone with ethyl chloroacetate with anhydrous potassium carbonate converted northebaine into *N*-ethoxycarbonylmethylnorthebaine (50) in high yield. A 45 min reflux in dimethylformamide also realized this conversion.

The most common method for the preparation of hydroxamic acids from esters is by treatment with hydroxylamine, freed from its hydrochloride *in situ* with sodium hydroxide solution.[41] Under these conditions the expected derivative (51) was isolated, although in low yield and as an impure foam even after chromatography. The impurities, identified from the mass spectrum, were the corresponding carboxylic acid ($C_{20}H_{21}NO_5$, M^+ 355.1418) and amide ($C_{20}H_{22}N_2O_4$, M^+ 354.1561).

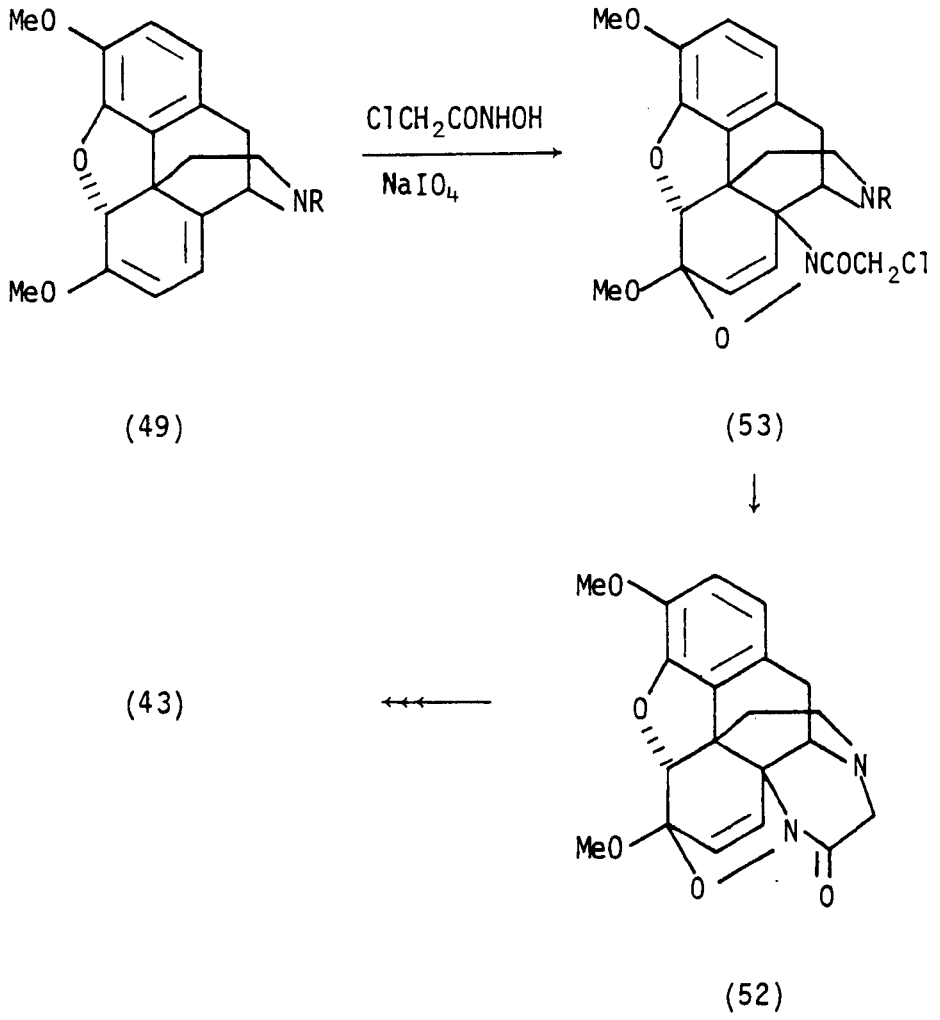
In an attempt to form the cyclised adduct (52) the hydroxamic acid was treated with sodium periodate. A t.l.c. of the product after work-up indicated that it was a mixture of at least six compounds, none of which was isolated or identified.

Due to the failure of the key reaction and the unsatisfactory preparation of the hydroxamic acid this route to the cyclised compound (52) was abandoned.

3.2 By a Nucleophilic Substitution Reaction

This approach to (43), outlined in Scheme VI (R = H) envisages cyclisation as nucleophilic displacement of the chlorine by the piperidine nitrogen.

α-Chloroacetohydroxamic acid ($ClCH_2CONHOH$) was prepared by the method of Jones and Werner.[42] Although the mass spectrum showed the molecular ion at *m/z* 109, 111, the melting point differed from that in the literature by ∿10°C and the n.m.r. resonance at δ7.30

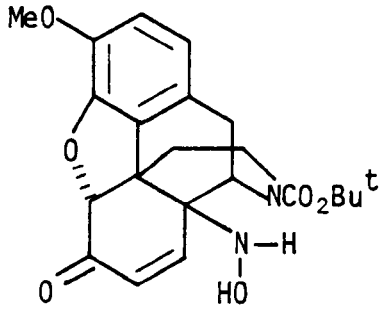


SCHEME VI

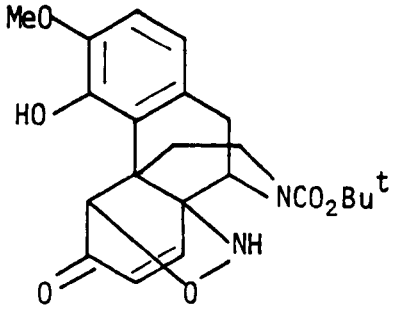
(exchangeable with D_2O) integrated as seven protons. Repeated analyses varied greatly, particularly in the value for nitrogen (5 - 10%) low and the exact composition of this hydroxamic acid was never established. Nevertheless, using three equivalents of both this compound and of periodate, Diels-Alder adducts of thebaine derivatives were successfully prepared (see p. 29 and 31). But, with northebaine the oxidation resulted in a mixture of products being obtained and their formation was largely attributed to the nucleophilic nitrogen reacting with the nitrosocarbonyl compound.

To overcome these complications, northebaine was converted into crystalline, and easily prepared, *N*-t-butoxycarbonyl derivative[43] (49; R = CO_2Bu^t). This compound was treated with nitrosocarbonylchloromethane ($ClCH_2CONO$), generated from α-chloroacetohydroxamic acid and tetraethylammonium periodate,[44] and the expected cycloadduct (53; R = CO_2Bu^t) was isolated in quantitative yield. The above oxidising agent, unlike sodium periodate, is soluble in organic solvents and so the reaction was carried out in a homogeneous solution. The inability of sodium periodate in the two-phase solvent system to bring about this reaction was presumably a consequence of the low solubility of the amide (49; R = CO_2Bu^t) in water.

Initial attempts to recrystallise the crude adduct from hot ethanol caused cleavage of the chloroacetyl moeity and, on the basis of further experimentation, it appeared that the cause was water dissolved in the ethanol. The product isolated was identified as the codeinone (54) from its spectroscopic properties and by rearrangement with sodium ethoxide to the phenol (55). The crude cycloadduct was essentially pure by n.m.r. and, due to its sensitivity towards hydrolysis,



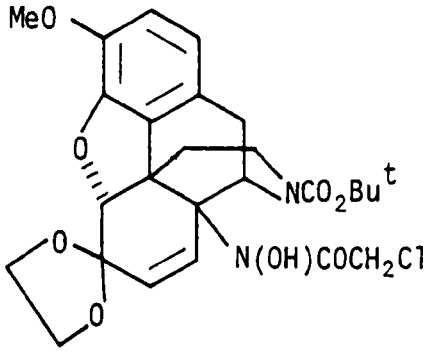
(54)



(55)

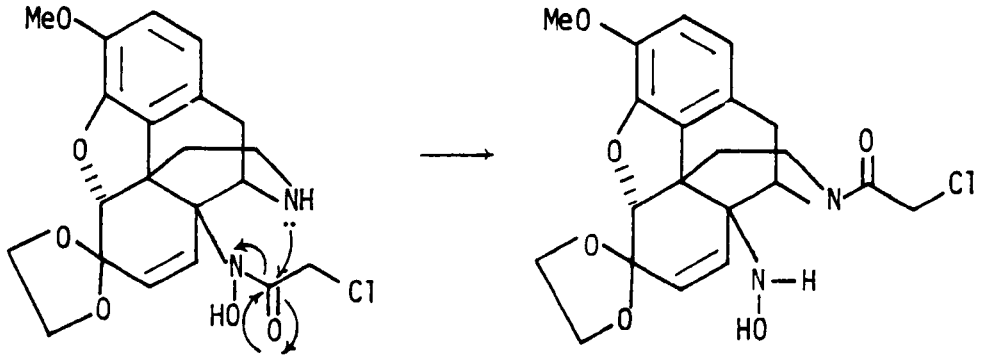
was used without purification in subsequent reactions.

t-Butoxycarbonyl groups are easily removed under mild acidic conditions,[45] conditions similar to those required for the hydrolysis of cycloadducts and the protection of the resulting codeinones as their ethylene acetals. However, the compound isolated from the reaction, in methylene chloride, between the cycloadduct (53; R = CO_2Bu^t) and anhydrous hydrogen chloride in ethylene glycol was the ethylene acetal (56).



(56)

The unsuccessful deprotection of the piperidine nitrogen was attributed to a lack of acidity and so more forcing conditions were applied to the cycloadduct. 10% Anhydrous hydrogen chloride in ethyl acetate achieved this deprotection, but it was accompanied by the rearrangement [(57) → (58)].



(57) (58)

Failure to produce a purple colour with ferric chloride solution was the first indication that the hydroxamic acid (57) had not been isolated. The mass spectral fragmentation pattern was crucial in identifying the product as the hydroxylamine (58). Table 1 lists the high mass fragment ions of the product (58), and for comparison those of the hydroxylamine (54) and the hydroxamic acid (56).

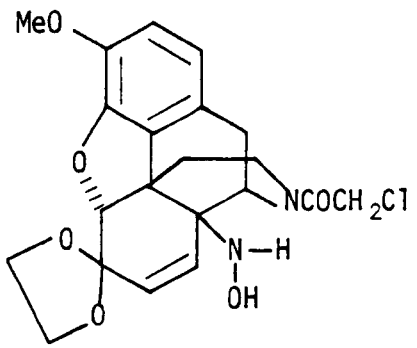
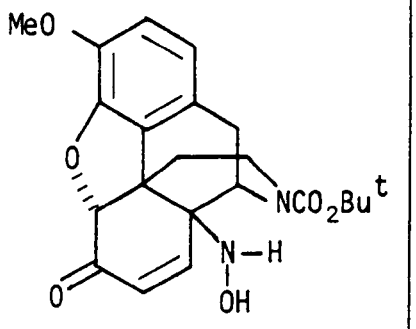
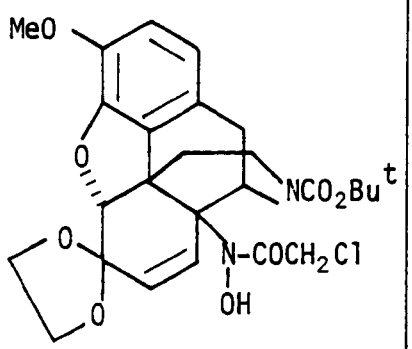
In (58), the chloroacetyl moiety was lost after the elimination of either nitric oxide or the nitroso species HNO. There were no peaks corresponding to an initial loss of chloroacetyl or parts thereof. This sequence of events, whereby the NO or HNO fragment was lost independently of the piperidine nitrogen side chain was paralleled in the hydroxylamine (54). A different mode of decomposition was observed for the molecular ion of the hydroxamic acid (56).

The yield of the hydroxylamine (58) after purification by column chromatography and crystallisation was 14%. The motherliquors from the crystallisation contained the major component of the reaction - a chlorinated derivative of (58) resulting from addition of hydrogen chloride to the 7,8 double bond. It was later found that the rearranged product could be obtained directly from the cycloadduct and in higher yield (37%) by carrying out the reaction in anhydrous methylene chloride.

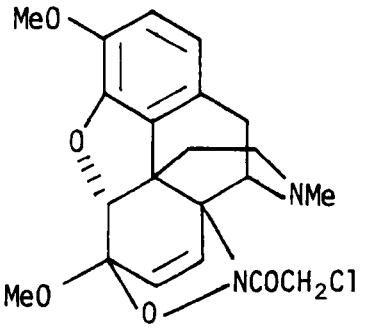
The mechanism of chloroacetyl migrations appears to involve nucleophilic attack by the piperidine nitrogen at the carbonyl group leading to the formation of a five membered cyclic intermediate. This result was surprising in the light of subsequent work in the thebaine series.

The thebaine cycloadduct (59) was prepared in the usual manner with sodium periodate as the oxidiser (*cf.* p. 29). However, attempts to crystallise this crude adduct resulted in cyclisation to the

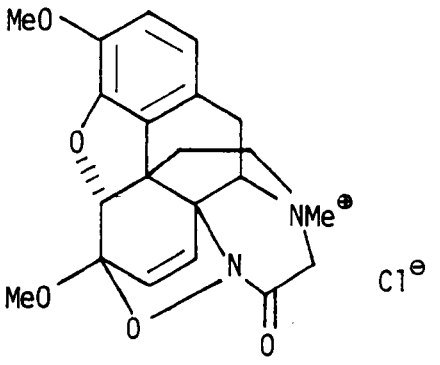
TABLE 1

Compound	Fragments (% rel. to base peak)
 (58)	*434.1267 (0.8); $[M]^{+\cdot}$ 418.1313 (4.1); $[M-O^{\cdot}]^{+}$ 406.1208 (7.7), 404.1234 (31.5); $[M-NO]^{+\cdot}$ 405.1254 (4.0), 403.1150 (8.6); $[M-HNO]^{+\cdot}$ 311.1246 (5.5); $[M-NO-NH_2COCH_2Cl]^{+\cdot}$ 310.1200 (6.9): $[M-HNO-NH_2COCH_2Cl]^{+\cdot}$
 (54)	414.1783 (6.1); $[M]^{+\cdot}$ 398.1844 (0.5); $[M-O^{\cdot}]^{+}$ 384.1769 (1.8); $[M-NO]^{+\cdot}$ 383.1744 (8.7); $[M-HNO]^{+\cdot}$ 358.1138 (58.6); $[M-C_4H_8]^{+\cdot}$ 341.1154 (33.7); $[M-C_4H_8-O^{\cdot}H]^{+}$ 328.1187 (15.8); $[M-NO-C_4H_8]^{+\cdot}$ 327.1118 (18.2); $[M-HNO-C_4H_8]^{+\cdot}$ 313.1191 (2.1); $[M-\dot{C}O_2Bu^t]^{+}$ 282.1126 (10.6); $[M-HNO-CO_2Bu^t]^{+}$
 (56)	536.1741 (10.4), 534.1750 (28.8); $[M]^{+\cdot}$ 480.1107 (15.1), 478.1114 (42.2); $[M-C_4H_8]^{+\cdot}$ 463.1107 (1.7), 461.1099 (5.4); $[M-C_4H_8-O^{\cdot}H]^{+}$ 427.1965 (8.4); $[M-N(O)COCH_2Cl]^{+\cdot}$ 371.1341 (100); $[M-C_4H_8-N(O)COCH_2Cl]^{+\cdot}$

* No molecular ion for $C_{21}H_{23}{}^{37}ClN_2O_6$

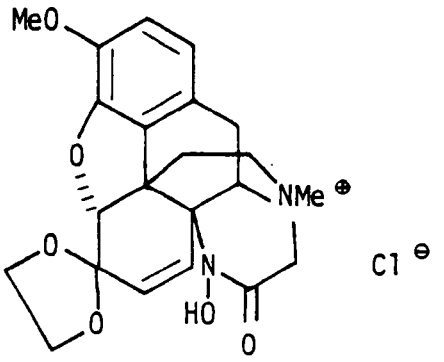


(59)



(60)

quaternary ammonium salt (60). Treatment of the cycloadduct with anhydrous hydrogen chloride in ethylene glycol gave the quaternary ammonium chloride (61), presumably formed from the open-chain hydroxamic acid which was not isolated. This type of cyclisation to a six-membered ring was exactly that



(61)

hoped for with the northebaine derivative (52). However, in that case attack at the carbonyl group can lead to a stable product.

Although the rearranged compound had not been the objective it still possessed the component parts of a bridge between the nitrogens. Two modes of cyclisation were conceivable, either attack by the hydroxylamine nitrogen on the methylene group with

displacement of chlorine leading to a six-membered ring or the corresponding attack from the hydroxylamine oxygen to form a seven-membered ring. In attempts to achieve either cyclisation (58) was heated in ethanol, toluene, acetone, dimethylformamide and dimethylformamide-triethylamine. Starting material was recovered in all but the last experiment when decomposition took place.

The quaternary ammonium chlorides from the thebaine series were the only compounds obtained with a bridge between the piperidine nitrogen and the 14-position.

CHAPTER 4

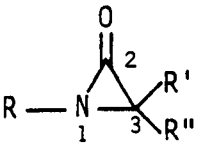
α-LACTAMS

"I'm called Little Buttercup - dear little Buttercup,
Though I could never tell why."

W.S. Gilbert from H.M.S. Pinafore Act I.

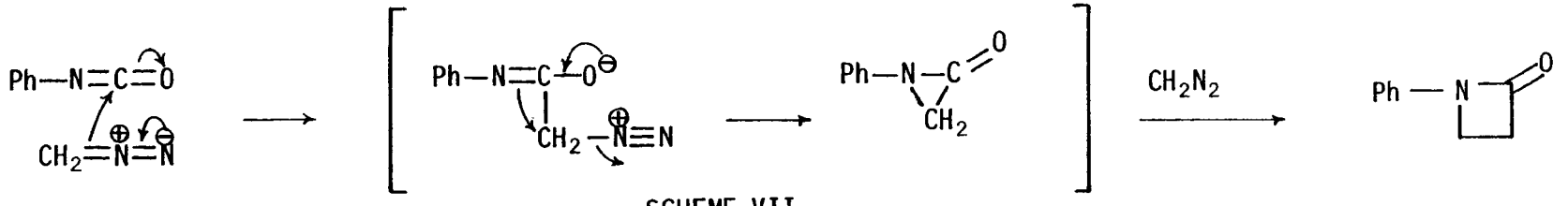
This chapter describes novel reactions of thebaine derivatives and some related model compounds which are thought to proceed through α-lactam intermediates. It is appropriate therefore to review briefly the relevant chemistry of α-lactams.

α-Lactams or aziridin-2-ones (62; R,R',R" = alkyl, aryl) are three membered cyclic amides. Heterocycles such as these have been postulated as reactive intermediates in, for example, the reaction of diazomethane with phenyl isocyanate[46] (Scheme VII), the reaction of oxaziranes with diphenylketene[47] (Scheme VIII), and the thermal rearrangement of *N*-aryl-isoxazolin-3-ones[48](Scheme IX).

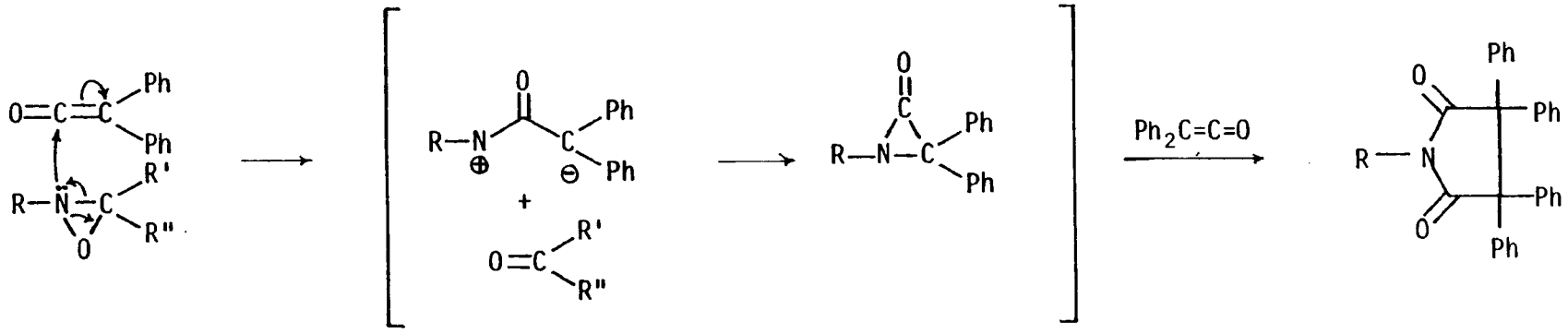


(62)

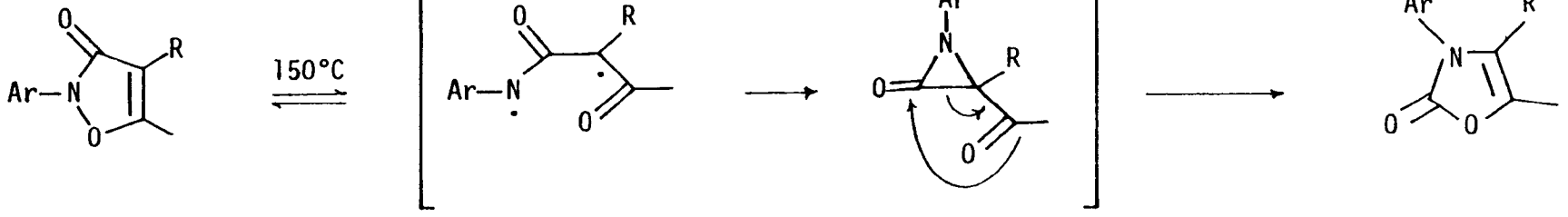
The synthesis of the first authentic α-lactam (63) was reported by Baumgarten in 1962[49] and involved cyclisation of *N*-chloro-*N*-t-butyl-phenylacetamide with potassium t-butoxide. Later a more general synthesis of α-lactams[50,51] was developed in which α-halo-amides (64) were treated with base, usually potassium t-butoxide, in a dry inert



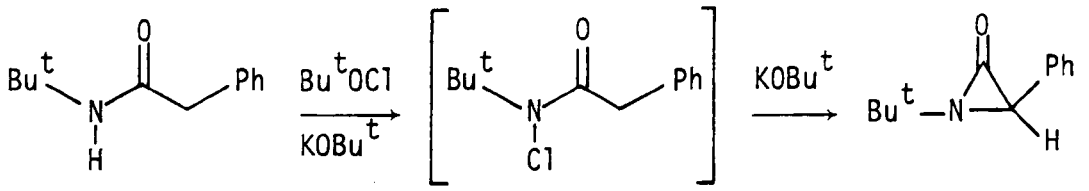
SCHEME VII



SCHEME VIII

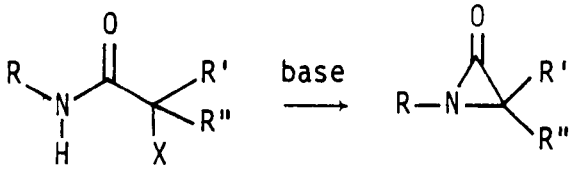


SCHEME IX



(63)

solvent. Two other methods have been reported. Addition of dichlorocarbene to *N*-neopentylidene-t-butylamine gave the dichloroaziridine which



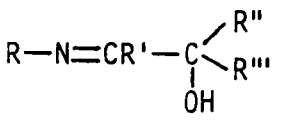
(64)

was treated with aqueous sodium hydrogen carbonate.[52] Also, the reaction between some amino acids and phosgene in the presence of triethylamine[53] has been reported to give α-lactams.

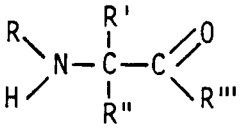
In each of the α-lactams which have been isolated, the heterocyclic ring is stabilised by the presence of a bulky group (t-butyl or 1-adamantyl) on the nitrogen. These compounds are also either mono or disubstituted at C-3 with a variety of alkyl or aryl groups. Bicyclic spiro α-lactams are also known.[54]

The α-lactam ring is opened by nucleophilic attack, for example, of alkoxide or halide ion at C-3 to yield the appropriate α-substituted amides (64; X = alkoxy or halo). Generally Grignard reagents (R''' MgX) also attack the α-carbon atom of α-lactams and cleave the alkyl carbon-nitrogen bond although, with highly sterically hindered species, attack takes place at the carbonyl carbon. The reagent and reaction conditions used also influence the reaction pathway and thus the type of product(s) isolated. For example, α-halo-amides,[55] α-hydroxy imines[56,57] (65) and

α-alkyl amides [together with (65)][57] have been independently obtained from Grignard reactions. Organolithium reagents (R'''Li) preferentially attack the carbonyl carbon of α-lactams to give α-amino ketones (66) or by further addition, the tertiary alcohols.[58]



(65)

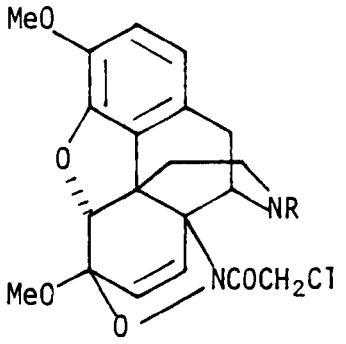


(66)

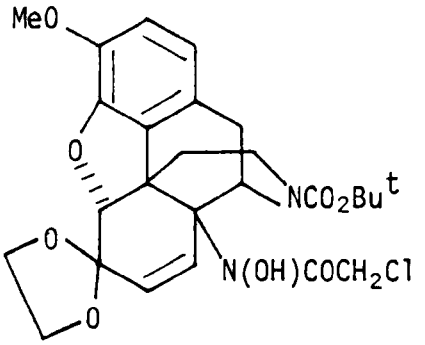
4.1 In Experiments with Thebaine Derivatives

Since a sulphur atom is midway in size between a one-carbon and a two-carbon chain, amide side chains at position 14 in thebaine derivatives incorporating such an atom would be slightly different in length from their known carbon analogues. Also, the presence of sulphur would modify the lipophilic properties of the derivatives and permit syntheses of the more polar sulphoxides and sulphones. In both the northebaine derivatives (53; R = CO_2Bu^t) and (56) substitution of the chlorine atom by a mercapto group followed by a series of reactions similar to those discussed earlier would lead to the novel compounds (67; R' = alkyl, aryl).

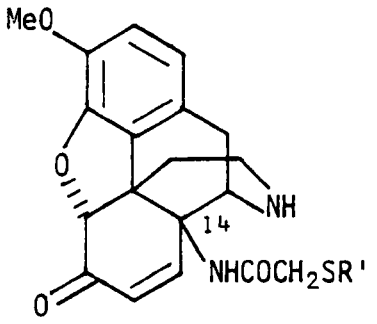
To this end, the hydroxamic acid (56) was treated in ethanol for 1 h at room temperature with one equivalent each of thiophenol and sodium ethoxide. Work-up afforded one compound which was identified as the 14-aminocodeinone derivative (68) (see Chapter 5 for a detailed discussion). As apparently the thiophenol was not involved in this transformation, a similar experiment without the thiophenol was carried out. The amine (68) was isolated in 44% yield.



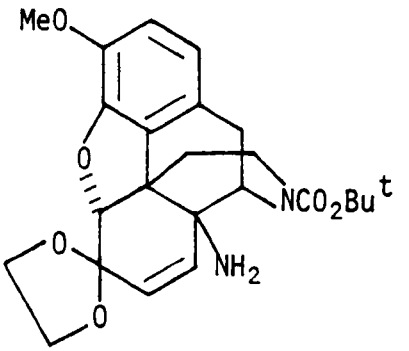
(53; R = CO_2Bu^t)



(56)

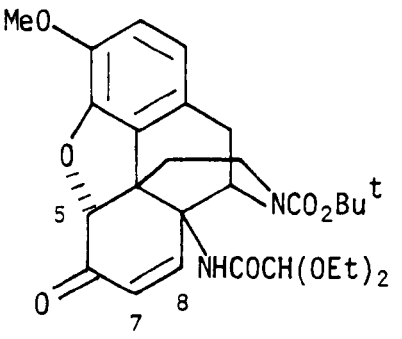


(67)



(68)

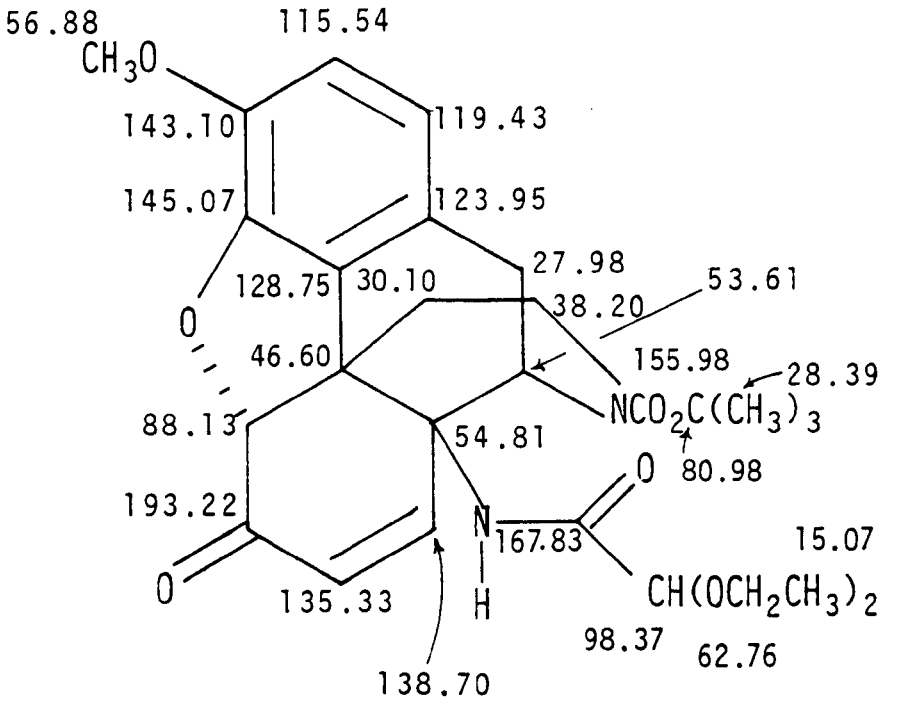
An alternative approach using the cycloadduct (53; R = CO_2Bu^t) was therefore investigated. The stability of (53; R = CO_2Bu^t) towards sodium ethoxide was studied first. Thus, treatment of the cycloadduct with an excess of sodium ethoxide solution in ethanol gave a mixture of products. However, one compound crystallised (20% yield) from an ethyl acetate solution of this mixture and was identified as the norcodeinone (69) from its spectroscopic properties. Thus the mass spectrum showed a molecular ion at *m/z* 528.2484 but apart from this no significant peaks in the high mass region were observed. The ^1H n.m.r. spectrum contained a two-proton singlet at δ6.22 arising from



(69)

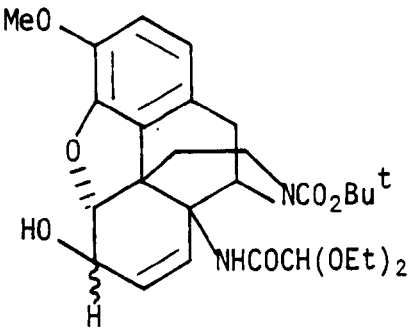
7-H and 8-H, and signals due to a t-butyl group (δ1.47) and an aromatic methoxy group (δ3.85). Also present in the spectrum were two methine singlets at δ4.72 and 5.09 and that at lower field was attributed to 5-H by comparison with a related spectrum (see below). Evidence for the diethyl acetal moiety of the side chain was obtained from the ^{1}H n.m.r. spectrum by the presence of a singlet at δ4.72, two triplets at δ1.20 (J 7 Hz) and 1.24 (J 7 Hz) and a broad quintet (two overlapping quartets) at δ3.62 (J 7 Hz). Absorptions in the i.r. at 3 390 and 1 695 cm^{-1} suggested the existence of an amide group. ^{13}C N.m.r. chemical shifts also agreed with the structure and are shown in Figure 1. Carbons 1-16 were assigned by comparison with literature values.[59,60]

Reduction of (69) with sodium borohydride in ethanol gave the norcodeinone (70). In the ^{1}H n.m.r. spectrum of (70) the C<u>H</u>(OEt)$_2$ proton gave a sharp singlet at δ4.70 whereas 5-H, together with 6-H, gave a broad hump at δ4.95. This established the assignments of the singlets at δ4.72 and 5.09 in the ^{1}H n.m.r. spectrum of the norcodeinone (69) (see above).

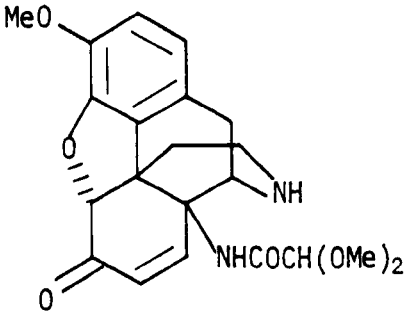


(69)

FIGURE 1

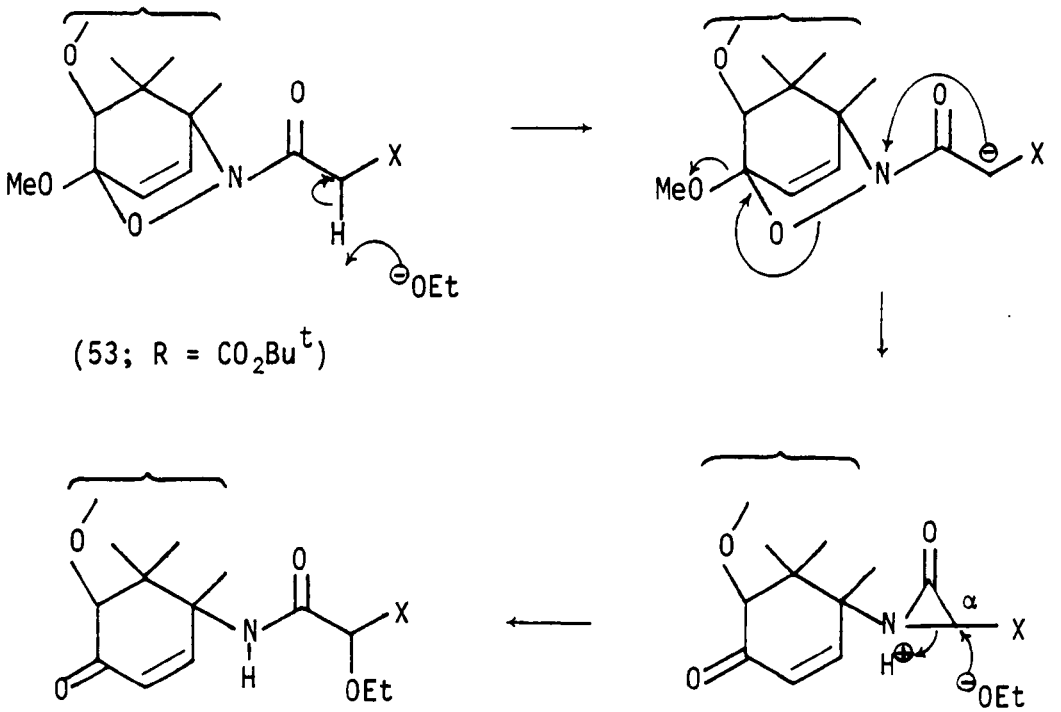


(70)



(71)

Acid catalysed hydrolysis of a diethyl acetal such as (69) should give the corresponding aldehyde. Thus the acetal (69) was dissolved in methanol and treated with aqueous hydrochloric acid for 30 min at 60°C. However a basic work-up only afforded a low yield of the dimethyl acetal (71).



(53; R = CO_2Bu^t)

(69)

(72)

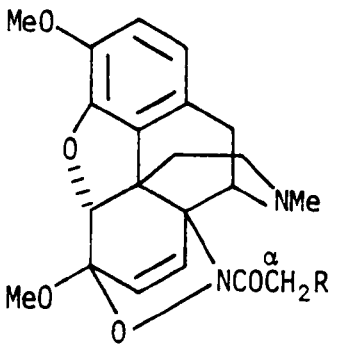
X = Cl or OEt

SCHEME X

The mechanism proposed for the formation of the norcodeinone (69) from the cycloadduct (53; R = CO_2Bu^t) is illustrated in Scheme X. Initial removal of an acidic methylene proton by ethoxide generates a carbanion which attacks the nitrogen. Concomitant cleavage of the nitrogen-oxygen bond and elimination of the 6-methoxy group gives the

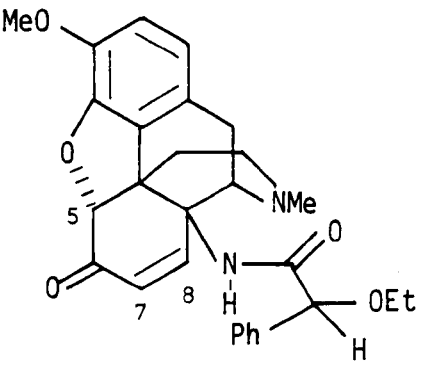
α-lactam intermediate (72). Nucleophilic attack by ethoxide at the α-carbon of (72) followed by cleavage of the alkyl carbon-nitrogen bond gives the norcodeinone (69). To account for the nature of the terminal part of the side-chain, substitution of the chlorine by an ethoxy group must also be included in the above Scheme.

Further investigations into this novel reaction were carried out with the readily available thebaine cycloadducts. Initially the cycloadduct (73; R = H) was prepared and treated with sodium ethoxide. Refluxing in ethanol for 5 h with one equivalent of the base yielded only the starting cycloadduct. This result suggested that the ethoxide was failing to abstract one of the methyl hydrogens, presumably due to a lack of acidity of the latter.



(73)

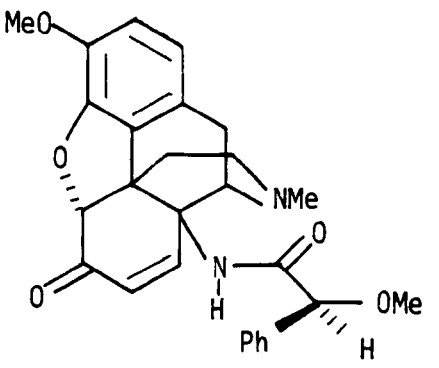
An electron withdrawing group such as phenyl or indeed chlorine on the α-carbon should increase the acidity of the neighbouring hydrogens and thus facilitate hydrogen abstraction. Accordingly, the cycloadduct (73; R = Ph) was prepared and treated with one equivalent of sodium ethoxide. Early attempts at this reaction afforded the product (74) as a mixture of two diastereoisomers. The ^1H n.m.r. spectrum of the mixture was in effect two superimposed spectra, *i.e.* there were two distinct resonances for each of the following: N-H, 5-H, 7-H, 8-H, and



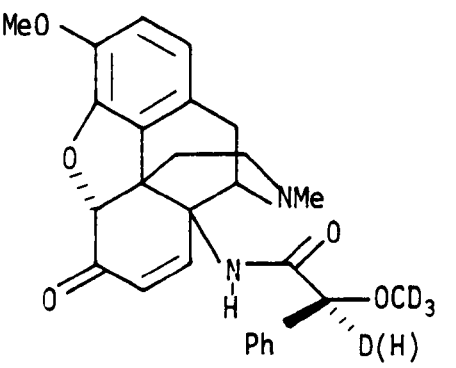
(74)

the various protons in the $CHOCH_2CH_3$ moeity. With careful control of the reaction time (30 min at room temperature) and work-up (see Experimental) the product consisted largely of a single diastereoisomer which was obtained pure and crystalline. It was also found that treatment of the cycloadduct with a catalytic amount of the base for 65 h yielded the same diastereoisomer and that the pure diastereoisomer could be partially converted into the other isomer with sodium ethoxide.

Furthermore, treatment of the cycloadduct (73; R = Ph) with sodium methoxide in methanol at room temperature overnight (16 h) yielded only one diastereoisomer (75a), which was shown to have the (*S*)-configuration at the new chiral centre (see p. 46). Under more



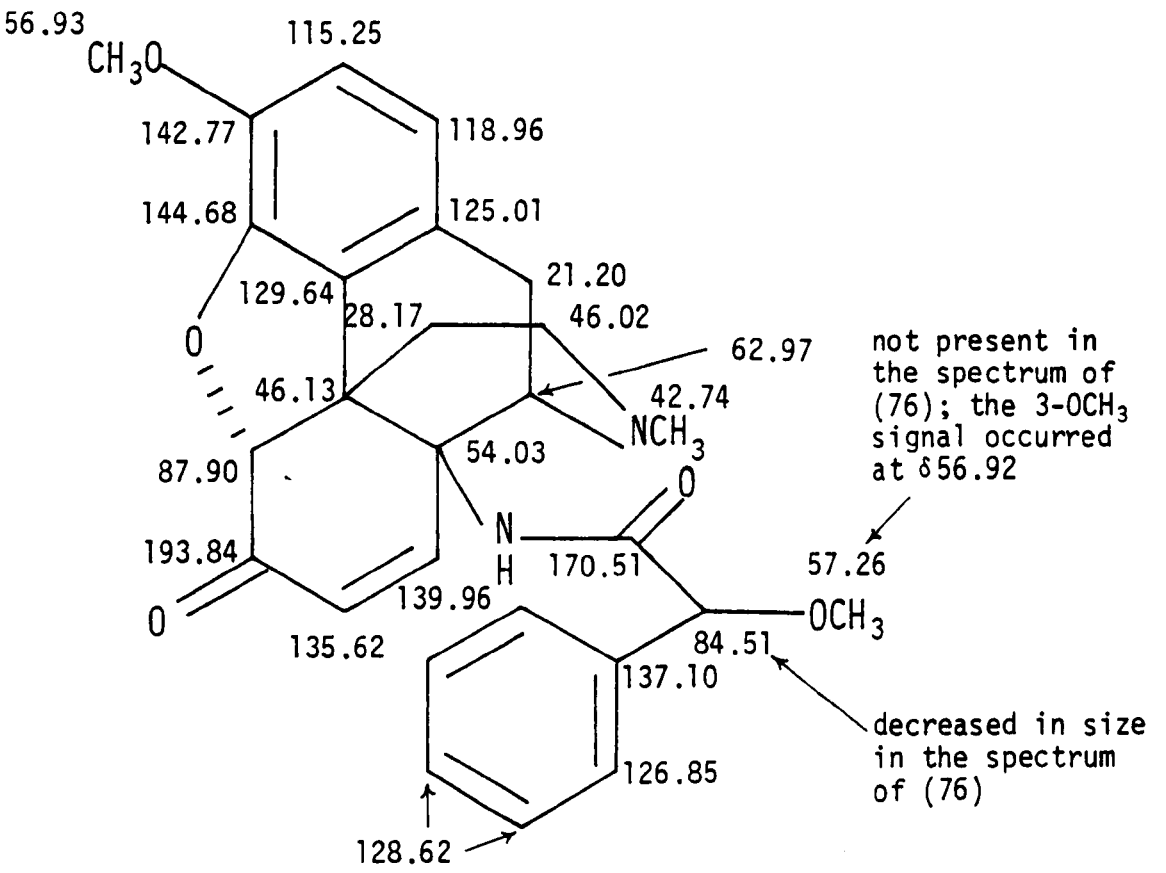
(75a)



(76)

severe reaction conditions (an overnight reflux with sodium methoxide) the cycloadduct was converted into the diastereoisomeric mixture. In the presence of sodium deuteriomethoxide and methanol-d_4 the cycloadduct reacted to yield a crystalline mixture of the tri- and tetradeuterio analogues of the (*S*)-diastereoisomer (76) in the ratio 3:2. The ^1H n.m.r. spectrum of (76) lacked the resonance due to the side-chain methoxy protons and, from the integration, only 40% of the molecules contained a benzylic hydrogen (δ4.54). Thus the rate of α-lactam formation was approximately equal to that of deuterium exchange in the cycloadduct.

A ^{13}C n.m.r. spectrum of the (*S*)-diastereoisomer (75a) was recorded and Figure 2 illustrates the signal assignment. Annotated

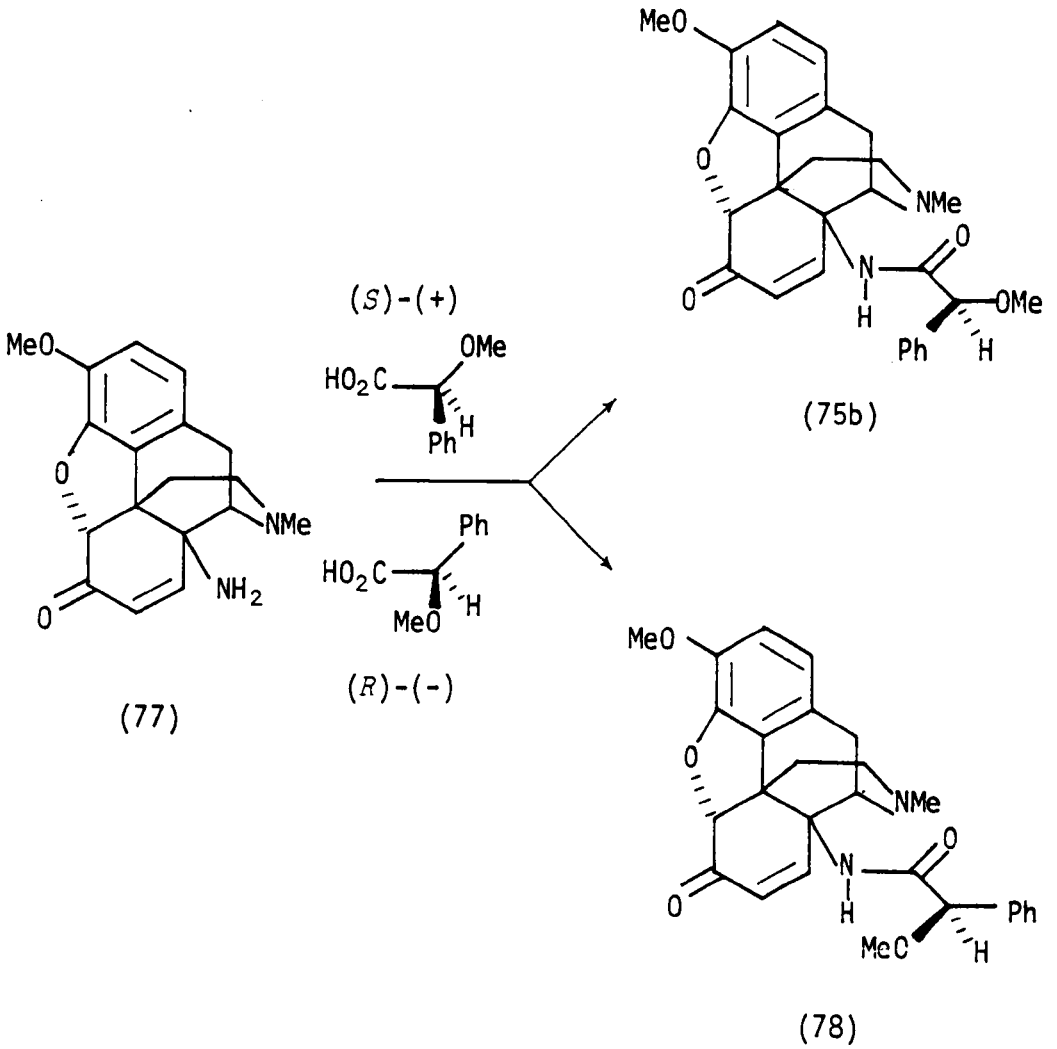


(75)

FIGURE 2

on the diagram are the salient differences between this spectrum and the ^{13}C n.m.r. spectrum of the deuteriated mixture (76).

To establish the configuration of the new chiral centre in (75a) 14β-aminocodeinone (77, supplied by Reckitt and Colman Products Ltd.) was coupled, in parallel experiments using dicyclohexylcarbodiimide, with (*S*)-(+)- and (*R*)-(-)-α-methoxyphenylacetic acid (Scheme XI). These acids were prepared according to the literature method[61] by methylating (*S*)-(+)- and (*R*)-(-)-α-mandelic acid with dimethyl sulphate.



SCHEME XI

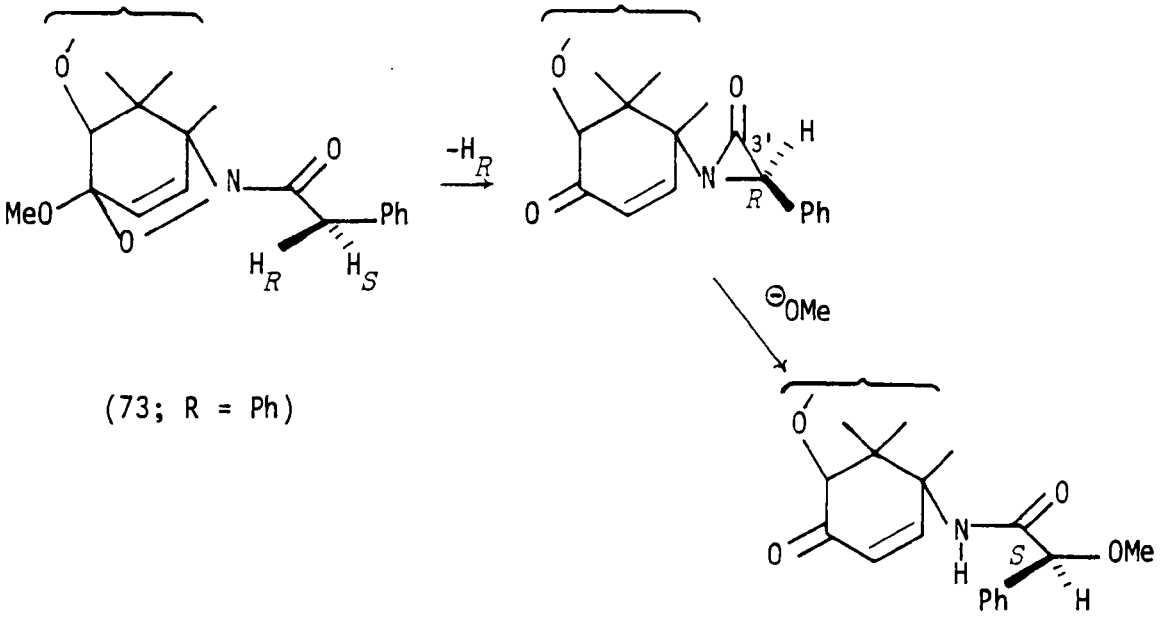
The ^{1}H n.m.r. chemical shifts and the melting points of the above pair of diastereoisomers were compared with those of the stereoselective reaction product (75a) and the relevant details are given in Table 2. Thus the close agreement in the data cited for (75a) and (75b) proved that the new chiral centre in (75a) possessed the (*S*)-configuration.

TABLE 2

	(75a)	(75b)	(78)
δ(CHOC<u>H</u>$_3$)	3.37	3.38	3.43
δ(C<u>H</u>Ph)	4.54	4.55	4.58
δ(5-H)	4.69	4.68	4.93
δ(7-H and 8-H)	6.20	6.19	6.06
δ(Ph)	7.41 (br s)	7.25-7.55 (m)	7.32 (s)
m.p. (°C)	178-179	178-179	202-203

In view of this conclusion it was proposed that in the aforementioned reaction the α-lactam with the (*R*)-configuration at C-3' was formed stereoselectively and, attack by methoxide at this position gave the desired product (Scheme XII). The benzylic hydrogens in (73; R = Ph) are chemically different, they are diastereotopic, but in an examination of the molecular model of this compound the (*pro*-*R*)-hydrogen did not appear to occupy more advantageous positions, with respect to abstraction, than those of the (*pro*-*S*)-hydrogen. It appears therefore that the selectivity in the reaction must reflect the preferred orientation of the carbanion at the moment of attack on nitrogen.

The diastereoisomers (75) and (78) were tested for pharmacological activity but at the time of writing the results were not known.



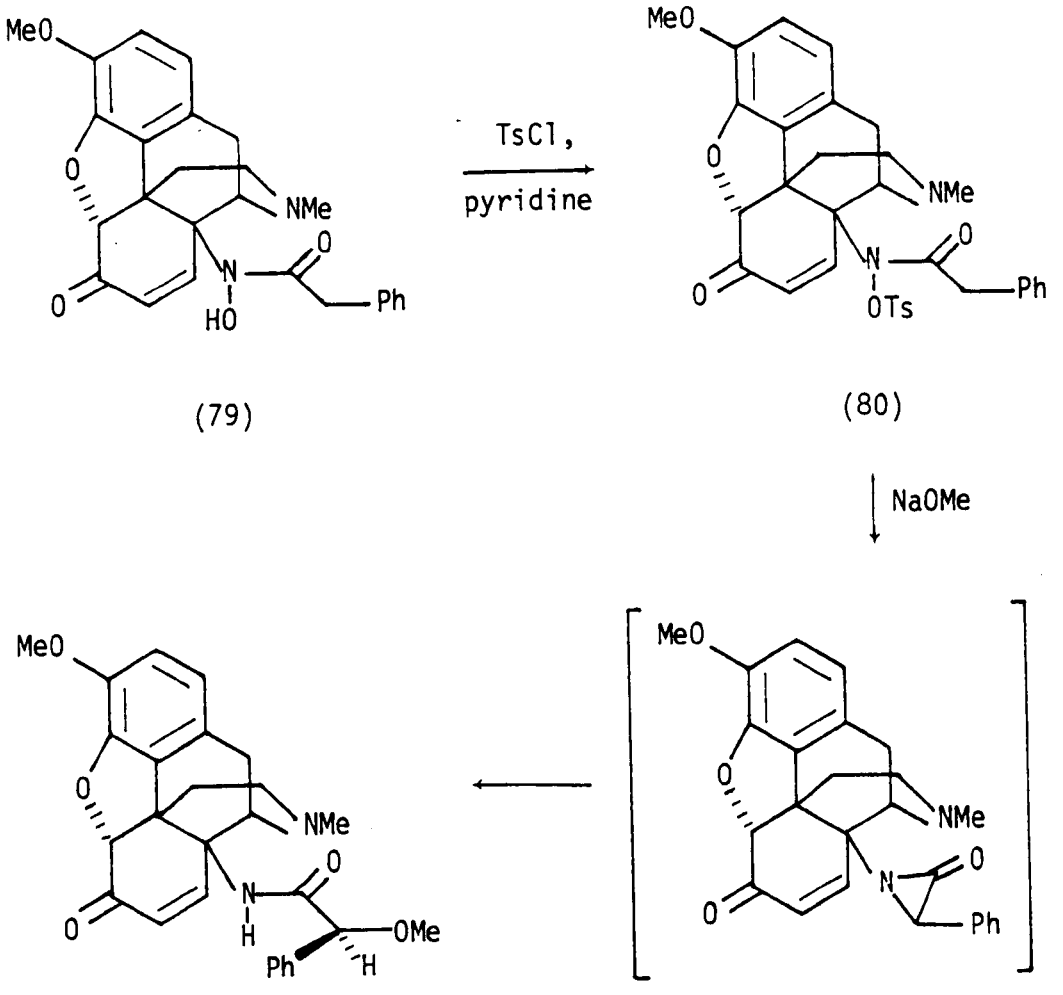
(73; R = Ph)

(75a)

SCHEME XII

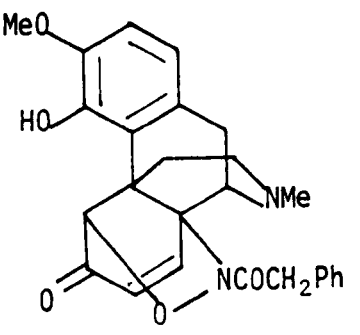
In the preamble to this chapter it was noted that the first authentic α-lactam was prepared through cyclisation of *N*-chloro-*N*-t-butylphenylacetamide. The structural similarity between this amide and the *O*-tosyl hydroxamic acid (80) suggested that this latter compound should cyclise with base to give an α-lactam, identical to that postulated in the stereoselective reaction. Thus, in the presence of sodium methoxide, the tosylate (80) should be converted *via* an α-lactam, into the diastereoisomer (75) (Scheme XIII).

Acid catalysed hydrolysis of the cycloadduct (73; R = Ph) yielded the hydroxamic acid (79) which crystallised from chloroform-methanol as the hemi-hydrate. The structure of this hydroxamic acid was confirmed by its conversion, with sodium ethoxide in ethanol, into the phenol (81).



(79) (80) (75)

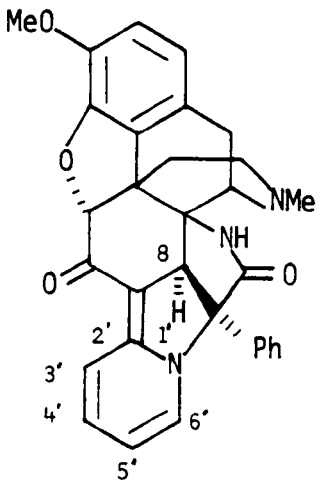
SCHEME XIII



(81)

Attempted tosylation of the hydroxamic acid (79) with toluene-*p*-sulphonyl chloride in pyridine resulted, after an aqueous work-up, in the isolation of an orange gum. The ^{1}H n.m.r. spectrum of this material contained a large number of signals particularly in the aromatic region. A singlet at δ2.52 ($C\underline{H}_3C_6H_4$) in the spectrum suggested that the desired tosylate (80) may have been one of the reaction products. In an optimistic experiment, the crude residue from the tosylate reaction was treated with sodium methoxide in methanol (see Experimental) in the hope that any tosylate formed would be converted into the diastereoisomer (75).

However, much to our surprise, a yellow compound [30% from the hydroxamic acid (79)] crystallised from this solution. On account of its yellow colour the compound was named 'buttercup' and was eventually assigned the structure of the anhydro-base (82) from its spectroscopic properties and by comparison with model compounds.



(82)

The mass spectrum revealed a molecular formula $C_{31}H_{27}N_3O_4$ which, when compared with that of the starting material (79) ($C_{26}H_{26}N_2O_5$), suggested the incorporation of a molecule of pyridine with loss of water and, surprisingly, loss of two hydrogens. The ^1H n.m.r. spectrum, recorded at 250 MHz in $CDCl_3$ (Figure 3), exhibited the usual *O*-methyl and *N*-methyl resonances at δ3.90 and 2.19 respectively. Singlets at δ4.59 (1H) and 7.51 (5H) were assigned to 5-H and the mono-substituted benzene ring, and the aromatic protons 1-H and 2-H gave an AB quartet (δ6.55 and 6.72). The broad one-proton resonance at δ7.56 (partly obscured by the Ph signal) disappeared on addition of D_2O and this, together with absorptions at 3 415 and 1 720 cm^{-1} in the i.r. spectrum indicated the secondary amide function. The remaining four low-field protons, which appeared as distinct multiplets, formed the ABCD system of the reduced pyridine ring. Analysis of this system is shown in Table 3.

Further evidence for a reduced pyridine ring in buttercup was obtained by carrying out the attempted tosylation reaction in pyridine-d_5. The residue from this procedure was treated with sodium methoxide in methanol as before. A mass spectrum of the resulting yellow needles showed a molecular ion at *m/z* 509.2255 which corresponded to the formula $C_{31}H_{23}D_4N_3O_4$. The ^1H n.m.r. spectrum was identical to that shown in Figure 3 except that the four multiplets cited in Table 3 were missing. Furthermore, doublets at δ112.81, 118.62, 134.56, and 140.59 in the ^{13}C n.m.r. spectrum of (82) (see Figure 4 for signal assignment) were absent in the analogous spectrum of the deuteriated material.

The methine singlet at δ3.83 in the ^1H n.m.r. spectrum was eventually assigned to 8-H and this signal was considerably sharpened upon addition of D_2O. It was concluded, therefore, that 8-H was weakly coupled to N-H. The appearance of a sharp singlet at δ3.49 (1.5H)

FIGURE 3

^{1}H n.m.r. spectrum of buttercup

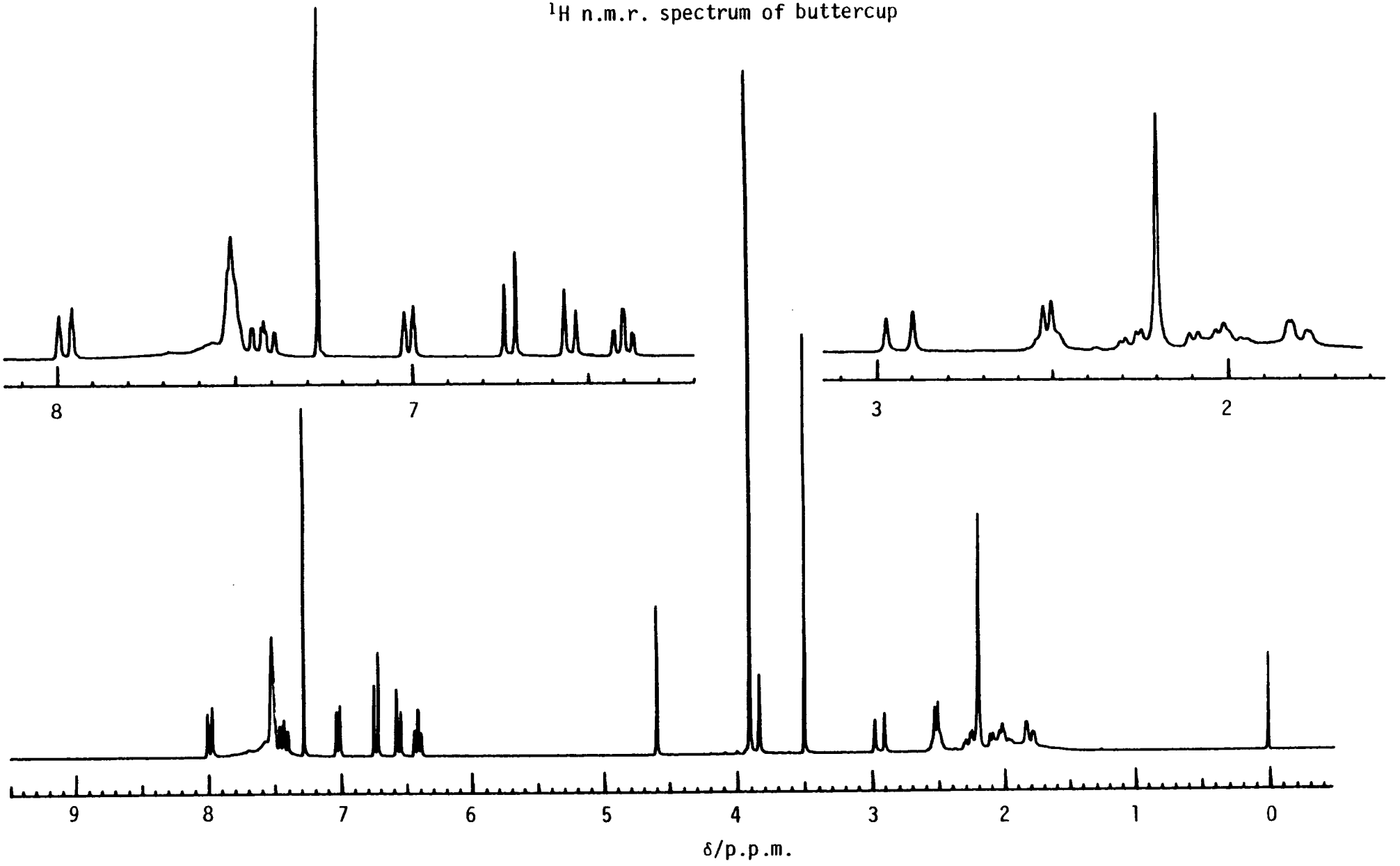
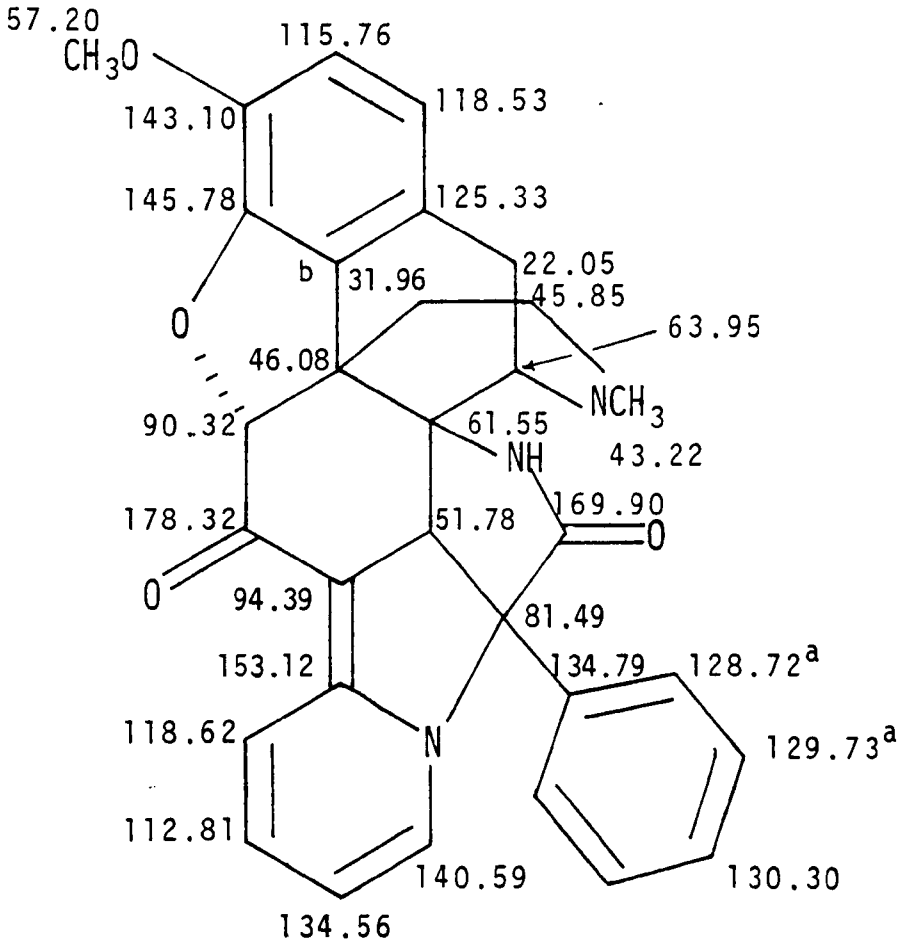


TABLE 3

Chemical shift (δ)	Multiplicity	Coupling constants (Hz)						Assignment
		$^3J(3'4')$	$^4J(3'5')$	$^5J(3'6')$	$^3J(4'5')$	$^4J(4'6')$	$^3J(5'6')$	
6.40	dt	7	-	-	7	1.5	-	4'-H
7.01	td	7	1.5	1.5	-	-	-	3'-H
7.42	ddd	-	1.5	-	7	-	9	5'-H
7.97	td	-	-	1.5	-	1.5	9	6'-H



(82)

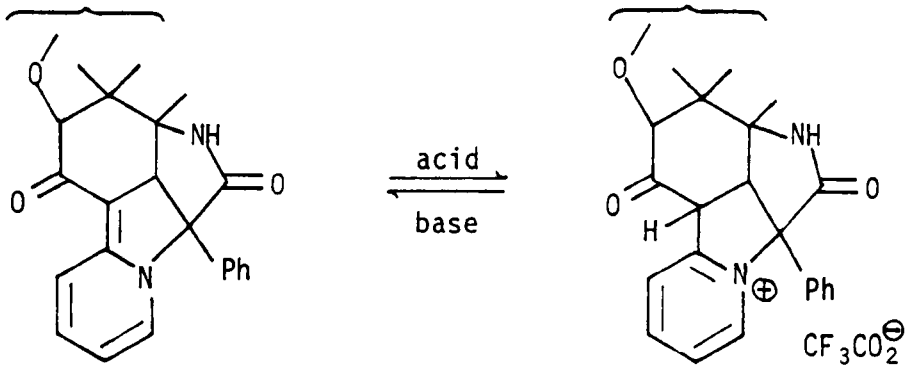
[a] Assignments may be reversed. [b] Obscured by signals at *ca.* δ130.

FIGURE 4

suggested that buttercup had been isolated as the hemi-methanolate. However, as the most satisfactory elemental analysis obtained corresponded to the hydrate-hemi-methanolate the exact composition of the yellow crystals was in doubt.

The u.v. spectrum of buttercup showed two strong absorptions at 339.5 and 435 nm due to the $\pi \rightarrow \pi^*$ transitions of the extended dihydropyridine chromophore. On addition of trifluoroacetic acid the

dihydropyridine system was aromatised and the resulting pyridinium trifluoroacetate gave rise to a new u.v. spectrum (λ_{max} 352 nm). This reaction was reversible; addition of base regenerated the dihydropyridine system with the u.v. absorption bands at 339.5 and 435 nm.



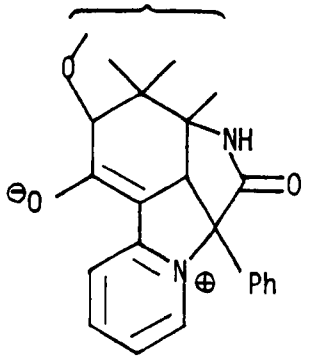
Yellow

λ_{max} 339.5, 435 nm

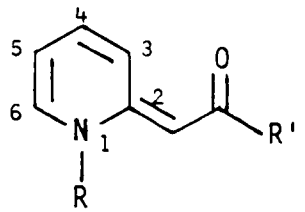
Colourless

λ_{max} 352 nm

The most notable feature in the i.r. spectrum was a strong ketone carbonyl absorption at 1 485 cm^{-1}. This, together with an abnormally high-field signal for C-6 in the ^{13}C n.m.r. spectrum emphasised the importance of the zwitterionic formulation:



The structure of buttercup was confirmed by comparison with model compounds. Several *N*-alkylated anhydro-bases have been reported in the literature, and those which most closely resemble the substituted dihydropyridine moeity of buttercup are (83a),[62,63] (83b),[64] and (83c).[65] All the spectroscopic data documented for these three compounds (see Table 4) are in good agreement with those obtained for buttercup.



(83)

a; R = Me, R' = Ph

b; R = CH_2Ph, R' = Ph

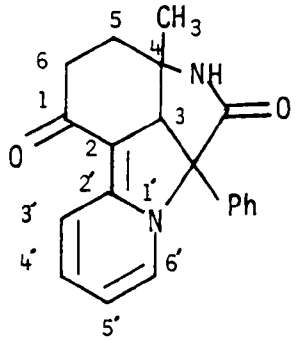
c; R = CH_2Ph, R' = Me

d; R = R' = Me

TABLE 4

Compound	ν_{max} in cm^{-1}	λ_{max} in nm (ε)	λ_{max} + HCl
83a	1 501 (C=O)		
83b	-	255 (15 300), 340 (12 800), 422 (27 400)	260 (27 000)
83c	1 505 (C=O)		

With the view to obtaining ^{1}H and ^{13}C n.m.r. spectra for further comparative purposes the anhydro-base (83c) and the hitherto unknown compound (83d) were prepared (Scheme XIV). The model compound (84), which was named 'neo-buttercup', was also synthesised (see later) in order to obtain evidence for the mechanism of formation of buttercup.

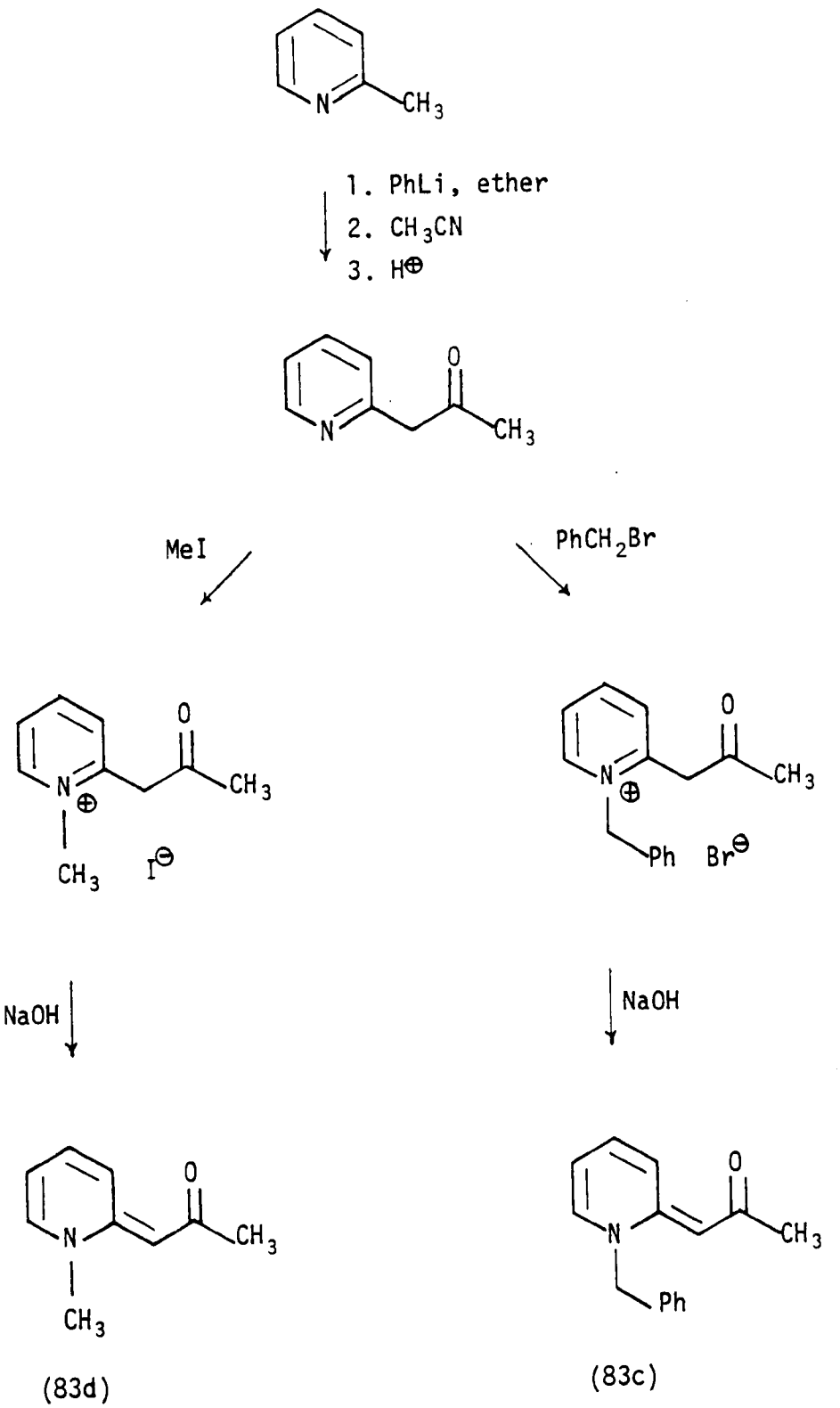


(84)

The ^{1}H n.m.r. spectrum of (84) is shown in Figure 5 and the ^{13}C n.m.r. signal assignments of (83c), (83d), and (84) are illustrated in Figure 6. The pertinent spectroscopic data of buttercup and those of the model compounds are collated in Tables 5 and 6.

Generally the spectroscopic data of buttercup compares well with those of the model compounds. In particular, the abnormally low frequencies of the ketone carbonyl absorption in the i.r. spectrum and the carbonyl carbon resonances in the ^{13}C n.m.r. spectrum of each of the model compounds closely parallel those of buttercup. Thus each of the four anhydro-bases has pronounced zwitterionic character.

The u.v. spectrum of buttercup and of neo-buttercup is shifted to longer wavelength compared with that of (83c) and (83d) and this may be a result of a slight twist in the conjugated system in each of the molecules (*cf.* ref. 66). In the ^{1}H n.m.r spectrum of buttercup and of neo-buttercup the 6'-H signal is *ca.* 0.5-1 p.p.m. upfield of the corresponding signal in (83c) and (83d).



SCHEME XIV

FIGURE 5a

^{1}H N.m.r. spectrum of neo-buttercup

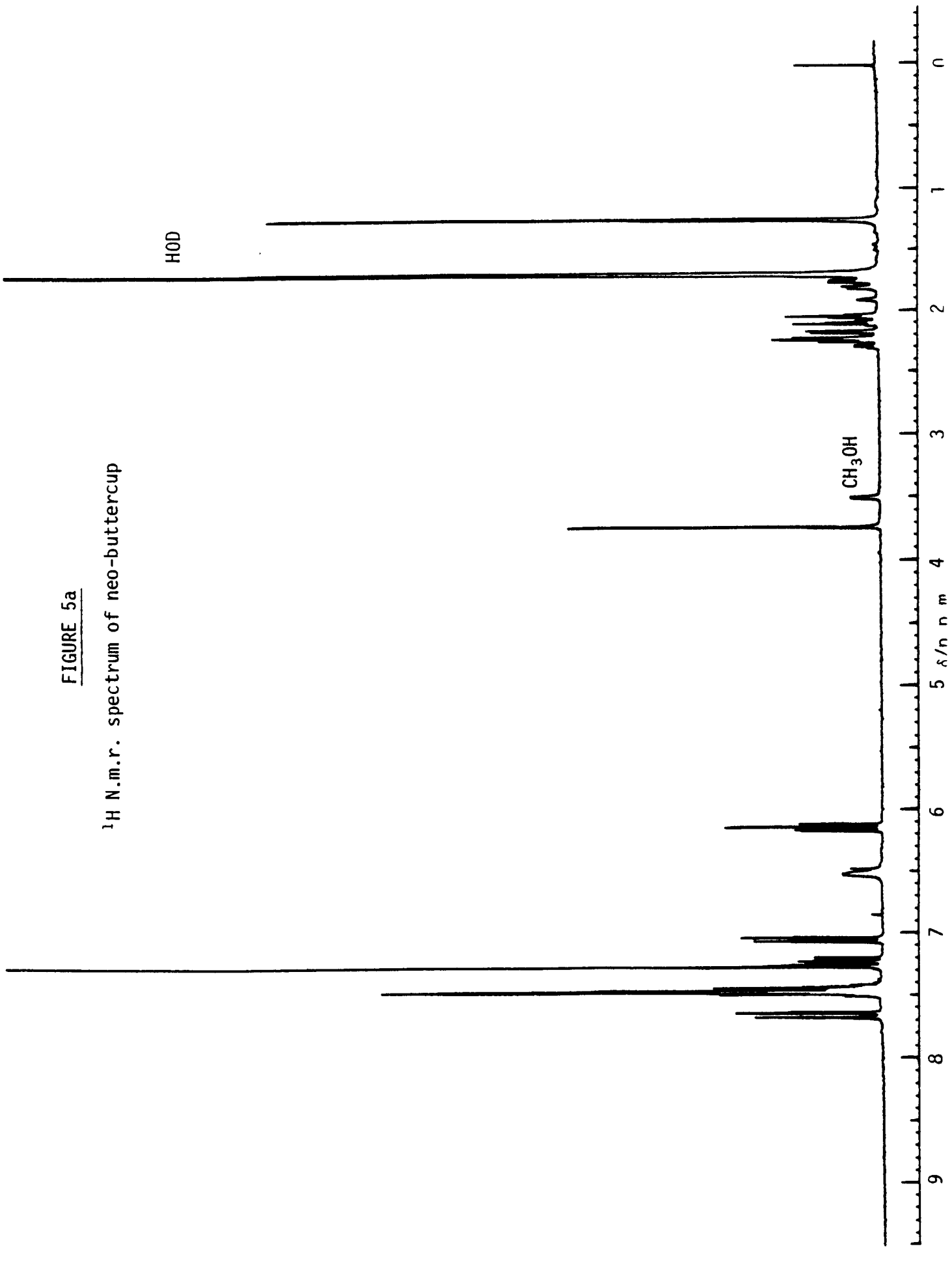
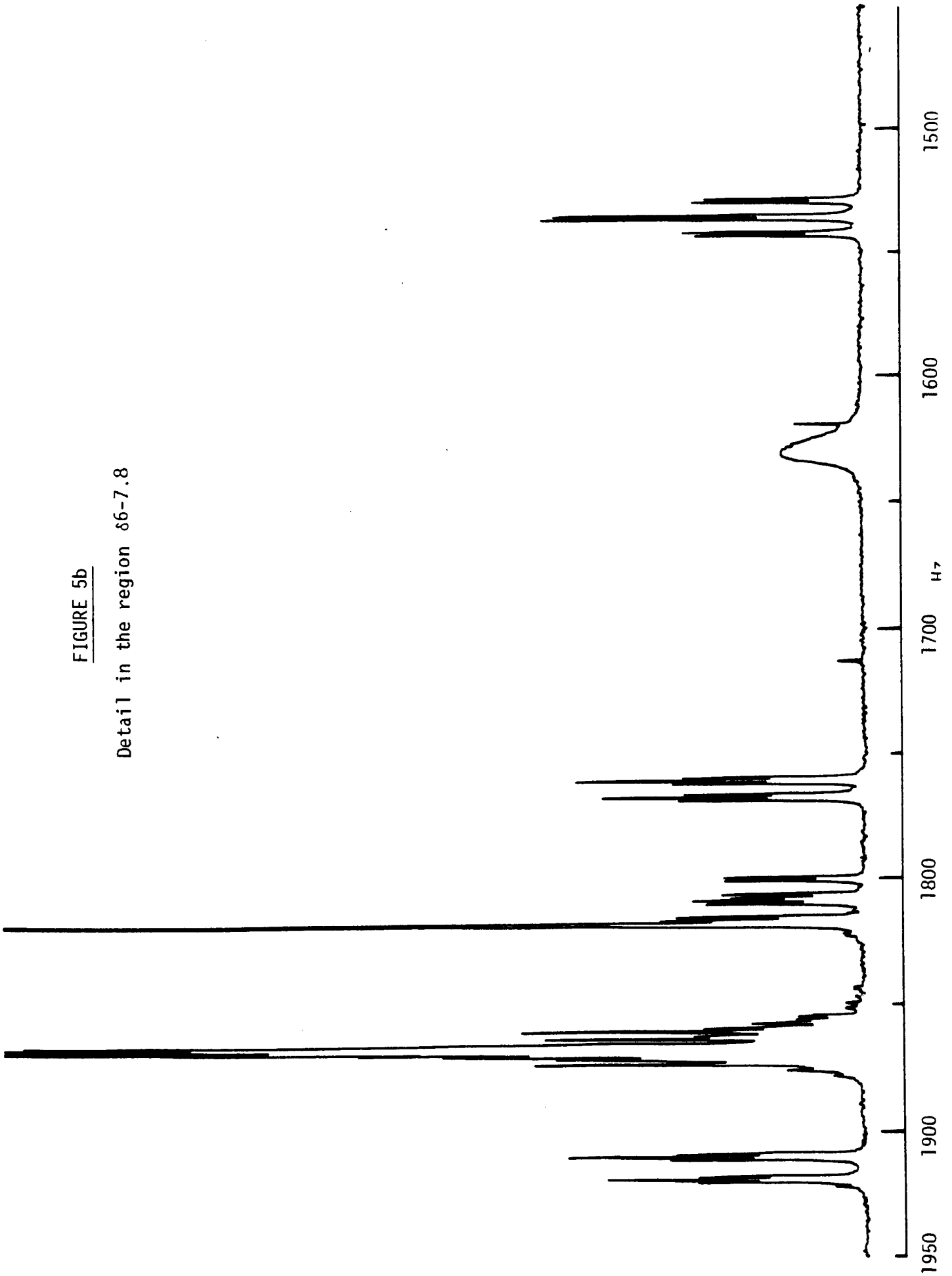
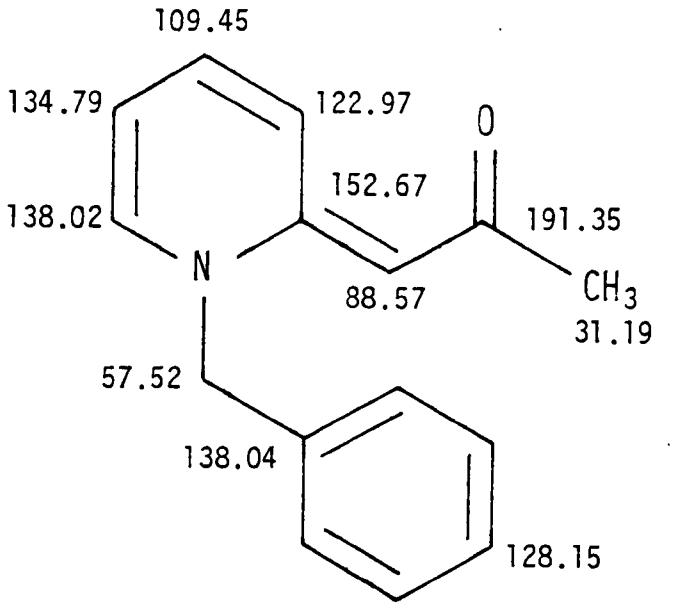


FIGURE 5b

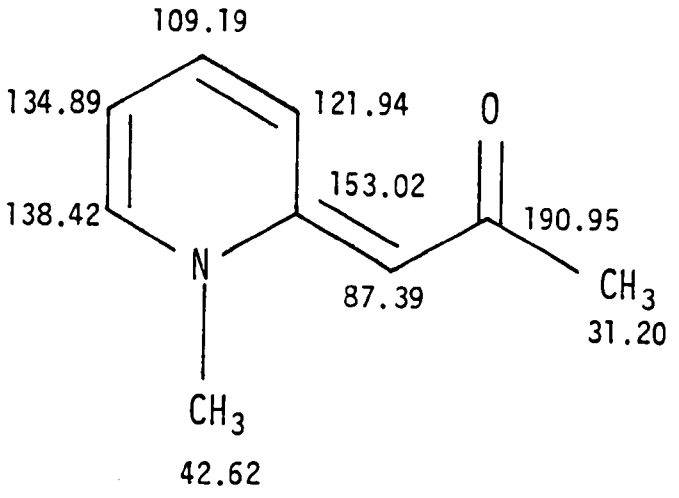
Detail in the region δ6-7.8



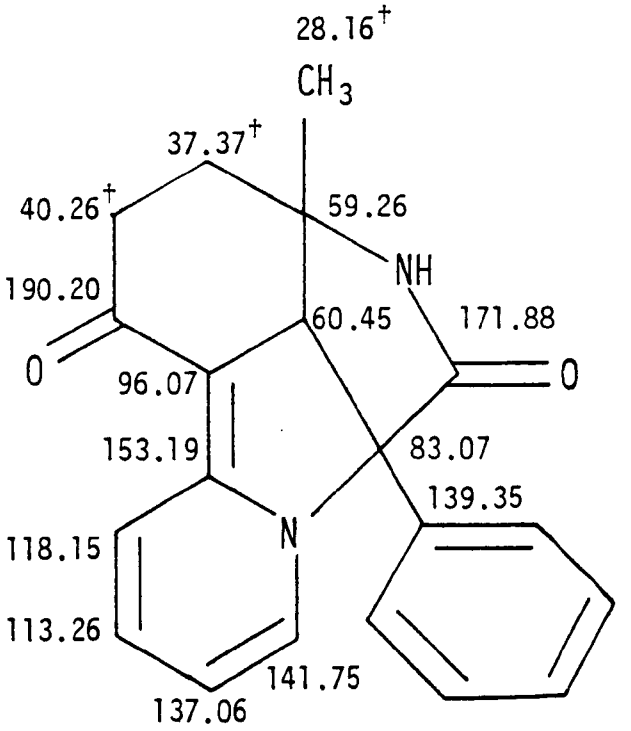


remaining aromatics: 126.77, 129.11

(83c)



(83d)



remaining aromatics: 128.90, 130.64.

† multiplicities not observed.

(84)

Note: Spectrum of (84) recorded in CD_3OD due to insolubility of sample in $CDCl_3$.

FIGURE 6

TABLE 5

I.r.[a] and u.v.[b] spectral data

Compound	ν_{max} (cm^{-1}) (C=0)	λ_{max} (nm)	λ_{max} + TFA
82	1 485; 1 485[c]	339.5, 435	352
84	1 500; 1 500[c]	336, 435	360
83c	1 505	326, 396	346
83d	1 505	322, 390	340

[a] KBr discs unless otherwise stated. [b] In EtOH. [c] In $CHCl_3$.

TABLE 6

Comparison of ^1H[a] and ^{13}C n.m.r. chemical shifts (δ) in the dihydropyridine ring

Compound	4-H	3-H	5-H	6-H	[c]C=0
82[b]	6.40 (dt)	7.01 (br td)	7.42 (ddd)	7.97 (br td)	178.32
84[b]	6.14 (dt)	7.05 (td)	7.23 (ddd)	7.65 (td)	190.20
83c	6.18 (dt)	7.00 - 7.55 (m)		8.93 (dd)	191.35
83d	6.13 (dt)	6.96 - 7.25 (m)		8.88 (td)	190.95

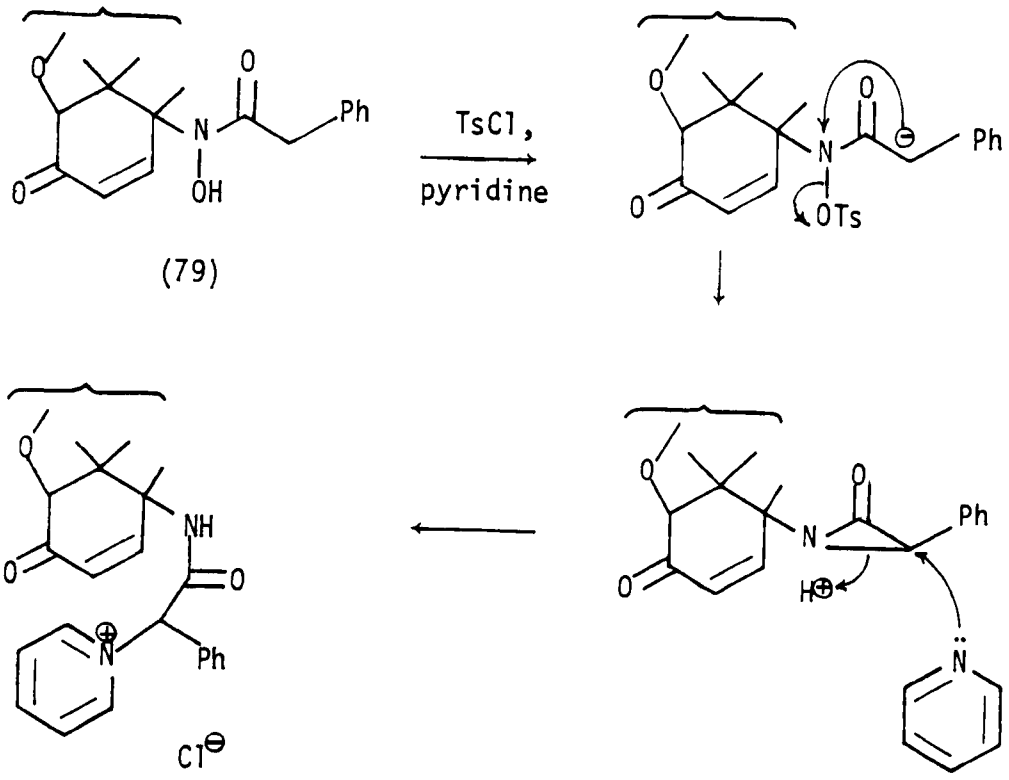
[a] 250 MHz for (82) and (84). [b] Numbering superscripts omitted for clarity. [c] Normal values for unsaturated ketones *ca.* 200 p.p.m.

An examination of molecular models revealed that in the more favourable conformations of (82) and (84) the benzene ring lies over 6'-H, *i.e.* this proton is shielded and thus resonates at higher field.

In buttercup, and in neo-buttercup, the lactam and pyrroline rings were reasoned to be *cis*-fused since the corresponding *trans*-fused system would be very highly strained.

The mechanism proposed for the formation of buttercup (82) from the hydroxamic acid (79) is shown in Scheme XV. After initial formation of the tosylate, removal by pyridine of one of the benzylic protons leads to the production of an α-lactam intermediate. Nucleophilic ring opening by pyridine gives the pyridinium chloride (85), which presumably is the crude material isolated from the reaction. Sodium methoxide abstracts the remaining acidic proton to generate an ylid which adds, as a 1,3-dipole, to the double bond of the enone. Finally, aromatisation of this dihydropyridine gives buttercup.

Similarly, neo-buttercup (84) was obtained from the hydroxamic acid (88) (see Scheme XVI) by treatment with toluene-*p*-sulphonyl chloride in pyridine followed by sodium methoxide in methanol. The required starting hydroxamic acid was prepared in three steps from *p*-methylanisole. Monti *et al.*[67] have reported that Birch reduction of *p*-methylanisole with lithium in dry liquid ammonia containing t-butanol and tetrahydrofuran gives a high yield (78%) of 1-methoxy-4-methyl-1,4-cyclohexadiene. In our hands this procedure gave a 1:1 mixture of the 1,4- and 1,3-dienes in 76% yield. Further equilibration of this material with a catalytic amount of toluene-*p*-sulphonic acid afforded, after distillation, a colourless oil which contained 72% of the desired 1,3-diene and 28% of the 1,4-diene. Treatment of this oil with phenylacetohydroxamic acid and sodium periodate in ethyl acetate and aqueous buffer (pH 5.8) yielded a complex mixture of products. The crude mixture was chromatographed on a column of silica but only one component (21%), identified as the

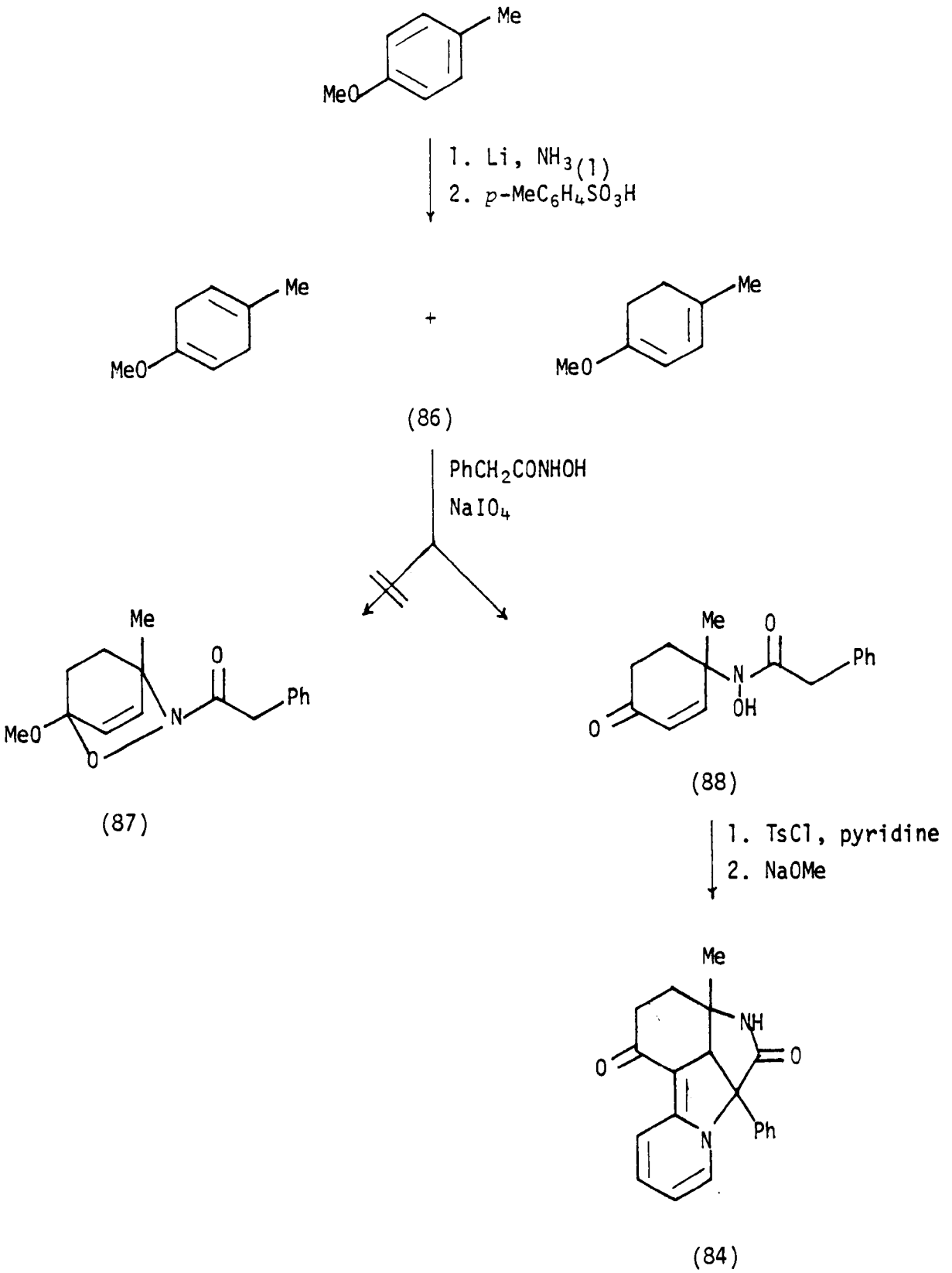


(79)

(85)

(82)

SCHEME XV


Me
MeO
1. Li, $NH_{3(l)}$
2. p-$MeC_6H_4SO_3H$
Me
MeO
+
Me
MeO
(86)
$PhCH_2CONHOH$
$NaIO_4$
Me
O
Ph
MeO
N
O
(87)
Me
O
Ph
N
OH
O
(88)
1. TsCl, pyridine
2. NaOMe
Me
NH
O
O
Ph
N
(84)

SCHEME XVI

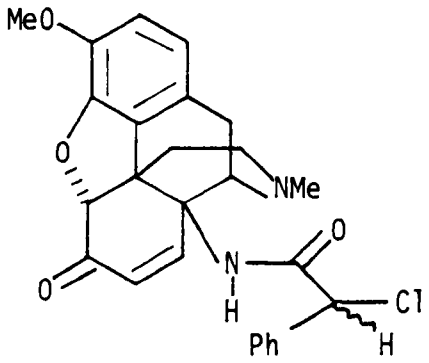
hydroxamic acid (88), was obtained pure and crystalline. The other products were eluted from the column as oily mixtures and were not identified. Presumably the hydroxamic acid was formed by hydrolysis of the cycloadduct (87), the expected product.

As the cycloadduct (87) was desirable as a model for the stereoselective reaction, attempts were made to obtain it from the above oxidation by modifying the experimental conditions. Thus, by using a variety of buffers the oxidation was carried out at pH 6.8, 7.5, and 9.2 but in each case mixtures ensued which were not investigated further. A mixture was also obtained when the reaction was repeated with tetraethylammonium periodate as oxidant.

Circumstantial evidence supporting the formation of an α-lactam intermediate in the reaction leading to buttercup was obtained as follows. In a procedure developed with aliphatic hydroxamic acids (see Section 4.2), the model hydroxamic acid (88) was treated with trifluoromethanesulphonic anhydride in methylene chloride containing triethylamine at -70°C. An i.r. spectrum of the reaction mixture showed an intense absorption band at 1845 cm^{-1} indicating the presence of an α-lactam. Pyridine was added to the reaction mixture at -70°C, the solution allowed to attain room temperature and the solvent was then evaporated. Treatment of the residue with sodium methoxide as before yielded neo-buttercup. A similar procedure on the thebaine hydroxamic acid (79) failed to show any sign of an α-lactam but this could be due to interference in the reaction by the tertiary amine group.

The compound isolated from the reaction between the hydroxamic acid (79) and toluene-*p*-sulphonyl chloride and pyridine was believed to be the pyridinium chloride (85). To prove this hypothesis, an authentic sample of this salt was required so that upon treatment with sodium methoxide it would be converted into buttercup. To this

end, the α-chloro-amide (89), prepared from 14β-aminocodeinone and (±)-α-chlorophenylacetyl chloride, was treated with pyridine under several sets of reaction conditions (see Experimental). The chloro-amide was either recovered from the experiment or was decomposed by it.

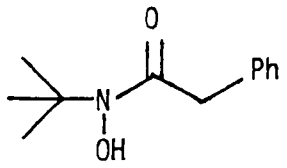


(89)

The final step in the proposed mechanism for the formation of buttercup involves dehydrogenation of a dihydropyridine (see Scheme XV). In an attempt to discover whether it involved atmospheric oxygen, the crude residue obtained from the first stage of the reaction was treated with sodium methoxide under oxygen-free nitrogen conditions. As buttercup was isolated in approximately the same yield and at approximately the same rate as before the oxidation was apparently not caused by oxygen in the air.

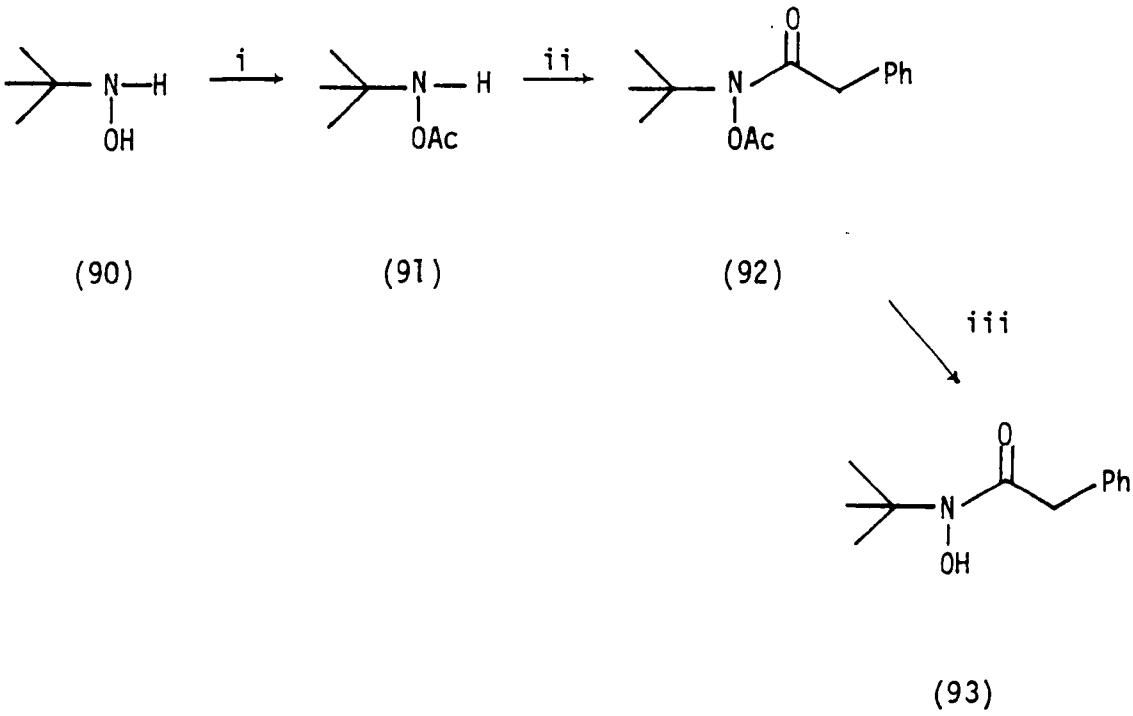
4.2 In Experiments with Aliphatic Compounds

The novel reactions discussed in Section 4.1 are thought to proceed *via* α-lactams which, in each case, are formed from hydroxamic acid derivatives. As part of a further investigation into these reactions the preparation of the model hydroxamic acid (93) was undertaken with the aim of subjecting it to reactions similar to those described earlier.



(93)

Perkins and co-workers[68] have reported the synthesis of *N*-t-butylphenylacetohydroxamic acid (93) in three steps from *N*-t-butylhydroxylamine (90) (Scheme XVII). Acetylation with acetic

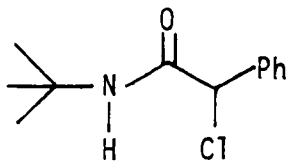


(90) (91) (92) (93)

SCHEME XVII *Reagents*: i, Ac_2O-K_2CO_3-ether; ii, $PhCH_2COCl$ -pyridine-benzene; iii, $Ba(OH)_2$-ethanol.

anhydride gave the *O*-acetyl derivative (91) which was converted into the diacylhydroxylamine (92) by treatment with phenylacetyl chloride in benzene containing pyridine. Removal of the *O*-acetyl group with barium hydroxide afforded the hydroxamic acid (93).

The attempted phenylacetylation under the literature conditions gave a 30% yield of the α-chloro-*N*-t-butylphenylacetamide (94),

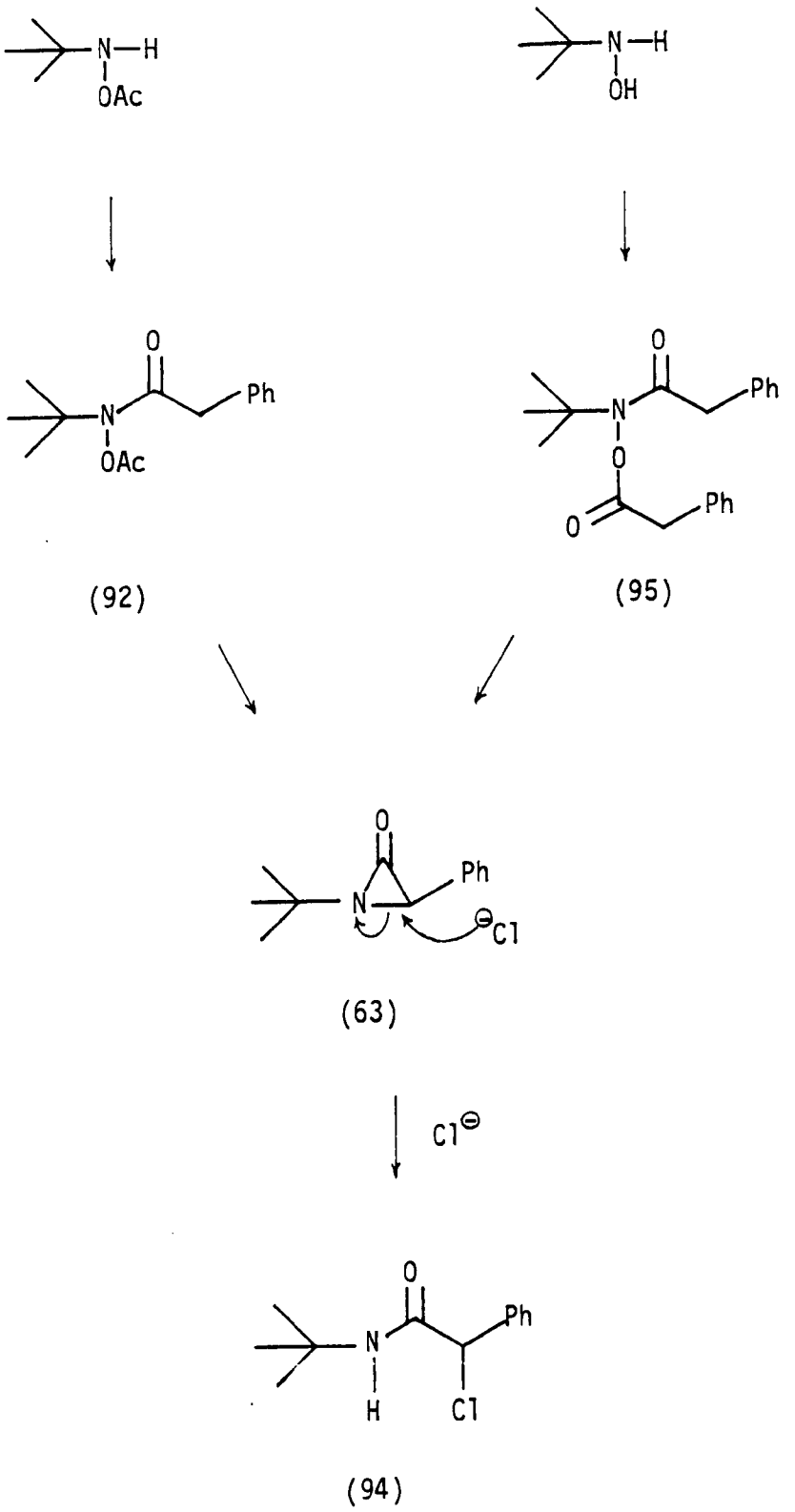


(94)

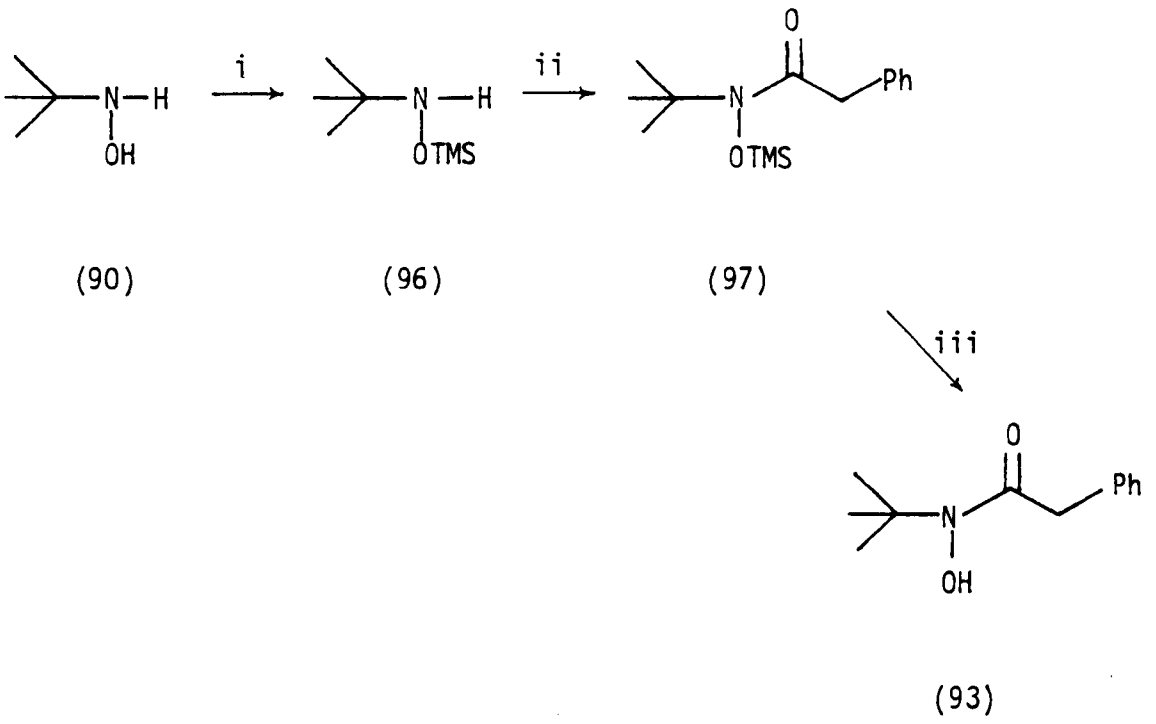
identified from its spectroscopic properties and by comparison with an authentic sample prepared from *N*-t-butylamine and α-chlorophenylacetyl chloride. The same product was also obtained from the reaction, in benzene, between *N*-t-butylhydroxylamine and two equivalents each of phenylacetyl chloride and pyridine. The mechanism of formation of the α-chloro-amide from the hydroxylamines (Scheme XVIII) involves an α-lactam intermediate. Attack by chloride ion at the α-carbon of (63) leads to the observed amide (94).

The hydroxamic acid (93) was eventually obtained from *N*-t-butylhydroxylamine in a one-pot synthesis (Scheme XIX) as follows. *N*-t-Butylhydroxylamine (90) was converted into the *O*-trimethylsilyl ether (96) by treatment with trimethylchlorosilane and triethylamine in methylene chloride. Addition of phenylacetyl chloride and triethylamine gave, presumably, the hydroxylamine (97) which was hydrolysed with dilute hydrochloric acid to give the hydroxamic acid (93) in 32% overall yield. The only data reported by Perkins and his co-workers for (93) was a melting point of 85-86°C and this disagreed with the melting point (129-130°C) presently found for this compound.

The *bis*phenylacetylhydroxylamine (95) was postulated as an intermediate in the reaction between *N*-t-butylhydroxylamine and phenylacetyl



SCHEME XVIII

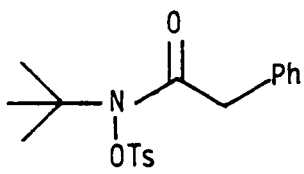


(90) (96) (97) (93)

SCHEME XIX *Reagents:* i, $TMSCl-NEt_3-CH_2Cl_2$; ii, $PhCH_2COCl-NEt_3-CH_2Cl_2$; iii, dil. HCl.

chloride. This compound was prepared from the hydroxamic acid (93) by treatment with phenylacetyl chloride but all attempts (see Experimental) to convert it into the α-chloro-amide (94) failed and starting material was recovered.

Reaction of *N*-t-butylphenylacetohydroxamic acid (93) with toluene-*p*-sulphonyl chloride in methylene chloride containing triethylamine afforded the α-chloro-amide (94) (29%) and not the desired tosylate (98). The mechanism followed a similar pathway to that depicted



(98)

in Scheme XVIII. Indirect evidence for the formation of an α-lactam intermediate was obtained by recording the i.r. spectrum of the reaction mixture at various intervals. Thus, a carbonyl band at 1850 cm^{-1} appeared and grew in intensity as the α-lactam was generated, and then diminished and finally disappeared as the chloride ion cleaved the ring to yield the α-chloro-amide (94). It was clear that the rate of formation of the chloro-amide was comparable to that of the α-lactam.

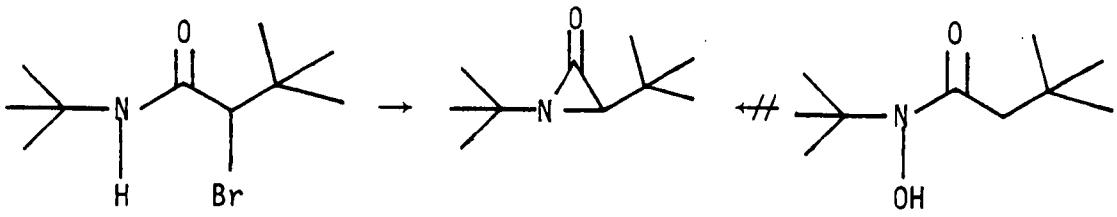
It was noted earlier that 1-t-butyl-3-phenylaziridin-2-one, the intermediate proposed in the above reaction, was the first α-lactam to be isolated. The two literature preparations[49,50] of this compound were attempted but, although in each case the α-lactam was formed (carbonyl absorption at 1 850 cm^{-1} in the i.r. spectrum), it could not be separated (fractional crystallisation) from the starting material.

As a result of these failures a synthesis of the α-lactam (63) from the hydroxamic acid (93) was developed in the following way. Trifluoromethanesulphonic (triflic) anhydride is a reagent used to form sulphonate esters (triflates),[69] which are similar to tosylates. However the triflate anion is a weaker nucleophile than the tosylate or chloride anions. In addition, the triflate group is much more reactive towards displacement than the corresponding tosylate group. Accordingly, triflic anhydride (1.2 mol equiv.) was added to a solution of *N*-t-butylphenylacetohydroxamic acid (1 mol equiv.) and triethylamine (2.2 mol equiv.) in dry methylene chloride at -70°C and afforded, after careful work-up (see Experimental), the α-lactam (63) as a low melting crystalline solid in 97% yield.

With tetrabutylammonium chloride as a chloride ion source in methylene chloride the α-lactam (63) gave the α-chloro-amide (94) in 53% yield. This result supports the idea that 1-t-butyl-3-phenylaziridin-2-one was an intermediate in the aforementioned aliphatic reactions and,

this in turn, gave support to the mechanisms envisaged for the novel reactions discussed in Section 4.1.

In order to investigate whether the hydroxamic acid route to α-lactams was generally valid, the synthesis, by the above method of 1,3-di-t-butylaziridin-2-one (99) was undertaken. This compound (99) is the most stable α-lactam known and is normally prepared by the cyclisation of the α-bromo-amide (100) with potassium t-butoxide.[52] Thus, *N*-t-butyl-(3,3-dimethylbutano)hydroxamic acid (101) was obtained from *N*-t-butylhydroxylamine by a similar procedure to that used for



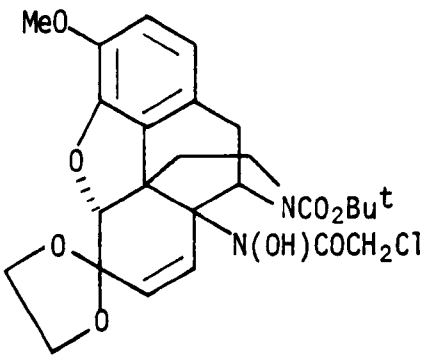
(100) (99) (101)

the preparation of (93). However, this hydroxamic acid could not be converted into the α-lactam (99) by treatment with triflic anhydride and triethylamine. The reaction was repeated using 1,5-diazobicyclo-[4.3.0]non-5-ene and again using lithium diisopropylamide in place of triethylamine (see Experimental) but no α-lactam was formed in either experiment, presumably because the methylene protons in the hydroxamic acid were not sufficiently acidic to be removed rapidly by these bases.

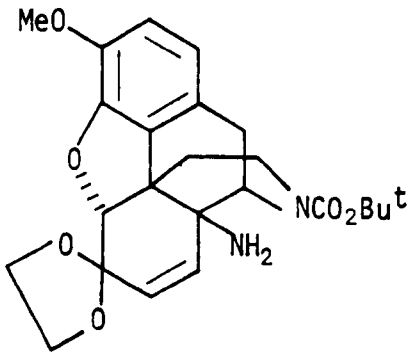
CHAPTER 5

1,2-OXAZETIDIN-3-ONES

All the work on α-lactams described in Chapter 4 stemmed from the reaction between the cycloadduct (53; R = CO_2Bu^t) and sodium ethoxide. It was also noted that the analogous treatment of the hydroxamic acid (56) led to the 14-aminocodeinone derivative (68).

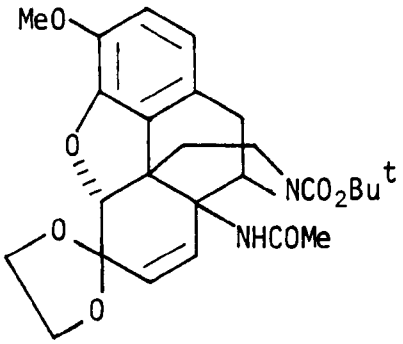


(56)

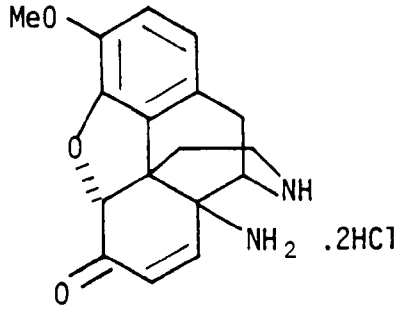


(68)

The structure of the amine (68) was based on spectroscopic data. In particular, the mass spectrum and elemental analysis established the molecular formula $C_{24}H_{30}N_2O_6$. The presence of a primary amine group was suggested by the two-proton exchangeable signal at δ1.85 in the ^1H n.m.r. spectrum and the absorptions at 3 390 and 3 320 cm^{-1} in the i.r. spectrum. The structure of (68) was confirmed by its conversion, with acetic anhydride and pyridine, into the amide (102) and to the known amine[17] (103), isolated as the dihydrochloride, by treatment with acid.



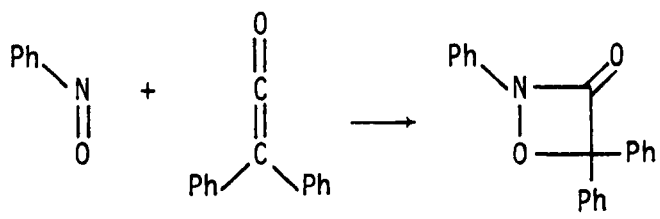
(102)



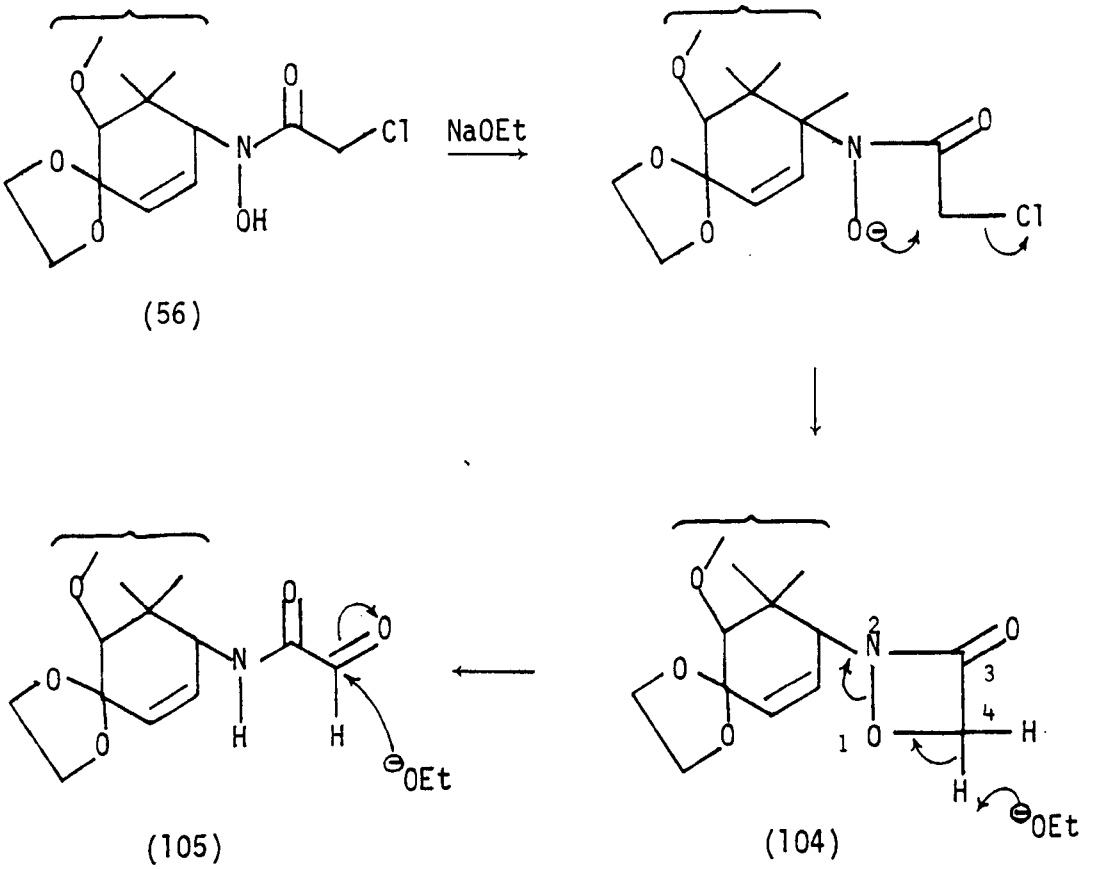
(103)

The mechanism of formation of (68) remains obscure. A tentative proposal (Scheme XX) involves an oxazetidinone intermediate (104) resulting from ring closure of the α-chlorohydroxamic acid. Ring cleavage of (104), envisaged as base abstraction of a proton at C-4, gives the glyoxalamide (105). An intramolecular hydride migration followed by cleavage of the resulting carbinolamine yields the final product (68).

Since the conversion of (56) into (68) was quite unexpected, further experiments were carried out to clarify the reactions of 1,2-oxazetidin-3-ones with base. A few stable 1,2-oxazetidin-3-ones have been reported in the literature. The first compound of this type 2,4,4-triphenyl-1,2-oxazetidin-3-one (106) was isolated in 1911 by Staudinger and Jelagin[70] by the cycloaddition of diphenyl ketene to nitrosobenzene:



(106)



(56)

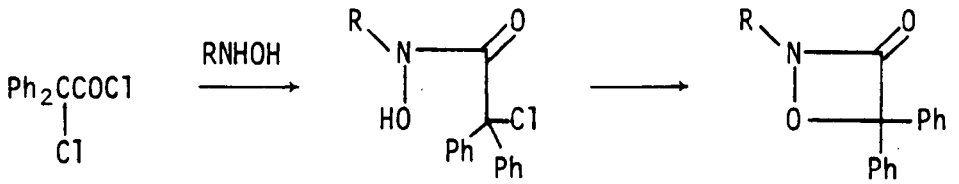
(104)

(105)

(68)

SCHEME XX

This method has been used more recently to prepare other 2,4,4-triaryl derivatives.[71] The main disadvantage of this route was caused by the competing cycloaddition leading to the unstable 1,2-oxazetidin-4-ones. A more satisfactory synthesis of *N*-substituted 4,4-diphenyl-1,2-oxazetidin-3-ones[72] (108) was found to be *via* ring closure of α-chlorohydroxamic acids (Scheme XXI). The hydroxamic acids (107; R = alkyl, aryl), formed from *N*-substituted hydroxylamines and chlorodiphenylacetyl chloride, were not isolated but underwent internal displacement of the chlorine atom by the hydroxylamine oxygen to give the oxazetidinones directly.

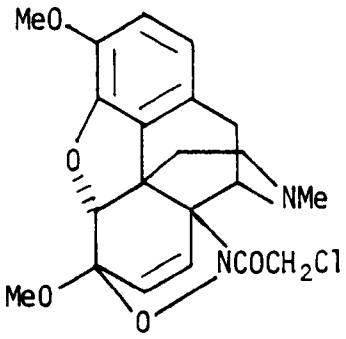


(107) (108)

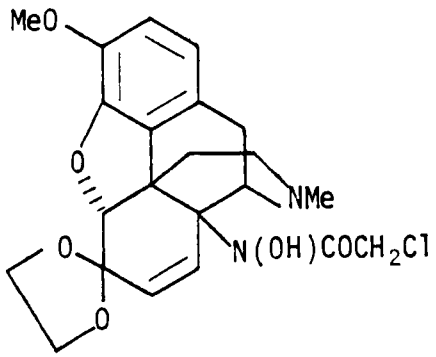
SCHEME XXI

During the course of earlier work it was found that treatment of the thebaine cycloadduct (59) with anhydrous hydrogen chloride in ethylene glycol followed by basification with sodium hydrogen carbonate and extraction gave a quaternary ammonium chloride (see Chapter 3). The open-chain hydroxamic acid (109) was presumably formed first but it was not isolated.

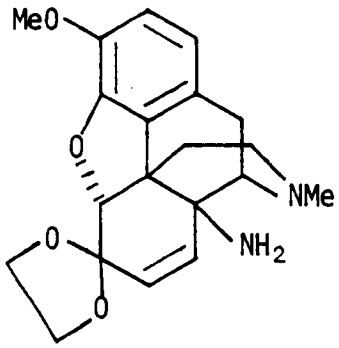
The experiment was repeated but, in the hope that the hydroxamic acid (109) would be converted into the 14β-aminocodeinone (110), the crude reaction mixture was treated with sodium methoxide solution. However, the only product isolated (29%) was the methyl ester (111). The mass



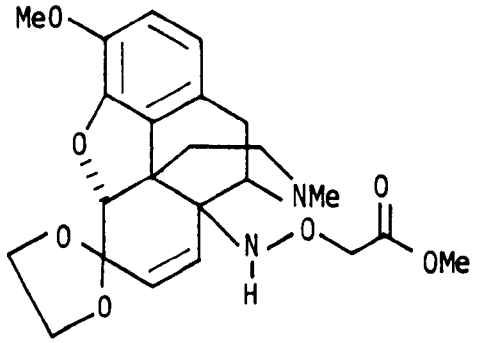
(59)



(109)



(110)

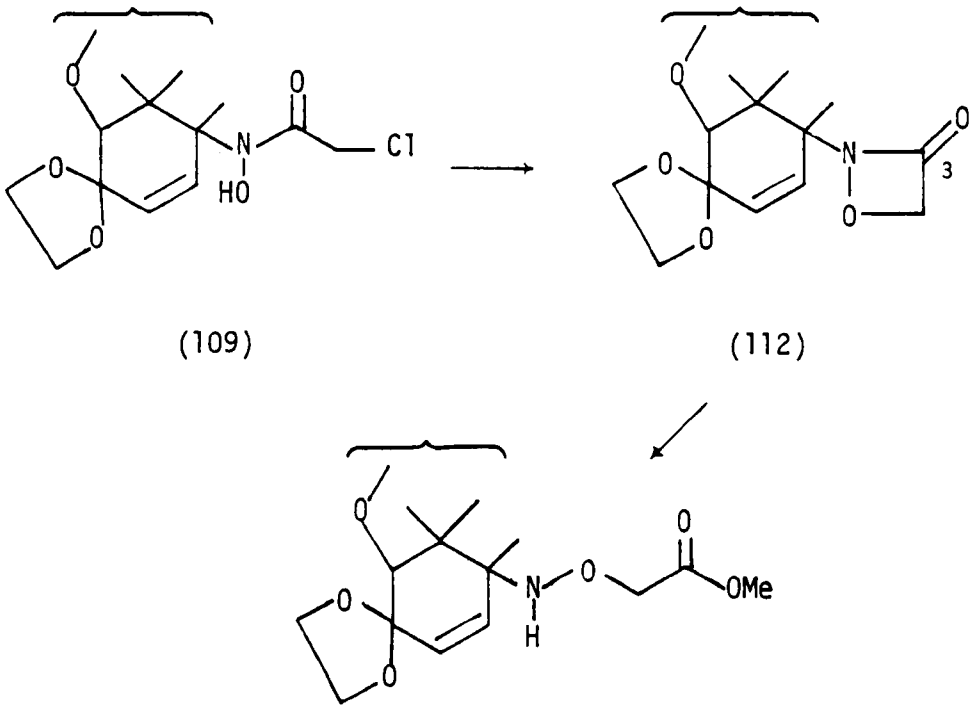


(111)

spectrum gave a molecular ion at *m/z* 444.1899 ($C_{23}H_{28}N_2O_7$) with fragments at *m/z* 413.1698 and 355.1653 corresponding to losses of OMe and OCH_2CO_2Me. The i.r. spectrum showed an ester carbonyl absorption at 1 750 cm^{-1} and the ^1H n.m.r. spectrum showed a singlet at δ3.77 due to the methoxy carbonyl protons and AB doublets at δ4.14 and 4.44 attributed to the OCH_2CO protons.

The mechanism suggested (Scheme XXII) for the formation of the ester (111) from the hydroxamic acid (109) involved the generation of an oxazetidinone intermediate (112). Attack by methoxide at C-3 of (112) followed by cleavage of the amide bond (N-C-3) gave the product (111).

Thus, the change of NCO_2Bu^t to NMe in the alkaloid nucleus was sufficient to alter the reaction course.

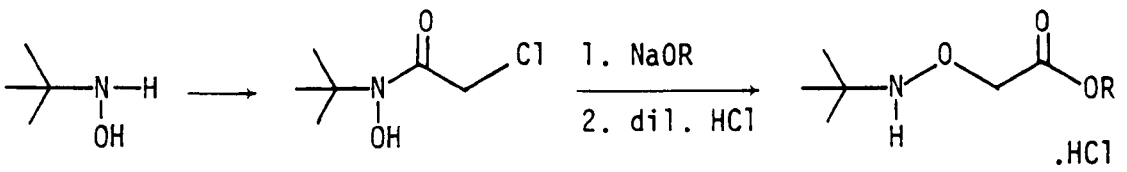


(109) (112)

(111)

SCHEME XXII

Analogous studies with a model α-chlorohydroxamic acid also yielded ester products (Scheme XXIII). α-Chloro-*N*-t-butylaceto-hydroxamic acid (113) was prepared from *N*-t-butylhydroxylamine using the one-pot procedure. The hydroxamic acid (113) was treated with sodium methoxide in methanol at room temperature for 2 h. Dilute hydrochloric acid was added, the solvent evaporated *in vacuo*, and extraction of the resulting residue afforded the methyl ester hydrochloride (114a) in 62% yield. The reaction was repeated in methanol-d_4 in an n.m.r. tube. Figure 7 is a schematic representation of the changes which took place in the ^1H n.m.r. spectrum as sodium deuteriomethoxide was added. Spectrum b, recorded after the addition of



(90) (113) (114)

a; R = Me

b; R = Et

SCHEME XXIII

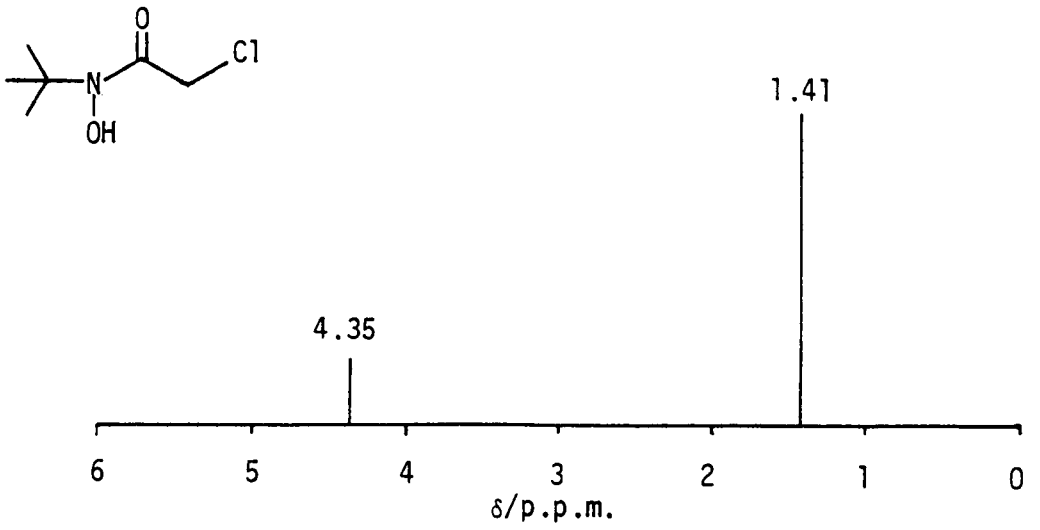
0.75 mol equiv. of base, showed signals corresponding to the starting material (δ1.41) and the product (δ1.07 and 4.27). The transitory signals at δ1.35 and 4.41 were attributed to the intermediate. The origin of the extra peak at δ5.14 remains obscure. Further addition of base caused a small peak at δ1.12 to appear in the spectrum but it was not established whether this was due to the t-butyl protons of t-butylamine, the other conceivable product.

Treatment of the hydroxamic acid (113) with sodium ethoxide followed by a similar work-up to the above gave a 72% yield of the ethyl ester hydrochloride (114b). A satisfactory elemental analysis of this compound was not obtained and it was assumed that (114b) was slightly hygroscopic.

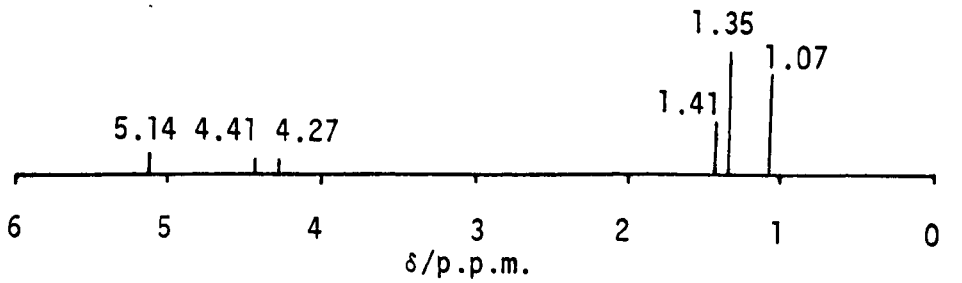
Thus it appears that the preferred mode of oxazetidinone ring opening is by cleavage of the N-C-3 bond. The alternative pathway, *viz.* cleavage of the N-O bond, suggested to account for the 14β-aminonorcodeinone (68) may be a result of the bulky t-butoxycarbonyl group in (56) preventing the approach of methoxide to C-3.

The later part of this mechanism (see Scheme XX) involves

(a) 0 mol equiv. of $NaOCD_3$



(b) 0.75 mol equiv. of $NaOCD_3$



(c) 1.1 mol equiv. of $NaOCD_3$

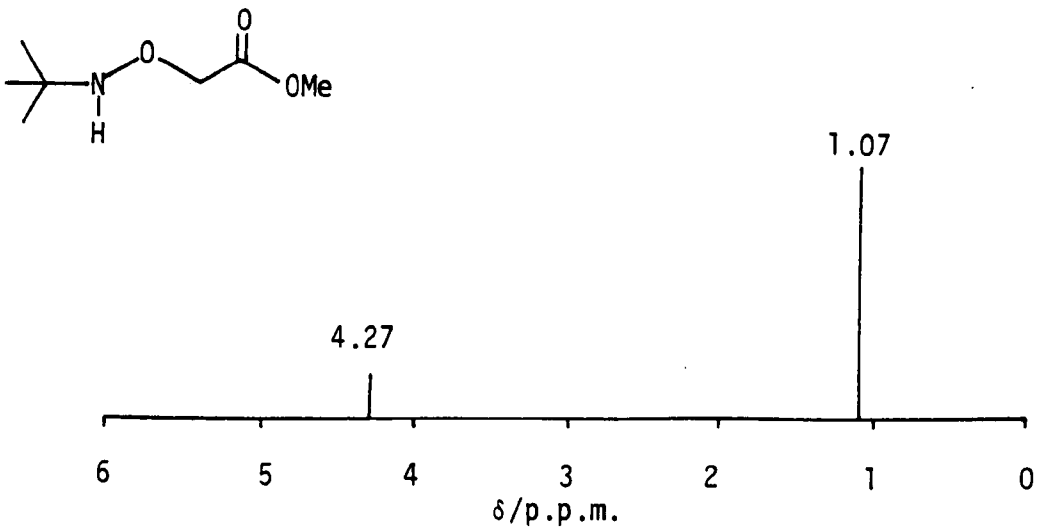
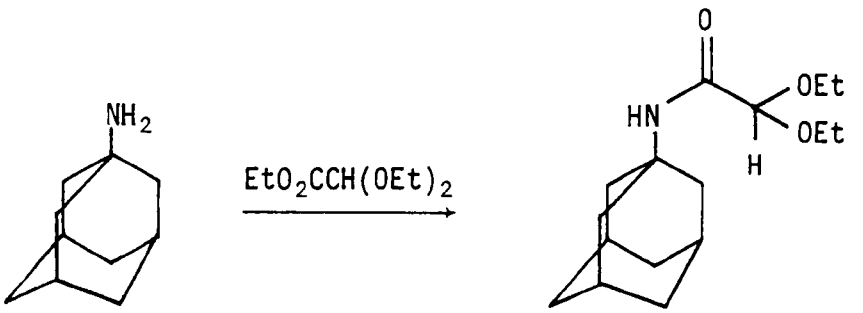
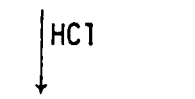


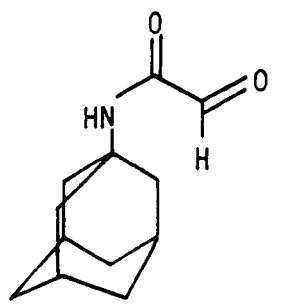
FIGURE 7

hydrolysis of a glyoxalamide to an amine. In order to investigate this process further, the synthesis (Scheme XXIV) of the model compound (117) was undertaken. The adamantylamide (116) was prepared in 72% yield from 1-aminoadamantane (115) and ethyl diethoxyacetate.



(115) (116)



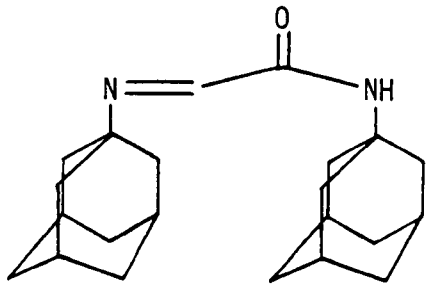


(117)

SCHEME XXIV

An attempt to hydrolyse the diethyl acetal of (116) with dilute hydrochloric acid in methanol gave a low yield of a white powder. The ^{1}H n.m.r. spectrum of this material showed a sharp singlet at $\delta 9.12$ which integrated as less than one proton. The mass spectrum indicated that the white powder was in fact a mixture of the

glyoxalamide (117) (*m/z* 207.1256, $C_{12}H_{17}NO_2$) and the Schiff base (118) (*m/z* 340.2512, $C_{22}H_{32}N_2O$). Thus it appeared that initially the desired compound (117) was formed but it then reacted further with the product of further hydrolysis, 1-aminoadamantane, to give the Schiff base.



(118)

CHAPTER 6

EXPERIMENTAL

Instrumentation and General Notes

Melting points were determined on a Reichert Kofler hot-stage apparatus. I.r. spectra were recorded on either a Perkin-Elmer 580 or 257 spectrometer and u.v. spectra on a Pye-Unicam SP 8-100 spectrometer. ^{1}H n.m.r. spectra were recorded at 90 MHz on a Perkin-Elmer R32 instrument and, where stated, at 250 MHz on a Brücker W.M. 250 instrument. ^{13}C n.m.r. spectra were recorded at 25.2 MHz on a Varian XL-100 spectrometer; chemical shifts in both cases are quoted as p.p.m. downfield from tetramethylsilane. Low resolution mass spectra were recorded at 70 eV on an A.E.I. M.S. 12 instrument and high resolution spectra on an A.E.I. M.S. 9 instrument coupled to a GEC-905 computer for data capture and processing. Optical rotations were recorded on an Optical Activity AA-100 polarimeter.

Preparative plate chromatography was carried out on Merck GF254 silica with detection of compounds by u.v. light. Column chromatography was carried out on Merck silica HF254 under reduced pressure using the method of Targett *et al.*[73] and on CAMAG M.F.C. neutral alumina Brockmann activity 1. Organic solutions were dried over anhydrous magnesium sulphate and evaporated on a rotary evaporator at *ca.* 50°C at 15 mm Hg unless otherwise stated. Petroleum ether refers to the fraction b.p. 60-80°C and ether refers to diethyl ether. Elemental analyses were carried out by the microanalytical service, Chemistry Department, Glasgow.

Dihydrothebaine-ϕ (26). - The procedure of Bentley *et al.*[23] using thebaine (6.22 g) and sodium (1.43 g) gave dihydrothebaine-ϕ (5.64 g, 90%). A sample was recrystallised from ethyl acetate - light petroleum, m.p. 151-153°C (lit.,[23] 154°C).

Dihydrothebaine-ϕ 4-Phenyl Ether (30). - The procedure of Sawa *et al.*[27] was followed and afforded, from dihydrothebaine-ϕ (3.13 g) and bromobenzene (3.12 g), dihydrothebaine-ϕ 4-phenyl ether which crystallised from isopropanol (2.15 g, 55%), m.p. 137-138°C (lit.,[27] 135-136°C).

Deoxydihydrothebaine-ϕ (28). - The procedure of Sawa *et al.*[27] using dihydrothebaine-ϕ 4-phenyl ether (1.01 g) and sodium (0.18 g) gave deoxydihydrothebaine-ϕ (0.61 g, 88%) as an oil.

β-Dihydrothebaine (27). - Sodium (4.51 g, 196 mmol) and a few crystals of hydrated ferric nitrate were added with stirring to dry liquid ammonia (*ca.* 250 ml). After *ca.* 30 min sodamide had formed. Thebaine (20.1 g, 64.6 mmol) was added followed by sodium (4.51 g, 196 mmol) and the mixture was stirred for 3 h at -33°C. After evaporation of the liquid ammonia, ethanol (25 ml) and water (275 ml) were added and the mixture filtered. Addition of solid carbon dioxide to the filtrate precipitated the products which were extracted into chloroform (4 x 100 ml). The combined extracts were washed with water, dried, and evaporated. The resultant brown oil was filtered through an alumina column [200 g, methanol-chloroform (1:19)]. Fractional crystallisation of the concentrated eluate from light petroleum-ethyl acetate yielded β-dihydrothebaine (8.56 g, 42%). N.m.r. spectroscopy showed this to be contaminated with dihydrothebaine-ϕ (*ca.* 20%).

β-Dihydrothebaine 4-Phenyl Ether (31). - β-Dihydrothebaine (6.19 g, 20 mmol), bromobenzene (6.38 g, 40 mmol), finely powdered anhydrous potassium carbonate (4.34 g, 31 mmol), and precipitated copper metal (0.64 g, 10 mmol) were refluxed with stirring in dry pyridine (100 ml) for 6 h. The mixture was filtered while still hot and the residue washed with hot pyridine. The filtrate was evaporated and the residual pyridine removed by azeotroping with toluene (4 x *ca.* 20 ml). The residue was dissolved in benzene, filtered, washed with water, dried, and evaporated. The resultant brown gum was purified by column chromatography on alumina (150 g) with methanol-chloroform (1:49) as eluant to afford *β-dihydrothebaine 4-phenyl ether* (4.48 g, 58%) as a dark viscous oil (Found: M^+, 389.1982. $C_{25}H_{27}NO_3$ requires M, 389.1991); δ($CDCl_3$) 2.33(3H,s,NMe), 3.47 (3H, s, 6-OMe), 3.59 (3H, s, 3-OMe), 4.79 (1H, brd, J_{8-H} 7 Hz, 7-H), 5.76 (1H, d, J_{7-H} 7 Hz, 8-H), and 6.65-7.40 (7H, m, aryl-H).

Attempted Reduction of β-Dihydrothebaine 4-Phenyl Ether (31) *with Sodium in Liquid Ammonia.* - A solution of β-dihydrothebaine 4-phenyl ether (150 mg, 0.39 mmol) in toluene (1.5 ml) was added to dry liquid ammonia (*ca.* 25 ml) at -50°to -55°C. Sodium (45 mg, 2 mmol) was added and the solution went orange. After stirring for 1 h a small amount of ammonium chloride was added to the mixture, the liquid ammonia was evaporated and water (10 ml) was added. The solution was extracted with ether (2 x 10 ml) and the combined extracts were washed with 5% sodium hydroxide solution (2 x 10 ml) and water (10 ml), dried, and evaporated to yield a yellow oil (79 mg). T.l.c. on silica [methanol-chloroform (1:1)] indicated that several products had formed.

Attempted Isomerisation of Deoxydihydrothebaine-ϕ (28) *with Dichloromaleic Anhydride.* - Deoxydihydrothebaine-ϕ (110 mg, 0.37 mmol) and dichloromaleic anhydride[30] (10 mg, 0.06 mmol) were refluxed in toluene (10 ml) for 2 h. After cooling, ether (20 ml) was added and the solution washed with 5% sodium hydroxide solution (2 x 10 ml) and water (10 ml), dried, and evaporated to yield unreacted starting material (90 mg), identified by n.m.r. spectroscopy.

Attempted Isomerisation of Deoxydihydrothebaine-ϕ (28) *with Sodamide.* - Deoxydihydrothebaine-ϕ (199 mg, 0.67 mmol) in toluene (2 ml) was added to sodamide [prepared from sodium (75 mg, 3.2 mmol)] in dry liquid ammonia (*ca.* 50 ml). After stirring for 90 min at -33°C the liquid ammonia was evaporated and water (30 ml) added. The solution was extracted with ether (2 x 30 ml) and the combined extracts were washed with 5% sodium hydroxide solution (2 x 30 ml) and water (30 ml), dried, and evaporated to give a yellow oil (128 mg). N.m.r. spectroscopy suggested that isomerisation could have occurred.

Attempted Trapping of the Sodamide Isomerisation Product with Nitrosocarbonylbenzene. - The foregoing isomerisation product (128 mg) in ethyl acetate (10 ml) and sodium periodate (138 mg, 0.65 mmol) in aqueous sodium acetate (0.2M, adjusted to pH 6 with concentrated hydrochloric acid) (5 ml) were stirred rapidly at 0°C. Benzohydroxamic acid[41] (90 mg, 0.66 mmol) was added slowly over 10 min, then rapid stirring was continued for 2 h. The mixture was basified with aqueous sodium hydrogen carbonate and the layers separated. The aqueous layer was extracted with ethyl acetate (2 x 10 ml) and the combined ethyl acetate layers were washed with aqueous sodium thiosulphate (2 x 10 ml) and water (10 ml), dried, and evaporated to a yellow gum (186 mg). T.l.c. on silica [methanol-chloroform (1:9)] and n.m.r. examination of the residue indicated that several products had been formed, none of which was identified.

6β,14β-(N-3-*Phenylpropanoylepoxyimino*)-5,6,14-O-*tetrahydrothebaine Phenyl Ether* (33; R = CH_2CH_2Ph). - β-Dihydrothebaine 4-phenyl ether (1.95 g, 5 mmol) in ethyl acetate (100 ml) and sodium periodate (1.61 g, 7.5 mmol) in aqueous sodium acetate (0.2M, adjusted to pH 6 with concentrated hydrochloric acid) (50 ml) were rapidly stirred at 0 C. Dihydrocinnamohydroxamic acid[41] (1.24 g, 7.5 mmol) in ethyl acetate (5 ml) was added slowly over 10 min, then rapid stirring was continued for 1 h. The mixture was basified with aqueous sodium hydrogen carbonate and the layers separated. The aqueous layer was extracted with ethyl acetate (2 x 50 ml) and the combined ethyl acetate layers were washed with 5% aqueous sodium thiosulphate (2 x 50 ml) and water (50 ml), dried, and evaporated to yield the *cycloadduct* (33; R = CH_2CH_2Ph) which crystallised as granules from ethyl acetate (1.30 g, 47%), m.p. 136-138°C (Found: C, 73.70; H, 6.76; N, 4.98; M^+, 522. $C_{34}H_{36}N_2O_5$ requires C, 73.89; H, 6.57; N, 5.07%; M, 522); ν_{max}(KBr) 1 685 cm^{-1}; δ($CDCl_3$) 2.39 (3H, s, NMe), 3.28 (3H, s, 6-OMe), 3.63 (3H, s, 3-OMe), 4.55 (1H, m, 9-H), 6.21 (1H, d, J_{8-H} 7 Hz, 7-H), and 6.65-7.40 (13H, m, aryl-H and 8-H).

Ethylene Acetal of 14β-(N-3-*Phenylpropanoylhydroxyamino*)*thebainone Phenyl Ether* (34; R = CH_2CH_2Ph). - The cycloadduct (33; R = CH_2CH_2Ph) (552 mg, 1 mmol) in dry methylene chloride (5 ml) was treated with anhydrous hydrogen chloride in ethylene glycol (0.3M; 15 ml). The reaction mixture was stirred at room temperature for 90 min, then basified with solid sodium hydrogen carbonate followed by saturated sodium hydrogen carbonate solution and water. The mixture was extracted with chloroform (4 x 10 ml) and the combined extracts were washed with brine (2 x 10 ml) and water, dried, and evaporated. The resulting oily solid consisted of the thebainone ethylene acetal and the thebainone (35; R = CH_2CH_2Ph, *cf.* p.90). The thebainone was precipitated by the addition of ethyl acetate and filtered off (255 mg, 42%). The filtrate

yielded the *ethylene acetal* (34; R = CH_2CH_2Ph) (270 mg, 46%) as a foam (Found: M^+, 582.2720. $C_{35}H_{38}N_2O_6$ requires M, 582.2730); ν_{max} 3 290 and 1 655 cm^{-1}; $\delta(CDCl_3)$ 2.36 (3H, s, NMe), 3.64 (3H, s, OMe), 3.55-4.05 (4H, m, OCH_2CH_2O), 4.15 (1H, m, 9-H), 5.74 (1H, d, J_{8-H} 10 Hz, 7-H), 6.65-7.45 (13H, m, aryl-H and 8-H), and 7.55 (1H, br s, OH).

Ethylene Acetal of 14β-(3-Phenylpropanoylamino)thebainone Phenyl Ether (35; R = CH_2CH_2Ph). - The ethylene acetal (34; R = CH_2CH_2Ph) (378 mg, 0.65 mmol) was dissolved in dry pyridine (10 ml). Dry sulphur dioxide was slowly bubbled through the solution for 30 min and then the solution was heated under reflux for 1 h. The mixture was cooled, diluted with sodium hydrogen carbonate solution and extracted with chloroform (4 x 10 ml). The combined extracts were dried and evaporated and the residual pyridine removed by azeotroping with toluene (4x). The residue was chromatographed on silica plates [methanol-chloroform (1:9)] to afford the *ethylene acetal* (35; R = CH_2CH_2Ph) (R_F 0.60) (112 mg, 30%) as a foam (Found: M^+, 566.2775. $C_{33}H_{38}N_2O_5$ requires M, 566.2781); ν_{max}(KBr) 1 670 cm^{-1}; $\delta(CDCl_3)$ 2.30 (3H, s, NMe), 3.65 (3H, s, OMe), 3.84 (4H, m, OCH_2CH_2O), 5.52 (1H, br s, NH), 5.14 (1H, d, J_{8-H} 11 Hz, 7-H), and 6.55-7.40 (13H, m, aryl-H and 8-H).

Attempted Reduction of Ethylene Acetal (35; R = CH_2CH_2Ph) with Lithium Aluminium Hydride. - The foregoing ethylene acetal (35; R = CH_2CH_2Ph) (83 mg, 0.15 mmol) in dry tetrahydrofuran (THF) (2 ml) was slowly added to lithium aluminium hydride (35 mg, 0.92 mmol) in dry THF (5 ml) under nitrogen. After being refluxed for 1 h the reaction mixture was cooled and quenched by the cautious dropwise addition of water and sodium hydroxide solution. Excess water was removed with anhydrous magnesium sulphate and the mixture was filtered through cellite and evaporated. The i.r. spectrum of the residue indicated that starting material was present.

14β-(N-3-*Phenylpropanoylhydroxyamino)thebainone Phenyl Ether* (36). - The cycloadduct (33; R = CH_2CH_2Ph) (55 mg, 0.1 mmol) in methanol (5 ml) containing 5M hydrochloric acid (3 ml) was heated at 60°C for 30 min. The mixture was basified with sodium hydroxide solution and extracted with chloroform (4 x 3 ml). The combined extracts were washed with water (3 ml), dried, and evaporated to yield the *thebainone* (36) which crystallised from ethanol as cuboids (24 mg, 45%), m.p. 241-242.5°C (Found: C, 73.46; H, 6.13; N, 5.30; M^+, 538.2464. $C_{33}H_{34}N_2O_5$ requires C, 73.58; H, 6.36, N, 5.20%; M, 538.2468); ν_{max}(KBr) 3 280, 1 670 (sh), and 1 655 cm^{-1}; δ[$(CD_3)_2SO$] 2.26 (3H, s, NMe), 3.54 (3H, s, OMe), 3.86 (1H, m, 9-H), 5.84 (1H, d, J_{8-H} 9 Hz, 7-H), 6.70 (1H, d, J_{7-H} 9 Hz, 8-H), 6.85-7.45 (12H, m, aryl-H), and 9.32 (1H, br s, exchangeable with D_2O, OH).

14β-(3-*Phenylpropanoylamino)thebainone Phenyl Ether* (37). - The thebainone (36) (190 mg, 0.35 ml) was dissolved in dry pyridine (10 ml). Dry sulphur dioxide was slowly bubbled through the solution for 30 min and then the solution was heated under reflux for 90 min. The mixture was cooled, diluted with sodium hydrogen carbonate solution, extracted with chloroform (4 x 5 ml), and the extracts were dried and evaporated. The residue was filtered through an alumina column (10 g) with chloroform as eluant to yield the *thebainone* (37) which crystallised from ethyl acetate as fine needles (113 mg, 61%), m.p. 223-224°C (Found: C, 75.60; H, 6.37; N, 5.44; M^+, 522. $C_{33}H_{34}N_2O_4$ requires C, 75.84; H, 6.56; N, 5.36%; M, 522); ν_{max}(KBr) 1 670 cm^{-1}; δ($CDCl_3$) 2.34 (3H, s, NMe), 3.67 (3H, s, OMe), 5.67 (1H, br s, NH), 6.00 (1H, d, J_{8-H} 10 Hz, 7-H), 6.60-7.40 (12H, m, aryl-H), and 7.55 (1H, d, J_{7-H} 10 Hz, 8-H).

β-Dihydrothebaine 4-(1-Phenyltetrazol-5-yl) Ether (39). - β-Dihydrothebaine (3.13 g, 10 mmol), 5-chloro-1-phenyltetrazole (3.61 g, 20 mmol), and finely ground anhydrous potassium carbonate (5.52 g, 40 mmol) in anhydrous acetone (50 ml) were refluxed with stirring for 4 days. After cooling, the solution was filtered and evaporated and the residue chromatographed on silica (145 g) under reduced pressure. The fractions eluted with 0-5% methanol-chloroform contained excess reagent. The fractions eluted with 10% methanol-chloroform afforded the *phenyltetrazolyl ether* (39) (2.63 g, 58%) as a pale yellow foam (Found: M^+, 457.2101. $C_{26}H_{27}N_5O_3$ requires M, 457.2114); δ($CDCl_3$) 2.39 (3H, s, NMe), 3.47 (3H, s, 6-OMe), 3.64 (3H, s, 3-OMe), 4.83 (1H, br d, J_{8-H} 6 Hz, 7-H), 5.82 (1H, d, J_{7-H} 6 Hz, 8-H), 6.82 (1H, d, J_{2-H} 9 Hz, 1-H), 7.04 (1H, d, J_{1-H} 9 Hz, 2-H), and 7.40-8.00 (5H, m, Ph).

6β,14β-(N-3-Phenylpropanoylepoxyimino)-5,6,14,0-tetrahydrothebaine 1-Phenyltetrazol-5-yl Ether (40). - The β-dihydrothebaine (39) (1.144 g, 2.5 mmol) in ethyl acetate (50 ml) and sodium periodate (0.803 g, 3.75 mmol) in aqueous sodium acetate (0.2M, adjusted to pH 6 with concentrated hydrochloric acid) (30 ml) were stirred rapidly at 0°C. Dihydrocinnamohydroxamic acid (0.619 g, 3.75 mmol) in ethyl acetate (6 ml) was added slowly over 12 min, then rapid stirring was continued for 1 h. The mixture was basified with aqueous sodium hydrogen carbonate and the layers separated. The aqueous layer was extracted with ethyl acetate (2 x 25 ml) and the combined ethyl acetate layers were washed with 5% aqueous sodium thiosulphate (2 x 25 ml) and water (25 ml), dried, and evaporated to yield the *cycloadduct* (40) which crystallised from ethanol as fine needles (0.717 g, 46%), m.p. 185-186.5°C (Found: C, 67.90; H, 5.85; N, 13.44; M^+, 620.2746. $C_{35}H_{36}N_6O_5$ requires C, 67.72; H, 5.86; N, 13.54%; M, 620.2747); ν_{max}(KBr) 1 685 cm^{-1}; δ($CDCl_3$) 2.40 (3H, s, NMe), 3.37 (3H, s, 6-OMe), 3.63 (3H, s, 3-OMe), 4.56 (1H, m, 9-H), 6.23 (1H, d, J_{8-H} 8 Hz, 7-H), and 6.75-7.95 (13H, m, aryl-H and 8-H).

14β-(N-3-*Phenylpropanoylhydroxyamino)thebainone* 1-*Phenyltetrazol*-5-*yl Ether* (41). - The cycloadduct (40) (192 mg, 0.31 mmol) in methanol (25 ml) containing 5M hydrochloric acid (15 ml) was heated at 60°C for 30 min. The residue was basified with sodium hydroxide solution and extracted with chloroform (4 x 10 ml). The combined extracts were washed with water, dried, and evaporated. The residue was chromatographed on silica plates [methanol-chloroform (1:9)] to afford the *thebainone* (41) (R_f 0.66) (96 mg, 51%) as a foam (Found: M^+, 606.2626. $C_{34}H_{34}N_6O_5$ requires M, 606.2590); ν_{max}(KBr) 1 660 and 1 650 cm^{-1}; δ($CDCl_3$) 2.35 (3H, s, NMe), 3.66 (3H, s, OMe), 4.34 (1H, m, 9-H), 6.08 (1H, d, J_{8-H} 11 Hz, 7-H), and 6.80-7.95 (13H, m, aryl-H and 8-H).

14β-(3-*Phenylpropanoylamino)thebainone* 1-*Phenyltetrazol*-5-*yl Ether* (42). - The thebainone (41) (150 mg, 0.25 mmol) was dissolved in dry pyridine (10 ml). Dry sulphur dioxide was slowly bubbled through the solution for 30 min and then the solution was heated under reflux for 90 min. The mixture was cooled, diluted with sodium hydrogen carbonate solution, extracted with chloroform (4 x 5 ml), and the extracts were dried and evaporated. The residue was chromatographed on silica plates to give the *thebainone* (42) (R_f 0.64) (74 mg, 51%) as a foam (Found: M^+, 590.2612. $C_{34}H_{34}N_6O_4$ requires M, 590.2641); ν_{max}(KBr) 1 665 and 1 650 (sh) cm^{-1}; δ($CDCl_3$) 2.30 (3H, s, NMe), 3.62 (3H, s, OMe), 3.78 (1H, br d, $J_{10\alpha-H}$ 6 Hz, 9-H), 5.94 (1H, d, J_{8-H} 10 Hz, 7-H), 6.20 (1H, br s, NH), and 6.80-7.90 (13H, m, aryl-H and 8-H).

Attempted hydrogenolyses of the Phenyltetrazolyl Ethers.- Attempts were made to carry out hydrogenolysis of the cycloadduct (40) and the thebainones (41) and (42). The experiments done are outlined in Table 7. Each experiment yielded only starting material which was identified by its n.m.r. spectrum.

TABLE 7

Expt.	Cmpd. No.	Solvent	Catalyst	Pressure
A	40	ethanol-THF (1:1)	5% Pd-C	atmospheric
B	40	ethyl acetate	5% Pd-C	atmospheric
C	41	ethyl acetate	5% Pd-C	atmospheric
D	42	ethyl acetate	5% Pd-C	atmospheric
E	42	ethyl acetate	10% Pd-C	atmospheric
F	42	ethanol	10% Pd-C	10 atmospheres

In experiments A, E, and F the weight of catalyst used was equivalent to one-tenth that of the starting material and in experiments B, C, and D two to four times this amount was used. The general procedure is demonstrated in the following example (experiment F). The thebainone (42) (85 mg, 0.14 mmol) in dry ethanol (8 ml) was hydrogenated at 10 atm. for 4.5 h with 10% palladium-charcoal catalyst (8.5 mg). The mixture was filtered through cellite and the filtrate concentrated.

Northebaine Hydrochloride. - The procedure of R.I. Gourlay,[14] a modification of the method of E. Lilley and Co.[39] was followed. Thus, thebaine (15.5 g, 50 mmol) and ethyl azodicarboxylate (9.57 g, 55 mmol) were heated under reflux in benzene (100 ml) for 3 h. The solvent was evaporated to yield the intermediate *N*-(1,2-diethoxycarbonylhydrazinomethyl)northebaine as an oil. This material was dissolved in ethanol (100 ml), water (75 ml), and ammonium hydroxide (sp. g. 0.88, 50 ml) and heated under reflux for 5 h, then left at room temperature overnight. The solution was extracted with methylene chloride (4 x 50 ml) and the extracts were dried and evaporated to yield a brown oil. This oil was dissolved in refluxing ethyl acetate (100 ml) and, on cooling, the by-product urethane precipitated which was removed by filtration. The

filtrate was evaporated and the residue dissolved in methanol and treated with 10% methanolic hydrogen chloride (22 ml) until the solution was just acidic. Northebaine hydrochloride precipitated from the solution (9.80 g, 59%). A sample was recrystallised from water, m.p. 269-271 °C (decomp.) [lit.,[39] 270-272 °C (decomp.)].

N-*Ethoxycarbonylmethylnorthebaine* (50). - Northebaine (0.684 g, 2.3 mmol), ethyl chloroacetate (0.27 ml, 2.5 mmol), and finely ground anhydrous potassium carbonate (1.273 g, 9.2 mmol) were heated under reflux in acetone (20 ml) for 20 h. The mixture was cooled and filtered and the filtrate evaporated. The residue was chromatographed on a column of alumina [15 g, toluene-chloroform (1:1)] to afford N-*ethoxycarbonylmethylnorthebaine* (0.682 g, 77%) as an oil (Found: M^+, 383.1738. $C_{22}H_{25}NO_5$ requires M, 383.1733); $\nu_{max}(CHCl_3)$ 1 745 cm^{-1}; $\delta(CDCl_3)$ 1.24 (3H, t, J_{CH_2} 7 Hz, CH_3), 3.40 (2H, s, CH_2CO), 3.56 (3H, s, 6-OMe), 3.82 (3H, s, 3-OMe), 4.19 (2H, q, J_{CH_3} 7Hz, CH_2CH_3), 5.00 (1H, d, J_{8-H} 7 Hz, 7-H), 5.24 (1H, s, 5-H), 5.53 (1H, d, J_{7-H} 7Hz, 8-H), 6.55 (1H, d, J_{2-H} 8 Hz, 1-H), and 6.66 (1H, d, J_{1-H} 8 Hz, 2-H).

N-*Hydroxyaminocarbonylmethylnorthebaine* (51). - Sodium hydroxide solution (10M, 0.17 ml, 1.7 mmol) was added to a stirred solution of hydroxylamine hydrochloride (59 mg, 0.85 mmol) in water (0.5 ml) and ethanol (0.5 ml) at 0°C. The solution was warmed to room temperature, *N*-ethoxycarbonylmethylnorthebaine (172 mg, 0.45 mmol) in ethanol (0.5 ml) was added dropwise and the solution was stirred for a further 2.5 h. The reaction mixture was acidified to pH 5.8 with 5% hydrochloric acid and the solvent was evaporated. The residue was treated with water, extracted with chloroform (4 x 5 ml) and the combined extracts were dried and evaporated. The residue was chromatographed on silica plates [methanol-chloroform (1:9)] to yield N-*hydroxyaminocarbonylmethylnorthebaine* (59 mg. 36%) as a foam (Found: M^+, 370.1546. $C_{20}H_{22}N_2O_5$ requires M, 370.1529); ν_{max} $(CHCl_3)$ 3 385 and 1 675 cm^{-1}; $\delta(CDCl_3)$ 3.60 (3H, s, 6-OMe),

3.84 (3H, s, 3-OMe), 5.02 (1H, d, J_{8-H} 7 Hz, 7-H), 5.27 (1H, s, 5-H), 5.55 (1H, d, J_{7-H} 7 Hz, 8-H), 6.18 (2H, br s, exchangeable with D_2O, OH and NH), and 6.63 (2H, br s, 1-H and 2-H).

Attempted Oxidative Cyclisation of N-*Hydroxyaminocarbonylmethylnorthebaine to* (52). - *N*-Hydroxyaminocarbonylmethylnorthebaine (30 mg, 0.08 mmol) in ethyl acetate (0.5 ml) was added to a stirred solution of sodium periodate (26 mg, 0.12 mmol) in aqueous sodium acetate (0.2M, adjusted to pH 6 with concentrated hydrochloric acid) (1 ml) at 0°C. The cooling bath was removed, the mixture was stirred for 3 h and then basified with aqueous sodium hydrogen carbonate. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 2 ml) and the combined ethyl acetate layers were washed with 5% aqueous sodium thiosulphate solution (2 x 2 ml) and water (2 ml), dried, and evaporated. T.l.c. on silica indicated that six products had been formed, two of which gave a positive ferric chloride test.

Hydroxylamine.[74,75] - To a stirring suspension of finely pulverised hydroxylamine hydrochloride (17.84 g, 0.26 mmol) in anhydrous ethanol (25 ml) was added sodium ethoxide solution [from sodium (5.76 g, 0.25 mmol) in anhydrous ethanol (100 ml)] dropwise over 4 h. The solution was rapidly filtered and the precipitate washed with a little ethanol. Ether (*ca.* 15 ml) was added to the filtrate and the solution cooled to -78°C. The precipitate hydroxylamine (4.72 g, 56%) was filtered onto a pre-cooled (-78°C) funnel and used immediately.

α-*Chloroacetohydroxamic Acid*.[42] - Ethyl chloroacetate (20 g, 0.16 mmol) was dissolved in anhydrous ethanol (50 ml) and hydroxylamine (4.4 g, 0.13 mmol) was added. The solution was stirred at 0°C for 0.5 h, then for 3 h at room temperature and finally left overnight in the refrigerator. α-Chloroacetohydroxamic acid crystallised from the solution (7.10 g, 40%). A specimen was recrystallised from ethyl acetate, m.p. 77-84°C (lit.,[42] 92-93°C); ν_{max}(KBr) 1 675 cm^{-1}; δ[$(CD_3)_2SO$] 3.95 (2H, s, CH_2), and

7.30 (7H, br s, exchangeable with D_2O); M^+ 111 and 109.

N-t-Butoxycarbonylnorthebaine[43] (49; R = CO_2Bu^t). - Northebaine (2.23 g, 7.5 mmol) was suspended in t-butanol (2.5 ml) and water (5 ml) at room temperature with finely ground anhydrous potassium carbonate (1.306 g, 7.5 mmol). Di-t-butyl dicarbonate (1.08 g, 8.25 mmol) was added slowly. The mixture was stirred for 1.5 h, diluted with water, and extracted with methylene chloride (2 x 50 ml). The combined extracts were washed with water, dried, and evaporated to give *N*-t-butyoxycarbonylnorthebaine which crystallised from methanol (2.41 g, 81%), m.p. 174°C (lit.,[43] 165-166°C); ν_{max}(KBr) 1 690 cm^{-1}; $\delta(CDCl_3)$ 1.45 (9H, s, Bu^t), 3.61 (3H, s, 6-OMe), 3.86 (3H, s, 3-OMe), 5.03 (1H, d, J_{8-H} 7 Hz, 7-H), 5.29 (1H, s, 5-H), 5.59 (1H, d, J_{7-H} 7 Hz, 8-H), 6.56 (1H, d, J_{2-H} 8 Hz, 1-H), and 6.69 (1H, d, J_{1-H} 8 Hz, 2-H).

6β,14β-(N-Chloroacetylepoxyimino)-6,14-dihydro-N-t-butoxycarbonylnorthebaine (53; R = CO_2Bu^t). - *N*-t-Butoxycarbonylnorthebaine (0.990 g, 2.5 mmol) and tetraethylammonium periodate[44] (2.40 g, 7.5 mmol) were stirred in chloroform (100 ml) at 0°C. α-Chloroacetohydroxamic acid (0.821 g, 7.5 mmol) in ethyl acetate (100 ml) was added slowly over 30 min, then stirring was continued for 1 h. The solution was washed with 5% aqueous sodium thiosulphate (2 x 50 ml) and water (50 ml), dried, and evaporated to yield the *cycloadduct* (53; R = CO_2Bu^t) (1.25 g, 99%) which crystallised from chloroform-ethanol as rhomboids, m.p. 178-179°C (Found: C, 59.32; H, 5.89; Cl, 7.38; N, 5.47; M^+, 506.1644, 504.1666. $C_{25}H_{29}ClN_2O_7$ requires C, 59.46; H, 5.79; Cl, 7.03; N, 5.55%; M, 506.1634, 504.1663); ν_{max}(KBr) 1 690 cm^{-1}; $\delta(CDCl_3)$ 1.48 (9H, s, Bu^t), 3.62 (3H, s, 6-OMe), 3.82 (3H, s, 3-OMe), 3.98 and 4.18 (2H, d, d, J 15 Hz, CH_2Cl), 4.61 (1H, s, 5-H), 6.08 (1H, d, J_{8-H} 10 Hz, 7-H), 6.22 (1H, d, J_{7-H} 10 Hz, 8-H), 6.57 (1H, d, J_{2-H} 8 Hz, 1-H), and 6.72 (1H, d, J_{1-H} 8 Hz, 2-H).

14β-Hydroxyamino-N-t-butoxycarbonylnorcodeinone (54). - The cycloadduct (53; R = CO_2Bu^t) (200 mg, 0.4 mmol) was dissolved in hot ethanol and the solution diluted with water. The precipitate was filtered off to give the *norcodeinone* (54) (90 mg, 55%), m.p. 218-219°C (Found: C, 63.46; H, 6.04; N, 6.76; M^+, 414.1783. $C_{22}H_{26}N_2O_6$ requires C, 63.75; H, 6.32; N, 6.76%; M, 414.1791); ν_{max}(KBr) 3 320, 3 260, and 1 680 cm^{-1}; δ[$(CD_3)_2SO$] 1.41 (9H, s, Bu^t), 3.74 (3H, s, OMe), 4.62 (1H, br s, 5-H), 6.06 (1H, br s, exchangeable with D_2O, OH or NH), 6.07 (1H, d, J_{8-H} 12 Hz, 7-H), 6.56 (1H, d, J_{7-H} 12 Hz, 8-H), 6.64 (1H, d, J_{2-H} 8 Hz, 1-H), 6.79 (1H, d, J_{1-H} 8 Hz, 2-H), and 7.71 (1H, br s, exchangeable with D_2O, OH or NH).

5β,14β-Epoxyimino-N-t-butoxycarbonylnorthebainone (55). - To a stirred suspension of the norcodeinone (54) (100 mg, 0.24 mmol) in anhydrous ethanol (2 ml) was added sodium ethoxide solution, prepared from sodium (20 mg, 0.87 mmol) in anhydrous ethanol (2 ml). Stirring was continued for 10 min at room temperature and then the ethanol was evaporated. The residue was dissolved in chloroform, washed with brine (2 x 10 ml) and water (10 ml), dried, and evaporated. The crude product was chromatographed on a silica plate [methanol-chloroform (1:9)] to yield the *phenol* (55) (R_f 0.56) (57 mg, 57%) as a foam (Found: M^+, 414.1796. $C_{22}H_{26}N_2O_6$ requires 414.1791); ν_{max}($CHCl_3$) 3 540, 3 250, and 1 690 cm^{-1}; δ($CDCl_3$) 1.45 (9H, s, Bu^t), 3.81 (3H, s, OMe), 4.92 (1H, br m, 9-H), 5.01 (1H, s, 5-H), 6.05 (1H, dd, J_{8-H} 10 Hz, and J_{5-H} 3 Hz, 7-H), 6.10 (2H, br s, exchangeable with D_2O, NH and OH), 6.65 (2H, s, 1-H and 2-H), and 6.86 (1H, d, J_{7-H} 10 Hz, 8-H).

14β-(N-Chloroacetylhydroxyamino)-N-t-butoxycarbonylnorcodeinone Ethylene Acetal (56). - The cycloadduct (53; R = CO_2Bu^t) (1.251 g, 2.48 mmol) in methylene chloride (10 ml) was treated with anhydrous hydrogen chloride in ethylene glycol (0.3M; 35 ml). The solution was stirred at room temperature for 90 min, then basified with solid sodium

hydrogen carbonate followed by saturated sodium hydrogen carbonate solution and water. The mixture was extracted with chloroform (4 x 50 ml) and the extracts were dried and evaporated. The product was chromatographed under reduced pressure on a silica column (25 g). The fractions eluted with benzene-chloroform (1:1) afforded the *ethylene acetal* (56) as granules, (0.654 g, 49%), m.p. 198.5-199.5°C (from ethanol) (Found: C, 58.54; H, 6.00; Cl, 6.56; N, 5.05; M^+, 536.1741, 534.1750. $C_{26}H_{31}ClN_2O_8$ requires C, 58.36; H, 5.84; Cl, 6.64; N, 5.24%; M, 536.1739, 534.1769); $\nu_{max}(CHCl_3)$ 3 245 and 1 685 cm^{-1}; $\delta(CDCl_3)$ 1.42 (9H, s, Bu^t), 3.85 (3H, s, OMe), 3.95-4.35 (6H, m, OCH_2CH_2O and CH_2Cl), 4.65 (1H, br s, 5-H), 5.70 (1H, br d, J_{8-H} 10 Hz, 7-H), 6.32 (1H, br d, J_{7-H} 10 Hz, 8-H), 6.54 (1H, d, J_{2-H} 8 Hz, 1-H), 6.70 (1H, d, J_{1-H} 8 Hz, 2-H), and 8.50 (1H, s, exchangeable with D_2O, OH).

14β-*Hydroxyamino*-N-*chloroacetylnorcodeinone Ethylene Acetal* (58). - The ethylene acetal (56) (1.27 g, 2.38 mmol) was dissolved in anhydrous ethyl acetate (20 ml). 10% Anhydrous ethyl acetate-hydrogen chloride (20 ml) was added and the solution shaken for 15 min. The reaction mixture was evaporated to dryness, the residue dissolved in chloroform (15 ml), sodium hydrogen carbonate added and the mixture then shaken for *ca.* 5 min. The inorganic material was filtered off and the filtrate evaporated. The residue was chromatographed under reduced pressure on a silica column (20 g). The fractions eluted with methanol-chloroform (1:19) were crystallised from ethyl acetate to afford the *ethylene acetal* (58) as granules, (145 mg, 14%), m.p. 172-174°C (Found: C, 57.70; H, 5.34; Cl, 8.18; N, 6.18; M^+, 434.1267. $C_{21}H_{23}ClN_2O_6$ requires C, 57.99; H, 5.33; Cl, 8.16; N, 6.44%; M, 434.1244); $\nu_{max}(CHCl_3)$ 3 575, 3 430, 3 300, and 1 630 cm^{-1}; $\delta(CDCl_3)$ 3.84 (3H, s, OMe), 4.19 (2H, s, CH_2CO), 3.90-4.30 (4H, m, OCH_2CH_2O), 4.46 (1H, s, 5-H), 5.48 (1H, br m, 9-H), 5.82 (1H, d J_{8-H} 11 Hz, 7-H), 6.12 (1H, d, J_{7-H} 11 Hz, 8-H), 6.58 (1H, d, J_{2-H} 8 Hz, 1-H), and 6.72 (1H, d, J_{1-H} 8 Hz, 2-H).

Alternative Preparation of 14β-Hydroxyamino-N-chloroacetylnorcodeinone Ethylene Acetal (58). - The cycloadduct (53; R = CO_2Bu^t) (1 g, 2 mmol) in anhydrous methylene chloride (10 ml) was treated with anhydrous hydrogen chloride in ethylene glycol (0.3M; 35 ml). The solution was stirred at room temperature for 90 min, then basified with solid sodium hydrogen carbonate followed by saturated sodium hydrogen carbonate solution and water. The mixture was extracted with chloroform (4 x 50 ml) and the extracts were dried and evaporated to give the ethylene acetal (58) which crystallised from ethyl acetate (0.321 g, 37%). The m.p. and the n.m.r. spectrum were identical to those obtained in the above route.

6β,14β-*(N-Chloroacetylepoxyimino)-6,14-dihydrothebaine* (59). - Thebaine (1.55 g, 5 mmol) in ethyl acetate (75 ml) and sodium periodate (3.21 g, 15 mmol) in aqueous sodium acetate (0.2M, adjusted to pH 5.8 with concentrated hydrochloric acid) (50 ml) was stirred rapidly at 0°C. α-Chloroacetohydroxamic acid (1.65 g, 15 mmol) was added slowly over 10 min, then rapid stirring was continued for 1 h. The mixture was basified with aqueous sodium hydrogen carbonate and the layers separated. The aqueous layer was extracted with ethyl acetate (2 x 50 ml) and the combined ethyl acetate layers were washed with 5% aqueous sodium thiosulphate (2 x 50 ml) and then water (50 ml). The dried ethyl acetate solution was evaporated to give the crude *cycloadduct* (59) (1.44 g, 69%) as a foam (Found: $[M - HCl]^+$, 382.1525, $[M - MeCl]^+$, 368.1380. $C_{21}H_{23}ClN_2O_5$ requires [M - HCl], 382.1529, [M - MeCl], 368.1372); ν_{max}(KBr) 1 695 cm^{-1}; δ($CDCl_3$) 2.44 (3H, s, NMe), 3.62 (3H, s, 6-OMe), 3.81 (3H, s, 3-OMe), 4.03 and 4.27 (2H, d,d, *J* 15 Hz, CH_2Cl), 4.61 (1H, br s, 5-H), 4.78 (1H, d, $J_{10\alpha\text{-}H}$ 8 Hz, 9-H), 6.11 (2H, br s, 7-H and 8-H), 6.58 (1H, d, $J_{2\text{-}H}$ 9 Hz, 1-H), and 6.71 (1H, d, $J_{1\text{-}H}$ 9 Hz, 2-H).

The Quaternary Ammonium Chloride (60). - The crude cycloadduct (59) (168 mg, 0.4 mmol) was dissolved in ethyl acetate (2 ml) and methanol (2 ml). Scratching induced precipitation of the *quaternary ammonium chloride* (60) which was recrystallised from methanol-ethyl acetate (33 mg, 20%), m.p. 219-220°C (Found: C, 60.18; H, 5.38; Cl, 8.27; N, 6.54; $[M - HCl]^+$, 382.1532, $[M - MeCl]^+$, 368.1352. $C_{21}H_{23}ClN_2O_5$ requires C, 60.21; H, 5.53; Cl, 8.47; N, 6.69%; [M - HCl], 382.1529, [M - MeCl], 368.1372); ν_{max}(KBr) 1 690 cm^{-1}; $\delta[(CD_3)_2SO]$ 3.30 (3H, s, NMe), 3.47 (2H, s, CH_2CO), 3.60 (3H, s, 6-OMe), 3.76 (3H, s, 3-OMe), 4.63 and 5.15 (2H, d,d, J 15 Hz, CH_2CO), 4.91 (1H, br s, 5-H), 6.24 (1H, d, J_{8-H} 9 Hz, 7-H), 6.70 (1H, d, J_{7-H} 9 Hz, 8-H), 6.71 (1H, d, J_{2-H} 8 Hz, 1-H), and 6.90 (1H, d, J_{1-H} 8 Hz, 2-H).

The Quaternary Ammonium Chloride (61). - The crude cycloadduct (59) (184 mg, 0.44 mmol) in methylene chloride (1 ml) was treated with anhydrous hydrogen chloride in ethylene glycol (0.3M; 5 ml). The solution was stirred at room temperature for 90 min, then basified with solid sodium hydrogen carbonate followed by saturated sodium hydrogen carbonate solution and water. The mixture was extracted with methylene chloride (4 x 5 ml) and the combined methylene chloride layers were washed with brine (2 x 5 ml) and water (5 ml), dried, and evaporated to a foam which crystallised from methanol. Recrystallisation from methanol gave the *quaternary ammonium chloride* (61) as the hydrate (77 mg, 38%), m.p. 230-232°C (Found: C, 56.36; H, 5.91; Cl, 7.85; N, 5.62; $[M-HCl]^+ \{-H_2O\}$, 412.1627, $[M-MeCl]^+ \{-H_2O\}$, 398.1496. $C_{22}H_{25}ClN_2O_6.H_2O$ requires C, 56.58; H, 5.83; Cl, 7.60; N, 6.00%; $[M - HCl]\{-H_2O\}$, 412.1634. $[M - MeCl]\{-H_2O\}$, 398.1478); ν_{max}(KBr) 1 680 cm^{-1}; $\delta[(CD_3)_2SO]$ 3.33 (3H, s, NMe), 3.84 (3H, s, OMe), 3.94 (4H, br s, OCH_2CH_2O), 4.82 (1H, s, 5-H), 5.74 (1H, d, J_{8-H} 9 Hz, 7-H), 5.90 (1H, d, J_{7-H} 9 Hz, 8-H), 6.72 (1H, d, J_{2-H} 8 Hz, 1-H), and 6.87 (1H, d, J_{1-H} 8 Hz, 2-H).

14β-(2,2-*Diethoxyethanoylamino*)-N-*t*-*butoxycarbonylnorcodeinone* (69). - The cycloadduct (53; CO_2Bu^t) (504 mg, 1 mmol) was dissolved in anhydrous ethanol (10 ml) and sodium ethoxide solution added (8.44 ml, 4 mol equiv.) [from sodium (108 mg, 4.7 mmol) in anhydrous ethanol (10 ml)]. After stirring for 20 min at room temperature the solvent was evaporated and water was added followed by solid carbon dioxide until pH 8. The aqueous solution was extracted with chloroform (4 x 10 ml) and the extracts were dried and evaporated. The residue was treated with a little ethyl acetate whereupon the *norcodeinone* (69) separated and was recrystallised from ethyl acetate as plates (104 mg, 20%), m.p. 205-206°C (Found: C, 63.70; H, 6.95; N, 5.24; M^+ 528.2484. $C_{28}H_{36}N_2O_8$ requires C, 63.62, H, 6.86; N, 5.30%; M, 528.2471); $\nu_{max}(CHCl_3)$ 3 390, 3 340 (sh), and 1 695 cm^{-1}; $\delta(CDCl_3)$ 1.20 (3H, t, J_{CH_2} 7 Hz, CH_2CH_3), 1.24 (3H, t, J_{CH_2} 7 Hz, CH_2CH_3), 1.47 (9H, s, Bu^t), 3.62 [4H, br dq, J_{CH_3} 7 Hz, $C(CH_2CH_3)_2$], 3.85 (3H, s, OMe), 4.72 [1H, s, $CH(OEt)_2$], 4.84 (1H, br m, 9-H), 5.09 (1H, s, 5-H), 6.22 (2H, s, 7-H and 8-H), 6.61 (1H, d, J_{2-H} 8 Hz, 1-H), and 6.74 (1H, d, J_{1-H} 8 Hz, 2-H); $\delta_C(CDCl_3)$ 15.07 (q), 27.98 (t?), 28.39 (q), 30.10 (t?), 38.20 (d?), 46.60 (s), 53.61 (d), 54.81 (s), 56.88 (q), 62.76 (t), 80.98 (s), 88.13 (d), 98.37 (d), 115.54 (d), 119.43 (d), 123.95 (s), 128.75 (s), 135.33 (d), 138.70 (d), 143.10 (s), 145.07 (s), 155.98 (s), 167.83 (s), and 193.22 (s).

14β-(2,2-*Diethoxyethanoylamino*)-N-*t*-*butoxycarbonylnorcodeine* (70). - To a stirring suspension of the norcodeinone (69) (62 mg, 0.12 mmol) in anhydrous ethanol (2 ml) was added sodium borohydride (5 mg, 0.13 mmol). Stirring was continued for 30 min at room temperature, the solvent was evaporated and water was added. The aqueous mixture was extracted with chloroform (4 x 3 ml) and the extracts were dried and evaporated. The residue was chromatographed on a silica plate [methanol-chloroform (1:9)] to afford the *norcodeine* (70) (R_f 0.61) (46 mg, 74%) as an oil (Found: M^+ 530.2627. $C_{28}H_{38}N_2O_8$ requires M, 530.2628); $\nu_{max}(CHCl_3)$ 3 690, 3 565,

3 420, 3 390, and 1 690 cm^{-1}; $\delta(CDCl_3)$ 1.21 [6H, br t, J_{CH_2} 7 Hz, $CH(OCH_2CH_3)_2$], 1.44 (3H, s, Bu^t), 3.60 [4H, br q, J_{CH_3} 7 Hz, $CH(OCH_2CH_3)_2$], 3.85 (3H, s, OMe), 4.70 [1H, s, $CH(OEt)_2$], 4.95 (2H, br s, 5-H and 6-H), 5.82 (1H, br m, 7-H and 8-H), 6.56 (1H, d, J_{2-H} 8 Hz, 1-H), 6.70 (1H, d, J_{1-H} 8 Hz, 2-H), and 7.00 (1H, br s, NH).

14β-*(2,2-Dimethoxyethanoylamino)norcodeinone* (71). - The norcodeinone (69) (53 mg, 0.1 mmol) in methanol (3 ml) containing concentrated hydrochloric acid (1 ml) and 5M hydrochloric acid (1 ml) was heated at 60°C for 30 min. The solution was basified with sodium hydroxide solution, extracted with chloroform (4 x 5 ml), and the extracts were dried and evaporated to yield the crude *norcodeinone* (71) (8 mg, 20%) which crystallised from ethyl acetate as fine needles, m.p. 169-172°C (Found: M^+, 400.1669. $C_{21}H_{24}N_2O_6$ requires 400.1634); $\nu_{max}(CHCl_3)$ 3 370 and 1 695 cm^{-1}; $\delta(CDCl_3)$ 3.40 (3H, s, $CHOCH_3$), 3.46 (3H, s, CHOMe), 3.84 (3H, s, 3-OMe), 4.62 [1H, s, $CH(OMe)_2$], 4.92 (1H, s, 5-H), 6.18 (2H, s, 7-H and 8-H), 6.55 (1H, d, J_{2-H} 8 Hz, 1-H), 6.70 (1H, d, J_{1-H} 8 Hz, 2-H), and 7.65 (1H, br s, exchangeable with D_2O, NH).

6β,14β-*(N-Phenylacetylepoxyimino)-6,14-dihydrothebaine* (73; R = Ph). - Thebaine (3.11 g, 10 mmol) in ethyl acetate (150 ml) and sodium periodate (3.21 g, 15 mmol) in aqueous sodium acetate (0.2M, adjusted to pH 5.8 with concentrated hydrochloric acid) (100 ml) were stirred rapidly at 0°C. Phenylacetohydroxamic acid[41] (2.27 g, 15 mmol) was added slowly over 15 min, then rapid stirring was continued for 1 h. The mixture was basified with aqueous sodium hydrogen carbonate and the layers separated. The aqueous layer was extracted with ethyl acetate (2 x 100 ml) and the combined ethyl acetate layers were washed with 5% sodium thiosulphate solution (2 x 100 ml), dried, and evaporated to give the cycloadduct (73; R = Ph) which crystallised from methanol-diisopropyl ether (3.83 g, 83%), m.p. 148-149°C (lit.,[14] 146-146.5°C); ν_{max}(KBr) 1 680 cm^{-1}; $\delta(CDCl_3)$ 2.40 (3H, s, NMe), 3.47 (3H, s, 6-OMe), 3.55, 3.81 (2H, d, d, J 16 Hz, CH_2Ph),

3.80 (3H, s, 3-OMe), 4.61 (1H, s, 5-H), 4.84 (1H, d, $J_{10\alpha\text{-}H}$ 7 Hz, 9-H), 5.93 (1H, d, $J_{8\text{-}H}$ 9 Hz, 7-H), 6.11 (1H, d, $J_{7\text{-}H}$ 9 Hz, 8-H), 6.53 (1H, d, $J_{2\text{-}H}$ 7 Hz, 1-H), 6.67 (1H, d, $J_{1\text{-}H}$ 7 Hz, 2-H), and 7.05-7.45 (5H, m, Ph).

14β-(*2-Ethoxy-2-phenylethanoylamino*)*codeinone* (74). - The cycloadduct (73; R = Ph) (93 mg, 0.2 mmol) was dissolved in anhydrous ethanol (2 ml) and sodium ethoxide solution added (0.64 ml, 1 mol equiv.) [from sodium (72 mg, 3.13 mmol) in anhydrous ethanol (10 ml)]. The solution was stirred at room temperature for 30 min, diluted with water, and evaporated to near dryness (at 20°C). Chloroform (5 ml) was added and the solution washed with brine (2 x 5 ml) and water (2 ml), dried, and evaporated to yield the *codeinone* (74) which crystallised from ethanol as granules (36 mg, 38%), m.p. 198-199°C (Found: C, 70.90; H, 6.55; N, 5.97; M^+, 474.2158. $C_{28}H_{30}N_2O_5$ requires C, 70.87; H, 6.37; N, 5.90%; M, 474.2155); $\nu_{max}(CHCl_3)$ 3 370, 3 210, and 1 690 cm^{-1}; $\delta(CDCl_3)$ 1.24 (3H, t, J_{CH_2} 7 Hz, CH_3), 2.47 (3H, s, NMe), 3.54 (2H, q, J_{CH_3} 7 Hz, CH_2), 3.80 (3H, s, OMe), 4.66 (1H, s, 5-H or C*H*Ph), 4.68 (1H, s, 5-H or C*H*Ph), 6.20 (2H, s, 7-H and 8-H), 6.54 (1H, d, $J_{2\text{-}H}$ 7 Hz, 1-H), 6.66 (1H, d, $J_{1\text{-}H}$ 7 Hz, 2-H), 7.25-7.55 (5H, m, Ph), and 7.88 (1H, br s, exchangeable with D_2O, NH).

14β-[*(S)-2-Methoxy-2-phenylethanoylamino*]*codeinone* (75a). - The cycloadduct (73; R = Ph) (93 mg, 0.2 mmol) was dissolved in anhydrous methanol (2 ml) and sodium methoxide solution added (0.75 ml, 1 mol equiv.) [from sodium (61 mg, 2.65 mmol) in anhydrous methanol (10 ml)]. The solution was stirred at room temperature for 16 h, diluted with water, and evaporated to dryness (at 20°C). Chloroform (5 ml) was added and the solution washed with brine (2 x 5 ml) and water (5 ml), dried, and evaporated. The residue was filtered through a short column of silica to give the *codeinone* (75a) which crystallised from ethanol as cuboids (34 mg, 37%), m.p. 178-179°C (Found: C, 70.58; H, 6.12; N, 6.24; M^+, 460.2028. $C_{27}H_{28}N_2O_5$ requires C, 70.42; H, 6.13; N, 6.08%; M, 460.1998);

ν_{max}($CHCl_3$) 3 370 and 1 690 cm^{-1}; δ($CDCl_3$) 2.46 (3H, s, NMe), 3.37 (3H, s, CHO*Me*), 3.80 (3H, s, 3-OMe), 4.54 (1H, s, C*H*Ph), 4.69 (1H, s, 5-H), 6.20 (2H, s, 7-H and 8-H), 6.55 (1H, d, J_{2-H} 8 Hz, 1-H), 6.68 (1H, d, J_{1-H} 8 Hz, 2-H), 7.41 (5H, br s, Ph), and 7.79 (1H, br s, exchangeable with D_2O, NH); δ_C($CDCl_3$) 21.20 (t), 28.17 (t), 42.74 (q), 46.02 (t), 46.13 (s), 54.03 (s), 56.93 (q), 57.26 (q), 62.97 (d), 84.51 (d), 87.90 (d), 115.25 (d), 118.96 (d), 125.01 (s), 126.85 (d), 128.62 (d), 129.64 (s), 135.62 (d), 137.10 (s), 139.96 (d), 142.77 (s), 144.68 (s), 170.51 (s),and 193.84 (s).

(S)-(+)-α-Methoxyphenylacetic Acid. - The procedure of Reeve and Christoffel[61] was followed using (+)-mandelic acid (7.61 g) and dimethyl sulphate (26 ml, 5.5 mol equiv.). (*S*)-(+)-α-Methoxyphenylacetic acid crystallised from ethyl acetate-light petroleum (2.57 g, 31%), m.p. 65-66°C (lit.,[76] 65-66°C); $[\alpha]_D^{25}$ +144.2° (c1 EtOH) (lit.,[76] +150°).

(R)-(-)-α-Methoxyphenylacetic Acid. - The procedure of Reeve and Christoffel[61] was followed using (-)-mandelic acid (7.61 g) and dimethyl sulphate (26 ml, 5.5 mol equiv.). (*R*)-(-)-α-Methoxyphenylacetic acid crystallised from ethyl acetate-light petroleum (2.61 g, 31%), m.p. 65-66°C (lit.,[76] 65-66°C); $[\alpha]_D^{25}$ -148.3° (c1, EtOH) (lit.,[76] -150.7°).

14β-[*(S)-Methoxy-2-phenylethanoylamino*]*codeinone* (75b) *from* 14β-*Aminocodeinone.* - 14β-Aminocodeinone (234 mg, 0.75 mmol) and (*S*)-α-methoxyphenylacetic acid (137 mg, 0.83 mmol) were dissolved in methylene chloride (15 ml). This solution was added to a solution of *NN*-dicyclohexylcarbodiimide (185 mg, 0.9 mmol) in methylene chloride (15 ml) and the reaction mixture was stirred at room temperature for 30 min. Glacial acetic acid (15 drops) was added, the precipitate filtered off and the filtrate concentrated. The residue was treated with acetone, whereupon more of the by-product precipitated and was filtered off. Evaporation of the filtrate afforded the codeinone (75b) which crystallised from ethyl acetate-light petroleum as cuboids (234 mg,

68%), m.p. 178-179°C, mixed m.p. (with 75a) 177-178°C, $[\alpha]_D^{25}$ +65° (c 0.5, EtOH) (Found: C, 70.56; H, 5.97; N, 6.35; M^+, 460.1981. Calc. for $C_{27}H_{28}N_2O_5$: C, 70.42; H, 6.13; N, 6.08%; M, 460.1998); $\nu_{max}(CHCl_3)$ 3 370 and 1 690 cm^{-1}; $\delta(CDCl_3)$ 2.46 (3H, s, NMe), 3.38 (3H, s, CHO*Me*), 3.80 (3H, s, 3-OMe), 4.55 (1H, s, C*H*Ph), 4.68 (1H, s, 5-H), 6.19 (2H, s, 7-H and 8-H), 6.54 (1H, d, J_{2-H} 8 Hz, 1-H), 6.68 (1H, d, J_{1-H} 8 Hz, 2-H), 7.25-7.55 (5H, m, Ph), and 7.75 (1H, br s, NH).

14β-[(R)-*Methoxy-2-phenylethanoylamino*]*codeinone* (78) *from* 14β-*Aminocodeinone*. - 14β-Aminocodeinone (234 mg, 0.75 mmol) and (*R*)-α-methoxyphenylacetic acid (137 mg, 0.83 mmol) were dissolved in methylene chloride (15 ml). This solution was added to a solution of *NN*-dicyclohexylcarbodiimide (185 mg, 0.9 mmol) in methylene chloride (15 ml) and the reaction mixture was stirred at room temperature for 30 min. Work-up as before afforded the *codeinone* (78) which crystallised from ethanol as prisms (291 mg, 84%), m.p. 202-203°C, $[\alpha]_D^{25}$ +94.6° (c 0.5, EtOH) (Found: C, 70.50; H, 6.23; N, 5.91; M^+, 460.2021. $C_{27}H_{28}N_2O_5$ requires C, 70.42; H, 6.13; N, 6.08%; M, 460.1998); $\nu_{max}(CHCl_3)$ 3 260 and 1 690 cm^{-1}; $\delta(CDCl_3)$ 2.44 (3H, s, NMe), 3.43 (3H, s, CHO*Me*), 3.82 (3H, s, 3-OMe), 4.58 (1H, s, C*H*Ph), 4.93 (1H, s, 5-H), 6.06 (2H, s, 7-H and 8-H), 6.56 (1H, d, J_{2-H} 8 Hz, 1-H), 6.69 (1H, d, J_{1-H} 8 Hz, 2-H), 7.32 (5H, s, Ph), and 7.87 (1H, br s, NH).

14β-(N-*2-Phenylethanoylhydroxyamino*)*codeinone* (79). - The cycloadduct (73; R = Ph) (1.15 g, 2.5 mmol) in methanol (50 ml) containing 6M hydrochloric acid (50 ml) was heated at 65°C for 30 min. The solution was basified with sodium hydrogen carbonate and extracted with chloroform (4 x 50 ml). The combined extracts were washed with water (50 ml), dried, and evaporated. The *codeinone* (79) crystallised from chloroform-methanol as the hemi-hydrate (0.453 g, 40%), m.p. 167-169°C (Found: C, 68.82; H, 5.91; N, 6.29; $[M]^+$ {$-\frac{1}{2}H_2O$} , 446.1847. $C_{26}H_{26}N_2O_5.\frac{1}{2}H_2O$ requires C, 68.55; H, 5.97; N, 6.15%; [M] {$-\frac{1}{2}H_2O$}, 446.1842); $\nu_{max}(CHCl_3)$

3 640, 3 580, 3 365, 3 250, 1 690, and 1 645 cm^{-1}; $\delta(CDCl_3)$ 2.45 (3H, s, NMe), 3.70 (1H, br d, $J_{10\alpha\text{-}H}$ 5 Hz, 9-H), 3.82 (5H, s, OMe and CH_2Ph), 5.03 (1H, s, 5-H), 6.12 (1H, br s, exchangeable with D_2O, OH), 6.14 (2H, s, 7-H and 8-H), 6.56 (1H, d, $J_{2\text{-}H}$ 8 Hz, 1-H), 6.68 (1H, d, $J_{1\text{-}H}$ 8 Hz, 2-H), and 7.28 (5H, s, Ph).

5β,14β-*(N-Phenylacetylepoxyimino)thebainone* (81). - To a stirred suspension of the codeinone (79) (61 mg, 0.13 mmol) in anhydrous ethanol (2 ml) was added sodium ethoxide solution (1.52 ml, 4.2 mol equiv.) [from sodium (83 mg, 3.6 mmol) in anhydrous ethanol (10 ml)]. Stirring was continued for 5 min at room temperature and then the ethanol was evaporated. The residue was dissolved in chloroform (10 ml) and the solution was washed with brine (2 x 10 ml) and water (10 ml), dried, and evaporated. The crude product was chromatographed on a silica plate [methanol-chloroform (1:9)] to yield the *phenol* (81) (R_f 0.45) (29 mg, 49%) as an oil (Found: M^+, 446.1842. $C_{26}H_{26}N_2O_5$ requires M, 446.1842); $\nu_{max}(CHCl_3)$ 3 540, 3 400, and 1 690 cm^{-1}; $\delta(CDCl_3)$ 2.44 (3H, s, NMe), 3.80 (3H, s, OMe), 4.27 (1H, br d, $J_{10\alpha\text{-}H}$ 7 Hz, 9-H), 5.17 (1H, br s, 5-H), 5.78 (1H, dd, $J_{8\text{-}H}$ 10 Hz, and $J_{5\text{-}H}$ 2 Hz, 7-H), 5.80 (1H, br s, exchangeable with D_2O, OH), 6.63 (2H, s, 1-H and 2-H), 7.00 (1H, d, $J_{7\text{-}H}$ 10 Hz, 8-H), and 7.25-7.45 (5H, m, Ph).

The Anhydro-base, 'buttercup' (82). - The codeinone (79) (90 mg, 0.2 mmol) in anhydrous pyridine (4 ml) was treated with toluene-*p*-sulphonyl chloride (40 mg, 0.2 mmol) for 6 h at room temperature. The solution was evaporated and the residual pyridine removed by azeotroping with toluene (4 x). The residue was dissolved in methanol (4 ml), sodium methoxide solution (1.57 ml, 4 mol equiv.) [from sodium (117 mg, 5.09 mmol) in methanol (10 ml)] was added and the solution stirred at room temperature overnight. The resultant precipitate was filtered off to give *'buttercup'* (82) (30 mg, 30%) which was recrystallised from chloroform-methanol as golden yellow needles, m.p. 285°C (decomp.)

(Found: C, 69.80; H, 5.53; N, 7.93; $[M]^+$ $\{-H_2O-\frac{1}{2}MeOH\}$, 505.2003. $C_{31}H_{27}N_3O_4.H_2O.\frac{1}{2}MeOH$ requires C, 70.11; H, 5.76; N, 7.79%; [M] $\{-H_2O - \frac{1}{2}MeOH\}$, 505.2001); λ_{max}(EtOH) 339.5 (ε 11 920) and 435 nm (ε 7 150); λ_{max}(EtOH + TFA) 352 nm (ε 7 920); ν_{max}(KBr) 1 720, 1 635, and 1 485 cm^{-1}; ν_{max}($CHCl_3$) 3 415, 1 720, 1 635, and 1 485 cm^{-1}; δ($CDCl_3$, 250 MHz) 2.19 (3H, s, NMe), 3.49 (1.5H, s, MeOH of crystallisation), 3.83 (1H, s, 8-H), 3.90 (3H, s, OMe), 4.59 (1H, s, 5-H), 6.40 (1H, dt, $J_{6'-H}$ 1.5 Hz, $J_{5'-H}$ 7 Hz, $J_{3'-H}$ 7 Hz, 4'-H), 6.55 (1H, d, J_{2-H} 8 Hz, H-1), 6.72 (1H, d, J_{1-H} 8 Hz, 2-H), 7.01 (1H, br td, $J_{6'-H}$ 1.5 Hz, $J_{5'-H}$ 1.5 Hz, $J_{4'-H}$ 7 Hz, 3'-H), 7.42 (1H, ddd, $J_{6'-H}$ 9 Hz, $J_{4'-H}$ 7 Hz, $J_{3'-H}$ 1.5 Hz, 5'-H), 7.51 (5H, br s, Ph), 7.56 (1H, br s, exchangeable with D_2O, NH), and 7.97 (1H, br td, $J_{5'-H}$ 9 Hz, $J_{4'-H}$ 1.5 Hz, $J_{3'-H}$ 1.5 Hz, 6'-H); δ_C($CDCl_3$) 22.05 (t), 31.96 (t), 43.22 (q), 45.85 (t), 46.08 (s), 51.78 (d), 57.20 (q), 61.55 (s), 63.95 (d), 81.49 (s), 90.32 (d), 94.39 (s), 112.81 (d), 115.76 (d), 118.53 (d), 118.62 (d), 125.33 (s), 128.72 (d), 129.73 (d), 130.30 (d), 134.56 (d), 134.79 (s), 140.59 (d), 143.10 (s), 145.78 (s), 153.12 (s), 169.90 (s), and 178.32 (s).

2-Pyridylacetone. - The method of Burger and Ullyot[77] was followed using α-picoline (25 g, 0.27 mol), lithium (3.25 g, 0.46 mol), bromobenzene (36.75 g, 0.23 mol), and acetonitrile (12.4 ml, 0.23 mol). 2-Pyridylacetone (8.45 g, 23%) was isolated as an oil, b.p. 110-115°C (*ca.* 5 mm Hg).

2-Acetonylidene-1-benzyl-1,2-dihydropyridine[65] (83c). - 2-Pyridylacetone (1.01 g, 7.5 mmol) and benzyl bromide (0.89 ml, 7.5 mmol) were heated together on a steam bath for 4 h. The viscous residue was triturated with acetone (6 x) to yield a syrupy quaternary bromide which was shaken with water and chloroform. The aqueous layer was cooled and basified with 5% aqueous sodium hydroxide. The resultant golden-yellow precipitate was filtered off to give the dihydropyridine (83c) (0.304 g, 18%), m.p. 125-127°C (decomp.) (lit.,[65] 124-125°C); λ_{max}(EtOH)

326 (ε 10 320) and 396 nm (ε 8 580); λ_{max}(EtOH + TFA) 346 nm (ε 1 680); ν_{max}(KBr) 1 640 and 1 505 cm^{-1}; δ($CDCl_3$) 1.96 (3H, s, CH_3), 4.91 (2H, s , CH_2), 4.96 (1H, s, CHCO), 6.18 (1H, dt, J_{6-H} *ca.* 1.5 Hz, J_{5-H} 6 Hz, J_{3-H} 6 Hz, 4-H), 7.00-7.55 (7H, m, 3-H, 5-H and Ph), and 8.93 (1H, dd, J_{5-H} 10 Hz, J_{4-H} *ca.* 1.5 Hz, 6-H); δ_C($CDCl_3$) 31.19 (q), 57.52 (t), 88.57 (d), 109.45 (d), 122.97 (d), 126.77 (d), 128.15 (d), 129.11 (d), 134.04 (s), 134.79 (d), 138.02 (d), 152.67 (s), and 191.35 (s).

2-Acetonylidene-1-methyl-1,2-dihydropyridine (83d). - 2-Pyridylacetone (1.01 g, 7.5 mmol) and methyl iodide (0.47 ml, 7.5 mmol) were heated together on a steam bath for 1 h. The viscous residue was triturated with acetone (6 x) to yield the quaternary ammonium iodide (1.193 g, 58%), m.p. 141-144°C.

The quaternary ammonium iodide (500 mg, 1.8 mmol) was dissolved in water, cooled to 0°C and basified with 5% aqueous sodium hydroxide. The aqueous solution was extracted with chloroform (6 x 10 ml) and the extracts were dried and evaporated to yield the *dihydropyridine* (83d) [223 mg, 40% (from 2-pyridylacetone)] which crystallised from ethyl acetate as golden yellow needles, m.p. 109-110°C (decomp.) (Found: C, 72.23; H, 7.59; N, 9.31; M^+, 149.0845. $C_9H_{11}NO$ requires C, 72.48; H, 7.38; N, 9.39%; M, 149.0841); λ_{max}(EtOH) 322 (ε 5 290) and 390 nm (ε 4 550); λ_{max} (EtOH + TFA) 340 nm (ε 600); ν_{max}(KBr) 1 640 and 1 505 cm^{-1}; δ($CDCl_3$) 2.10 (3H, s, $COCH_3$), 3.40 (3H, s, NCH_3), 4.93 (1H, s, CHCO), 6.13 (1H, dt, J_{6-H} 1.5 Hz, J_{5-H} 6.7 Hz, J_{3-H} 6.7 Hz, 4-H), 6.96-7.25 (2H, m, 3-H and 5-H), and 8.88 (1H, td, J_{5-H} 10 Hz, J_{4-H} 1.5 Hz, J_{3-H} 1.5 Hz, 6-H); δ_C($CDCl_3$) 31.20 (q), 42.64 (q), 87.39 (d), 109.19 (d), 121.94 (d), 134.89 (d), 138.42 (d), 153.02 (s), and 190.95 (s).

1-Methoxy-4-methyl-1,3-cyclohexadiene (86). - (a) *Birch reduction of* p-*methylanisole.* The procedure of Monti *et al.*[67] was followed using *p*-methylanisole (24.4 g, 0.2 mol), lithium (5.6 g, 0.8 mol), dry t-butanol (100 ml), and dry THF (100 ml) in dry liquid ammonia (500 ml). A 1:1 mixture of the 1,3- and 1.4-dienes was isolated which was distilled (18.86 g, 76%), b.p. 56-58°C (*ca.* 15 mm Hg).

(b) *Isomerisation of the diene mixture.* The procedure of Birch and Dastur[29] was followed and afforded, from the diene mixture (9 g) and toluene-*p*-sulphonic acid (9 mg), a liquid (7.76 g, 86%), b.p. 58-60°C (*ca.* 15 mm Hg). N.m.r. spectroscopy showed this to contain the 1,3-isomer (72%) and the 1,4-isomer (28%).

4-Methyl-4-(N-2-phenylethanoylhydroxyamino)-2-cyclohexenone (88). - The diene mixture (86) (3.44 g, 20 mmol of 1,4-diene) in ethyl acetate (300 ml) and sodium periodate (6.42 g, 30 mmol) in aqueous sodium acetate (0.2M, adjusted to pH 5.8 with concentrated hydrochloric acid) (200 ml) were stirred rapidly at 0°C. Phenylacetohydroxamic acid (4.53 g, 30 mmol) was slowly added over 15 min, then rapid stirring was continued for 1 h. The mixture was basified with aqueous sodium hydrogen carbonate and the layers separated. The aqueous layer was extracted with ethyl acetate (2 x 100 ml) and the combined ethyl acetate layers were washed with 5% sodium thiosulphate solution (2 x 100 ml) and water (100 ml), dried, and evaporated. The residue was chromatographed under reduced pressure on a silica column (100 g). The fractions eluted with ethyl acetate-light petroleum (1:1) and which gave a purple colour with ferric chloride solution were combined. Crystallisation from ethyl acetate afforded the *cyclohexenone* (88) [1.10 g, 21% (based on 1,4-diene)] as cuboids, m.p. 136-137°C (Found: C, 69.32; H, 6.74; N, 5.34; M^+, 259.1208. $C_{15}H_{17}NO_3$ requires C, 69.48; H, 6.61; N, 5.40; M, 259.1208); ν_{max}(KBr) 3 140 and 1 675 cm^{-1}; $\delta(CDCl_3)$ 1.50 (3H, s, CH_3), 1.85-2.85 (4H, m, CH_2CH_2CO), 3.81 (2H, s, CH_2Ph), 5.82 (1H, d, J_{3-H} 10 Hz,

2-H), 6.94 (1H, br s, exchangeable with D_2O, OH), 7.07 (1H, d, $J_{2\text{-H}}$ 10 Hz, 3-H), and 7.27 (5H, s, Ph).

The Anhydro-base, 'neo-buttercup' (84). - The cyclohexenone (88) (259 mg, 1 mmol) in anhydrous pyridine (5 ml) was treated with toluene-*p*-sulphonyl chloride (210 mg,1.1 mmol) for 38 h at room temperature. The solution was evaporated and the residual pyridine removed by azeotroping with toluene (4 x). The residue was dissolved in methanol (5 ml) and sodium methoxide solution (4.6 ml, 4 mol equiv.) [from sodium (199 mg, 8.65 mmol) in methanol (10 ml)] was added and the solution was stirred at room temperature for 5 h. The methanol was evaporated and the residue treated with water and extracted with chloroform (4 x 25 ml). The combined extracts were dried and evaporated to yield *'neo-buttercup'* (84) which crystallised from methanol-ethyl acetate as cuboids (72 mg). A second crop (8 mg) was obtained by chromatographing the mother liquors on silica plates [methanol-chloroform (1:9)] (R_f 0.32). Total yield 80 mg, 25%, m.p. 300-301°C (decomp.) (Found: C, 75.18; H, 5.76; N, 8.65; M^+, 318.1361. $C_{20}H_{18}N_2O_2$ requires C, 75.45; H, 5.70; N, 8.80; M, 318.1368); λ_{max}(EtOH) 336 (ε 4 880) and 435 nm (ε 2 120); λ_{max}(EtOH + TFA) 360 nm (ε 2 440); ν_{max}(KBr) 1 705, 1 635, and 1 500 cm^{-1}; ν_{max}($CHCl_3$) 3 415, 1 710, 1 640, and 1 500 cm^{-1}; δ($CDCl_3$, 250 MHz) 1.24 (3H, s, CH_3), 1.69-2.28 (4H, m, CH_2CH_2), 3.72 (1H, s, 3-H), 6.14 (1H, dt, $J_{6'\text{-H}}$ 1.5 Hz, $J_{5'\text{-H}}$ 7 Hz, $J_{3'\text{-H}}$ 7 Hz, 4'-H), 6.52 (1H, br s, NH), 7.05 (1H, td, $J_{6'\text{-H}}$ 1.5 Hz, $J_{5'\text{-H}}$ 1.5 Hz, $J_{4'\text{-H}}$ 7 Hz, 3'-H), 7.23 (1H, ddd, $J_{6'\text{-H}}$ 9 Hz, $J_{4'\text{-H}}$ 7 Hz, $J_{3'\text{-H}}$ 1.5 Hz, 5'-H), 7.41-7.50 (5H, m, Ph), and 7.65 (1H, td, $J_{5'\text{-H}}$ 9 Hz, $J_{4'\text{-H}}$ 1.5 Hz, $J_{3'\text{-H}}$ 1.5 Hz, 6'-H); δ_C(CD_3OD) 28.16, 37.37, 40.26, 59.26 (s), 60.45 (d), 83.07 (s), 96.07 (s), 113.26 (d), 118.15 (d), 128.90 (d), 130.64 (d), 137.06 (d), 139.35 (s), 141.75 (d), 153.19 (s), 171.88 (s), and 190.20 (s).

Alternative Preparation of 'neo-buttercup' (84). - A solution of the hydroxamic acid (88) (52 mg, 0.2 mmol) in dry methylene chloride (1 ml) containing triethylamine [0.61 ml (10% solution in methylene chloride), 0.44 mmol] was cooled to -70°C and trifluoromethanesulphonic anhydride (37 µl, 0.22 mmol) added. After stirring for 10 min at -70°C dry pyridine (80 µl, 1 mmol) was added and the solution warmed to room temperature (*ca.* 20 min). The solution was evaporated and the residue dissolved in methanol (1 ml) and treated with sodium methoxide solution (2 ml, 4 mol equiv.) [from sodium (90 mg, 3.9 mmol) in methanol (10 ml)]. After stirring at room temperature overnight the solvent was evaporated and water was added. The solution was extracted with chloroform (4 x 5 ml) and the extracts were dried and evaporated. The residue was chromatographed on a silica plate [methanol-chloroform (1:9)] (R_f 0.24) to afford 'neo-buttercup' (84) which crystallised from methanol (16 mg, 25%). The n.m.r. spectrum was identical to that obtained in the above route.

14β-*(2-Chloro-2-phenylethanoylamino)codeinone* (89). - A solution of (±)-α-chlorophenylacetyl chloride[78] (227 mg, 1.2 mmol) in ethyl acetate (10 ml) was added dropwise to a stirred solution of 14β-aminocodeinone (312 mg, 1 mmol) in ethyl acetate (10 ml) containing powdered anhydrous potassium chloride (552 mg, 4 mmol). Stirring was continued for 30 min, water was added and the two layers separated. The aqueous layer was extracted with ethyl acetate (2 x 20 ml) and the combined ethyl acetate layers were washed with water (20 ml), dried, and evaporated. The residue was chromatographed on silica plates [methanol-chloroform (1:9)] (R_f 0.66) to afford the *codeinone* (89) as a mixture of diastereoisomers which crystallised from methylene chloride-methanol as fine needles (257 mg, 55%), m.p. 218-220°C (decomp.) (Found: C, 67.27; H, 5.45; N, 6.03; M^+ 466.1519, 464.1513. $C_{26}H_{25}ClN_2O_4$ requires C, 67.16; H, 5.42; N, 6.03%; M, 466.1473, 464.1503); ν_{max}(KBr) 1 685 cm^{-1}; $\delta(CDCl_3)$ 2.42

(6H, s, NMes), 3.82 and 3.83 (each 3H, s, OMes), 4.75 and 4.88 (each 1H, s, 5-Hs), 5.29 and 5.35 (each 1H, s, C*H*Phs), 6.17 and 6.19 (each 2H, s, 7-Hs and 8-Hs), 6.58 (2H, d, $J_{2\text{-}H}$ 8 Hz, 1-Hs), 6.70 (2H, d, $J_{1\text{-}H}$ 8 Hz, 2-Hs), 7.25-7.60 (10H, m, Phs), and 7.82 and 8.11 (each 1H, br s, NHs).

Attempted Preparation of the Pyridinium Chloride (85). - The codeinone (89) (23 mg, 0.05 mmol) was stirred in dry pyridine (0.5 ml) overnight at room temperature. Evaporation of the solvent yielded starting material, identified by its n.m.r. spectrum. Starting material was also isolated when the codeinone was refluxed in, (i) 10% pyridine-benzene, and (ii) 10% pyridine-toluene. In refluxing pyridine the codeinone decomposed.

N-*t-Butylhydroxylamine* (90). - *N*-t-Butylhydroxylamine was prepared following the procedure of Calder, Forrester and Hepburn.[79] Thus, oxidation of *N*-t-butylamine with potassium permanganate to give 2-methyl-2-nitropropane which was reduced with aluminium amalgam to *N*-t-butylhydroxylamine in an overall yield of 24% (m.p. 63-64°C) (lit.,[79] 64-65°C).

α-*Chloro*-N-*t-butylphenylacetamide* (94) *from* N-*t-Butylamine*. - A solution of α-chlorophenylacetyl chloride[78] (4.52 g, 24 mmol) in anhydrous ether (20 ml) was added dropwise to a stirred solution of *N*-t-butylamine (5.07 ml, 48 mmol) in anhydrous ether (20 ml) at 0°C. Stirring was continued for 1 h, ether (60 ml) added and the mixture was washed with 5% hydrochloric acid (2 x 50 ml) and water (50 ml), dried, and evaporated to yield the amide (94) which crystallised from ethyl acetate-light petroleum (3.9 g, 73%), m.p. 131-132°C (lit.,[80] 128-130°C) (Found: M^+, 227.0893, 255.0912. Calc. for $C_{12}H_{16}ClNO$: M, 227.0891, 225.0920); $\nu_{max}(CHCl_3)$ 3 420 and 1 680 cm^{-1}; $\delta(CDCl_3)$ 1.36 (9H, s, Bu^t), 5.26 (1H, s, CH), 6.55 (1H, br s, exchangeable with D_2O, NH), and 7.25-7.50 (5H, m, Ph).

α-Chloro-N-t-butylphenylacetamide (94) *from* N-*t-Butylhydroxylamine*. - To a stirred solution of *N*-t-butylhydroxylamine (134 mg, 1.5 mmol) in dry ether (3 ml) containing powdered anhydrous potassium carbonate (414 mg, 3 mmol) was added acetic anhydride (0.14 ml, 1.5 mmol). After stirring for 4 h at room temperature the inorganic solids were filtered off, washed with ether and the filtrate was evaporated to afford *O*-acetyl-*N*-t-butylhydroxylamine (91) as an oil. This material was dissolved in dry benzene (3 ml) and dry pyridine (0.13 ml, 1.6 mmol) and phenylacetyl chloride (0.21 ml, 1.6 mmol) added. The mixture was heated under reflux for 3 h, cooled, diluted with benzene (7 ml), and washed with 5% hydrochloric acid (2 x 5 ml), 5% sodium hydroxide solution (2 x 5 ml), and water (5 ml). The dried benzene solution was evaporated to give an oily solid. The amide (94) was sublimed from this residue (bath temp. 110-120°C, *ca.* 15 mm Hg) and recrystallised from ethyl acetate-light petroleum (103 mg, 30%), mixed m.p. (with authentic amide) 131-132°C; $\delta(CDCl_3)$ 1.36 (9H, s, Bu^t), 5.25 (1H, s, CH), 6.52 (1H, br s, NH), and 7.25-7.50 (5H, m, Ph).

N-*t-Butylphenylacetohydroxamic Acid*[68] (93). - To a stirred solution of *N*-t-butylhydroxylamine (890 mg, 10 mmol) in methylene chloride (10 ml) was added triethylamine (1.6 ml, 11 mmol) and trimethylchlorosilane (1.4 ml, 11 mmol). The mixture was stirred for 10 min, cooled to 0°C and treated with triethylamine (1.6 ml, 11 mmol) followed, dropwise, by phenylacetyl chloride (1.45 ml, 11 mmol). After the mixture had warmed to room temperature (*ca.* 30 min) methylene chloride (10 ml) and 5% hydrochloric acid (10 ml) were added and the two layers separated. The organic layer was washed with 5% hydrochloric acid (10 ml) and water (10 ml), dried, and evaporated to give an oily solid. The crystals were filtered off and recrystallised from ethyl acetate-light petroleum to give the *hydroxamic acid* (93) as prisms (621 mg, 32%), m.p. 129-130°C (Found: C, 69.30; H, 8.25; N, 6.68; M^+, 207.1261. $C_{12}H_{17}NO_2$ requires C, 69.53;

H, 8.27; N, 6.76%; M, 207.1259); ν_{max}(CCl_4) 3 200, 1 670, and 1 615 cm^{-1}; δ($CDCl_3$) 1.37 (9H, s, Bu^t), 3.71 (2H, s, CH_2), 7.05 (1H, br s, exchangeable with D_2O, OH), and 7.20 (5H, br s, Ph).

NO-Diphenylacetyl-N-t-butylhydroxylamine (95). - To a solution of the hydroxamic acid (93) (42 mg, 0.2 mmol) in dry benzene (2 ml) was added dry pyridine [0.18 ml, (10% solution in dry benzene), 0.22 mmol] and phenylacetyl chloride (0.03 ml, 0.22 mmol). The solution was stirred at room temperature overnight, diluted with benzene (5 ml), and washed with 5% hydrochloric acid (2 x 3 ml), 5% sodium hydroxide solution (2 x 3 ml) and water (3 ml). The organic solution was dried and evaporated and the crude product was chromatographed on a silica plate [ethyl acetate-light petroleum (1:4)] to yield the *hydroxylamine derivative* (95) (R_f 0.45) (47 mg, 71%) as an oil (Found: M^+ 325.1673. $C_{20}H_{23}NO_3$ requires M, 325.1678); ν_{max}($CHCl_3$) 1 780 and 1 670 cm^{-1}; δ($CDCl_3$) 1.35 (9H, s, Bu^t), 3.37 (2H, s, $OCOCH_2Ph$), 3.71 (2H, s, $NCOCH_2Ph$), and 7.00-7.50 (10H, m, Phs).

Attempted Preparation of α-Chloro-N-t-butylphenylacetamide (94) *from NO-Diphenylacetyl-N-t-butylhydroxylamine* (95). - To a solution of the hydroxylamine derivative (95) (52 mg, 0.16 mmol) in methylene chloride (2 ml) was added tetrabutylammonium chloride (115 mg, 0.41 mmol) and triethylamine (0.05 ml, 0.36 mmol). The solution was refluxed for 3 h, cooled, diluted with methylene chloride (5 ml), and washed with 5% hydrochloric acid solution (2 x 2 ml), 5% sodium hydroxide solution (2 x 2 ml), and water (2 ml). The organic solution was dried and evaporated to yield starting material, identified by n.m.r. spectroscopy. Starting material was also recovered when the procedure was repeated using, (i) tetrabutylammonium chloride and triethylamine in methylene chloride at room temperature, (ii) tetrabutylammonium chloride and pyridine in benzene at room temperature, (iii) tetrabutylammonium chloride and pyridine in refluxing benzene, and (iv) pyridine

hydrochloride and pyridine in refluxing methylene chloride.

α-Chloro-N-t-butylphenylacetamide (94) *from* N-*t*-*Butylphenylaceto-hydroxamic acid* (93). - The hydroxamic acid (93) (126 mg, 0.61 mmol) in methylene chloride (4 ml) was treated with triethylamine (93 µl, 0.67 mmol) and toluene-*p*-sulphonyl chloride (117 mg, 0.61 mmol) for 2 days at room temperature. The solution was diluted with methylene chloride (5 ml) and washed with 5% hydrochloric acid (2 x 3 ml), 5% sodium hydroxide solution (2 x 3 ml), and water (3 ml). The organic solution was dried and evaporated to give an oily solid. The amide (94) was sublimed from this residue (bath temp. 110-120°C, *ca.* 15 mm Hg) and recrystallised from ethyl acetate-light petroleum (40 mg, 29%), mixed m.p. (with authentic amide) 130-131°C; δ($CDCl_3$) 1.37 (9H, s, Bu^t), 5.25 (1H, s, CH), 6.53 (1H, br s, NH), and 7.25-7.50 (5H, m, Ph).

1-t-Butyl-3-Phenylaziridin-2-one[49] (63). - A solution of the hydroxamic acid (93) (52 mg, 0.25 mmol) in dry methylene chloride (2 ml) containing triethylamine (77 µl, 0.55 mmol) was cooled to -70°C. Trifluoromethanesulphonic anhydride (47 µl, 0.29 mmol) was added, the solution was warmed to room temperature (*ca.* 30 min) and then diluted with methylene chloride (5 ml). The solution was washed with water (2 ml), dried, and evaporated. The residue was extracted with light petroleum (40-60°C) at room temperature and the extracts were evaporated to yield the aziridinone (63) (46 mg, 97%), m.p. 29-31°C (lit.,[49] 32-33°C) (Found: M^+ 189.1160. Calc. for $C_{12}H_{15}NO$: M, 189.1154); ν_{max}($CHCl_3$) 1 850 cm^{-1}; δ($CDCl_3$ at 0°C) 1.36 (9H, s, Bu^t), 3.87 (1H, s, CH), and 7.34 (5H, s, Ph).

α-Chloro-N-t-butylphenylacetamide (94) *from* N-*t*-*Butyl*-3-*phenyl-aziridinone* (63). - A solution of the aziridinone (63) (22 mg, 0.12 mmol) in methylene chloride (1 ml) containing tetrabutylammonium chloride (65 mg, 0.23 mmol) was stirred at room temperature overnight. Methylene chloride (5 ml) was added and the solution was washed with water (1 ml), dried, and evaporated. The residue was chromatographed on a silica

plate [ethyl acetate-light petroleum (1:4)] to yield the amide (94) (R_f 0.42) (14 mg, 53%) which crystallised from ethyl acetate-light petroleum, δ($CDCl_3$) 1.37 (9H, s, Bu^t), 5.25 (1H, s, CH), 6.52 (1H, s, NH), and 7.25-7.50 (5H, m, Ph).

N-t-Butyl-(3,3-dimethylbutano)hydroxamic Acid (101). - A solution of *N*-t-butylhydroxylamine (445 mg, 5 mmol) in dry methylene chloride (5 ml) containing triethylamine (0.8 ml, 5.8 mmol) was cooled to 0°C and trimethylchlorosilane (0.7 ml, 5.5 mmol) added. The mixture was stirred for 15 min, cooled to -70°C and treated with triethylamine (0.8 ml, 5.8 mmol) followed, dropwise over 30 min, by a solution of 3,3-dimethylbutanoyl chloride (0.76 ml, 5.5 mmol) in dry methylene chloride (5 ml). The mixture was allowed to attain room temperature, 5% hydrochloric acid (5 ml) was added and the two layers separated. The organic layer was washed with 5% hydrochloric acid (5 ml) and water (5 ml), dried, and evaporated to give an oil which partially crystallised from ethyl acetate. The product was filtered off and washed with light petroleum (40-60°C). The filtrate was extracted with sodium hydroxide solution and the combined extracts were acidified and extracted with light petroleum (40-60°C). These organic extracts were dried and evaporated to give a second crop. The combined crops were recrystallised from ethyl acetate to give the *hydroxamic acid* (101) (396 mg, 42%) as plates, m.p. 100-101°C (Found: C, 64.07; H, 11.41; N, 7.47; M^+, 187.1570. $C_{10}H_{21}NO_2$ requires C, 64.13; H, 11.30; N, 7.48%; M, 187.1572); ν_{max}($CHCl_3$) 3 540, 3 220, 1 645, and 1 615 cm^{-1}; δ($CDCl_3$) 1.00 (9H, s, CH *Bu*^{t}), 1.41 (9H, s, N*Bu*^{t}), 2.35 (2H, s, CH_2), and 7.48 (1H, br s, exchangeable with D_2O, OH).

Attempted Preparations of 1,3-*Di-t-butylaziridin-2-one* (99) *from* N-*t-Butyl-(3,3-dimethylbutano)hydroxamic acid* (101). - (a) *With triethylamine*. A solution of the hydroxamic acid (101) (47 mg, 0.25 mmol) in dry methylene chloride (2 ml) containing triethylamine (77 µl, 0.55 mmol) was cooled to -70 C and trifluoromethanesulphonic anhydride (50 µl, 0.3 mmol) added. The i.r. spectrum of the reaction mixture showed no characteristic aziridinone carbonyl absorption. After attaining room temperature the mixture was diluted with methylene chloride, washed with water, dried and evaporated. The n.m.r. spectrum of the residue was unclear.

(b) *With* 1,5-*diazabicyclo*[4.3.0]*non*-5-*ene* (DBN). The procedure was as above using DBN in place of triethylamine. The i.r. spectrum of the reaction mixture showed no aziridinone carbonyl absorption and the n.m.r. spectrum of the residue after work-up was unclear.

(c) *With lithium diisopropylamide*. A solution of the hydroxamic acid (101) (20 mg, 0.11 mmol) in dry methylene chloride (1 ml) containing triethylamine [170 µl (10% solution in methylene chloride), 0.12 mmol] was cooled to -70°C. Trifluoromethanesulphonic anhydride (20 µl, 0.12 mmol) was added, followed, after 5 min, by lithium diisopropylamide (170 µl, 0.12 mmol) [prepared from diisopropylamine (0.25 ml, 1.77 mmol) and butyl lithium (1.5M; 1.18 ml, 1.77 mmol) in THF (1 ml)]. The i.r. spectrum of the reaction mixture showed no aziridinone carbonyl absorption. The n.m.r. spectrum of the residue after work-up suggested that the *N*-t-butyl group had been lost.

14β-*Amino*-*N*-*t-butoxycarbonylnorcodeinone Ethylene Acetal* (68) . - The ethylene acetal (56) (134 mg, 0.25 mmol) was dissolved in anhydrous ethanol (5 ml), sodium ethoxide solution added (2 ml, 4 mol equiv.) [from sodium (113 mg, 4.9 mmol) in anhydrous ethanol (10 ml)] and the solution was stirred for 0.5 h at room temperature. Water was then added, the ethanol was evaporated and the aqueous residue extracted

with chloroform (4 x 5 ml). The combined extracts were dried and evaporated to yield the *amine* (68) which crystallised from ethyl acetate as granules, (44 mg, 44%), m.p. 231-232°C (Found: C, 64.94; H, 6.80; N, 5.98; M^+, 442.2079. $C_{24}H_{30}N_2O_6$ requires C, 65.14; H, 6.83; N, 6.33%; M, 442.2104); $\nu_{max}(CHCl_3)$ 3 390, 3 320, and 1 685 cm^{-1}; $\delta(CDCl_3)$ 1.45 (9H, s, Bu^t), 1.85 (2H, br s, exchangeable with D_2O, NH_2), 3.86 (3H, s, OMe), 3.90-4.30 (4H, m, OCH_2CH_2O), 4.53 (1H, br s, 5-H), 5.69 (1H, d, J_{8-H} 9 Hz, 7-H), 5.92 (1H, d, J_{7-H} 9 Hz, 8-H), 6.53 (1H, d, J_{2-H} 8 Hz, 1-H), and 6.70 (1H, d, J_{1-H} 8 Hz, 2-H).

14β-*Acetylamino*-N-*t*-*butoxycarbonylnorcodeinone Ethylene Acetal* (102). - The amine (68) (45 mg, 0.1 mmol) was dissolved in pyridine (2 ml) and acetic anhydride (2 drops) added. The solution was stirred at room temperature for 1 h and then the solvent was evaporated. The residual pyridine was removed by azeotroping with toluene (4 x) to give the *amide* (102) which crystallised as the hydrate (30 mg, 59%), m.p. 196-197°C (Found: C, 62.13; H, 7.03; N, 5.39; $[M]^+\{-H_2O\}$, 484.2182. $C_{26}H_{32}N_2O_7.H_2O$ requires C, 62.13; H, 6.82; N, 5.58%; $[M]\{-H_2O\}$, 484.2209); $\nu_{max}(CHCl_3)$ 3 635, 3 440, 3 380 (sh), and 1 685 cm^{-1}; $\delta(CDCl_3)$ 1.44 (9H, s, Bu^t), 1.90 (3H, s, CH_3), 3.85 (3H, s, OMe), 3.90-4.30 (4H, m, OCH_2CH_2O), 4.51 (1H, br s, 9-H), 5.46 (1H, br s, 5-H), 5.67 (1H, d, J_{8-H} 10 Hz, 7-H), 5.85 (1H, br s, exchangeable with D_2O, NH), 6.30 (1H, d, J_{7-H} 10 Hz, 8-H), 6.54 (1H, d, J_{2-H} 8 Hz, 1-H), and 6.70 (1H, d, J_{1-H} 8 Hz, 2-H).

14β-*Aminonorcodeinone Dihydrochloride*[17] (103). - The amine (68) (20 mg, 0.045 mmol) was dissolved in 3% anhydrous methanolic hydrogen chloride (1 ml) and the solution left overnight at room temperature. Water (6 drops) was added and the solution was heated at 60°C for 0.5 h. Evaporation of the solvent afforded the norcodeinone dihydrochloride (103) (12 mg, 71%), m.p. > 320°C (Found: $[M]^+\{-2HCl\}$, 298.1309. Calc. for $C_{17}H_{18}N_2O_3.2HCl$: $[M]\{-2HCl\}$, 298.1317); $\nu_{max}(KBr)$ 2 930, 2 810, 2 500 (sh),

and 1 690 cm^{-1}; δ(D_2O, internal reference t-BuOH) 3.82 (3H, s, OMe), 5.17 (1H, s, 5-H), 6.27 (1H, d, J_{2-H} 10 Hz, 1-H), 6.92 (2H, s, 7-H and 8-H) and 7.10 (1H, d, J_{1-H} 10 Hz, 2-H),

14β-*Methoxycarbonylmethoxyaminocodeinone Ethylene Acetal* (111). - The crude cycloadduct (59) (106 mg, 0.25 mmol) in methylene chloride (1 ml) was treated with anhydrous hydrogen chloride in ethylene glycol (1M; 1 ml). The solution was stirred at room temperature for 90 min and then added to an excess of sodium methoxide solution (5 ml, 11 mol equiv.) [from sodium (127 mg, 5.5 mmol) in methanol (10 ml)]. The solution was stirred for a further 30 min, diluted with water (5 ml), and extracted with methylene chloride (6 x 5 ml). The combined extracts were washed with brine (2 x 5 ml) and water (5 ml), dried, and evaporated. The residue was chromatographed on a silica plate [methanol-chloroform (1:9)] to yield the *methyl ester* (111) (R_f 0.47) (33 mg, 29%) as an oil (Found: M^+, 444.1899. $C_{23}H_{28}N_2O_7$ requires M, 444.1896); ν_{max}($CHCl_3$) 3 260 and 1 750 cm^{-1}; δ($CDCl_3$) 2.33 (3H, s, NMe), 3.77 (3H, s, COOMe), 3.92 (3H, s, 3-OMe), 3.95-4.15 (4H, m, OCH_2CH_2O), 4.14 and 4.44 (2H, d, d, J 16 Hz, CH_2CO), 4.77 (1H, s, 5-H), 5.70 (2H, s, 7-H and 8-H), 6.54 (1H, d, J_{2-H} 8 Hz, 1-H), 6.70 (1H, d, J_{1-H} 8 Hz, 2-H), and 7.88 (1H, br s, exchangeable with D_2O, NH).

α-*Chloro*-N-*t*-*butylacetohydroxamic Acid* (113). - To a stirred solution of *N*-t-butylamine (890 mg, 10 mmol) in methylene chloride (10 ml) was added triethylamine (1.6 ml, 11 mmol) and trimethylchlorosilane (1.4 ml, 11 mmol). The mixture was stirred for 10 min and then treated with triethylamine (1.6 ml, 11 mmol) followed, dropwise, by a solution of chloroacetyl chloride (0.88 ml, 11 mmol) in methylene chloride (5 ml). Stirring was continued for 10 min and then the mixture was washed with 5% hydrochloric acid (2 x 25 ml) and water (25 ml), dried and evaporated. The product was purified on a chromatotron (2 mm plate). Elution with ethyl acetate-light petroleum (3:1) afforded the *hydroxamic acid* (113)

which crystallised slowly from ether-light petroleum (40-60°C) (438 mg, 27%) as cuboids, m.p. 78-80°C (Found: C, 43.73; H, 7.59; Cl, 21.44; N, 8.53; M^+, 167.0527, 165.0566. $C_6H_{12}ClNO_2$ requires C, 43.50; H, 7.30; Cl, 21.43; N, 8.46%; M, 167.0527, 165.0557); $\nu_{max}(CCl_4)$ 3 200 and 1 645 cm^{-1}; $\delta(CDCl_3)$ 1.42 (9H, s, Bu^t), 4.37 (2H, s, CH_2), and 8.47 (1H, br s, exchangeable with D_2O, OH).

N-*(Methoxycarbonylmethoxy)-t-butylamine Hydrochloride* (114a). - To a solution of the hydroxamic acid (113) (50 mg, 0.3 mmol) in methanol (1 ml) was added sodium methoxide solution (0.56 ml, 1.1 mol equiv.) [from sodium (135 mg, 5.9 mmol) in methanol (10 ml)]. The solution was stirred at room temperature for 2 h, acidified with 5% hydrochloric acid and evaporated to dryness. The residue was extracted with methylene chloride and the inorganic material filtered off and washed with methylene chloride (twice). The filtrate was evaporated to yield the *hydroxylamine hydrochloride* (114a) which crystallised from ethyl acetate as cuboids (37 mg, 62%), m.p. 120-122°C (decomp.) (Found: C, 42.30; H , 7.96; Cl, 18.31; N, 6.92; $[M]^+$ {-HCl}, 161.1048. $C_7H_{15}NO_3.HCl$ requires C, 42.52; H, 8.16; Cl, 17.96; N, 7.09%; [M] {-HCl}, 161.1052); $\nu_{max}(CHCl_3)$ 2 680, 2 600, 2 475, and 1 760; $\delta(CDCl_3)$ 1.50 (9H, s, Bu^t), 3.85 (3H, s, OMe), and 4.97 (2H, s, CH_2).

N-*(Ethoxycarbonylmethoxy)-t-butylamine Hydrochloride* (114b). - To a solution of the hydroxamic acid (113) (50 mg, 0.3 mmol) in ethanol (1 ml) was added sodium ethoxide solution (0.86 ml, 1.1 mol equiv.) [from sodium (89 mg, 3.9 mmol) in ethanol (10 ml)]. The solution was stirred at room temperature for 1 h, acidified with 5% hydrochloric acid and evaporated to dryness. The residue was extracted with methylene chloride and the inorganic material filtered off and washed with methylene chloride (twice). The filtrate was evaporated to yield the *hydroxylamine hydrochloride* (114b) which crystallised from ethyl acetate (46 mg, 72%), m.p. 112-114°C (Found: $[M]^+$ {-HCl}, 175.1197. $C_8H_{17}NO_3.HCl$ requires

[M] {-HCl}, 175.1208); ν_{max}($CHCl_3$) 2 680, 2 600, 2 460, and 1 755 cm^{-1}; δ($CDCl_3$) 1.30 (3H, t, J_{CH_2} 7 Hz, CH_2CH_3), 1.50 (9H, s, Bu^t), 4.30 (2H, q, J_{CH_3} 7 Hz, CH_2CH_3), 4.94 (2H, s, CH_2CO), and 9.55 (2H, br s, exchangeable with D_2O, $\overset{+}{N}H_2$).

2,2-Diethoxyacetyl-1-adamantylamine (116). - 1-Aminoadamantane (2.65 g, 17.5 mmol), ethyl diethoxyacetate[81] (3.39 g, 19.3 mmol) in sodium ethoxide solution (1.10 ml, 0.1 mol equiv.) [from sodium (182 mg, 7.9 mmol) in dry ethanol (5 ml)] were heated together in a distillation apparatus. When all the ethanol had distilled off (*ca.* 30 min) the residual liquid was diluted with ether (100 ml) and washed with 5% aqueous oxalic acid (2 x 50 ml) and water (50 ml). The ethereal solution was dried and evaporated to give a brown oil which was distilled (Kugelrohr) (air bath temp. 195-205°C, 0.2 mbar Hg) to yield the *adamantylamide* (116) (3.56 g, 72%) as a pale yellow oil (Found: M^+, 281.1988. $C_{16}H_{27}NO_3$ requires M, 281.1991); ν_{max}(film) 3 410 and 1 690 cm^{-1}; δ($CDCl_3$) 1.18 (6H, t, J_{CH_2} 7 Hz, CH_3s), 1.63 (6H, br s, 3 x $CHCH_2CH$), 1.97 (9H, br s, adamantyl CHs and remaining CH_2s), 3.59 and 3.61 (4H, q,q, J_{CH_3} 7 Hz, 2 x CH_2CH_3), 4.60 [1H, s, $CH(OEt)_2$], and 6.25 (1H, br s, exchangeable with D_2O, NH).

Alternative Preparation of α-Chloro-N-t-butylphenylacetamide (94) *from N-t-Butylhydroxylamine*. - To a solution of *N*-t-butylhydroxylamine (134 mg, 1.5 mmol) in dry benzene (3 ml) was added dry pyridine (0.29 ml, 3.6 mmol) and phenylacetyl chloride (0.44 ml, 3.3 mmol). The mixture was heated under reflux for 3 h, cooled, diluted with benzene (7 ml), and washed with 5% hydrochloric acid (2 x 5 ml), 5% sodium hydroxide solution (2 x 5 ml), and water (5 ml). The dried benzene solution was evaporated to give an oily solid. The amide (94) was sublimed from this residue (bath temp. 110-120°C, *ca.* 15 mm Hg) and recrystallised from ethyl acetate-light petroleum (114 mg, 34%), mixed m.p. (with authentic amide) 131-132°C; δ($CDCl_3$) 1.37 (9H, s, Bu^t), 5.26 (1H, s, CH), 6.50 (1H, br s, NH), and 7.25-7.50 (5H, m, Ph).

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