SYNTHETIC ROUTES TO 14-AMINOCODEINONE DERIVATIVES

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for the Degree of

Doctor of Philosophy

by

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SUMMARY

The synthesis of 14β-acylaminocodeinones has been achieved *via* the Diels-Alder addition of nitrosocarbonyl-compounds to the activated diene system of thebaine. Several variations on this route have been investigated and the most efficient yields the desired products in greater than 60% yield from thebaine. The analgesic properties and structure/activity relationships of several of these compounds and their precursors with differing alkyl and aryl side chains have been established.

One of the steps in this synthetic route was the reduction of a substituted hydroxamic acid to an amide, which was accomplished with phosphorus trichloride or sulphur dioxide in pyridine. The use of these reagents in the reduction of simple substituted hydroxamic acids has been investigated.

The reactions of thebaine with dinitrogen trioxide and electrophilic aminating agents such as mesitylsulphonylhydroxylamine have also been studied but both methods failed to provide a synthesis of 14β-aminocodeinone derivatives.

Preliminary investigations into the chemistry of 5,6-dihydrothebaine (β-dihydrothebaine) phenyl ether have shown that this compound reacts with tetranitromethane to yield 14β-nitro-substituted compounds, and forms cyclo-adducts with nitrosocarbonyl-compounds.

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Chapter 1 INTRODUCTION

1.1 General Introduction

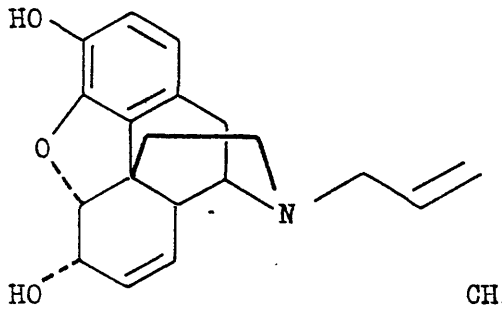
Opium, the dried sap from the poppy Papaver somniferum has been used medicinally since the days of the classical Grecian empire to produce analgesia and euphoria, to reduce anxiety, and to facilitate sleep. Laudanum was prepared by the 16th century Swiss physician Paracelsus by the extraction of opium, but the main active constituent, morphine (1) was not isolated until 1803 by the German pharmacist Freidrich Sertürner.[1] Among the other constituents of opium are codeine (2), isolated by Pierre-Jean Robinquet in 1832, which is used as a cough suppressant, papaverine (3), which is a muscle relaxant, and thebaine (4) which is non-narcotic and too toxic for clinical use. The structure elucidation of morphine was undertaken by Gulland and Robinson[2] in 1925 and the first synthesis was carried out by Gates and Tschudi[3] in 1956.

Not all the effects of the opiates are beneficial. As well as their analgesic activity, they can induce narcosis, respiratory depression, physical and psychological dependence liability, euphoria and disphoria, cough suppression, nausea, and constipation. Attempts to separate the desirable from the undesirable effects have proved exceedingly elusive with for example the Bayer Company in the 1890's introducing heroin (5) as a 'non-addictive' analgesic.

Early attempts to synthesise improved analgesics concentrated on trying to establish which parts of the morphine molecule were essential for analgesic activity, and which parts were extraneous. The 3-hydroxymorphinans[4] (6) and benzomorphans[5] (7) are both active analgesics and 4-phenylpiperidines eg. pethidine (8) are clinically useful drugs.[6] However, these compounds still suffered from the side effects of morphine.

An important discovery in morphine chemistry was that replacement of the N-methyl group, by N-allyl[7], N-propyl or N-cyclopropylmethyl, usually transformed the compound from an agonist into an antagonist[8]. A morphine agonist is a compound which has all the effects of morphine, while a pure morphine antagonist has none of these effects but blocks the action of morphine agonists. Two important morphine antagonists are naloxone (9) and nalorphine (10), which can be used as antidotes for narcosis caused by morphine agonists. Diprenorphine (11), a mixed agonist - antagonist is used in the veterinary field as an antidote to etorphine (12) an agonist which is between 10^3 and 10^4 times as potent as morphine.[9]

Etorphine and diprenorphine are examples of 6,14-bridged compounds, prepared by the Diels-Alder addition of a substituted alkene to the diene system of thebaine[10,11]. Several of these compounds have been prepared and the structure activity relationships have indicated[12] that maximum activity was obtained



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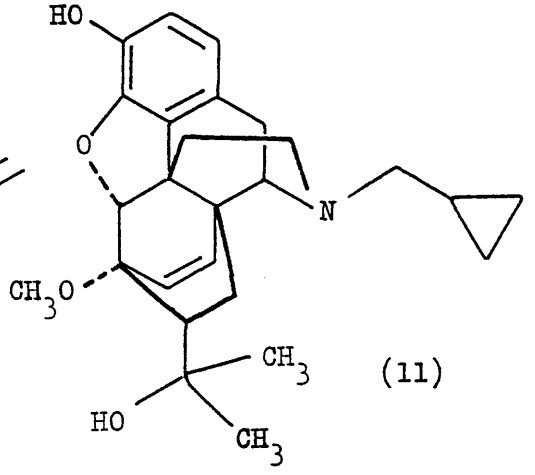

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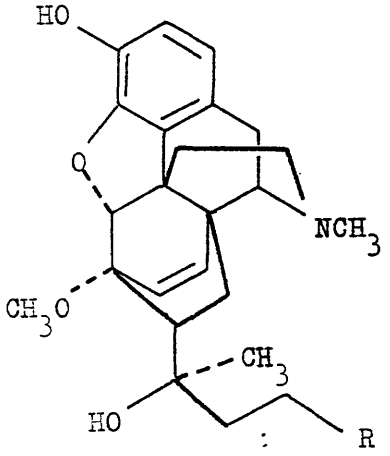
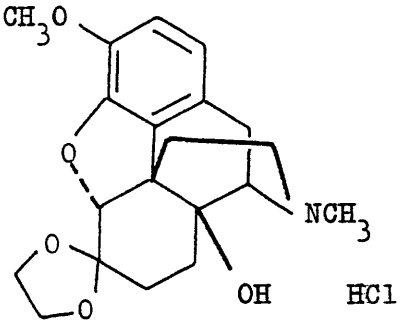


(12) R = CH_3

(13) R = Ph



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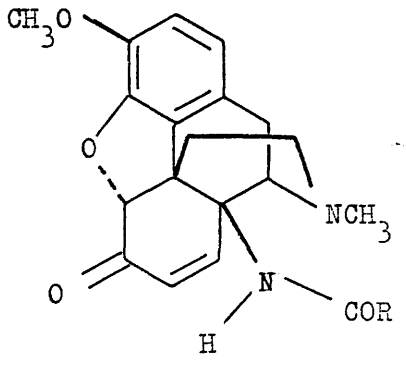
(15) H - Tyr - Gly - Gly - Phe - Met - OH

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



(17)

with the compound (13). In this compound the most important factor appears to be the location of the hydrophobic benzene ring and its geometry relative to the rest of the opiate molecule.

Another group of compounds that show enhanced activity are the 14β-hydroxycodeinones[13]. For example, the modified 14β-hydroxydihydrocodeinone (14) (administered orally) is a more potent analgesic than morphine (given by injection). It has been indicated that this compound has a lower addictive liability than morphine[14]. 14β-Aminocodeinones have been prepared[15,16] and are also potent analgesics, presumably due to the similarity in the hydrophilic environment of the hydroxyl and amino groups.

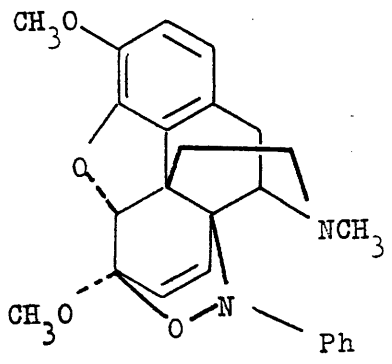
The mode of action of opiates on the central nervous system has,in the past few years, received a great deal of attention[8,9,17]. It has been shown that the opiates bind stereospecifically to receptor sites on the surface of neuronal cells in the brain, and the more potent the opiate is pharmacologically, the stronger is the binding to the brain tissue[8,17]. The direct correlation between specific binding and pharmacological activity is complicated by the differing lipid solubility of the opiates. For example, etorphine, which is around 6 000 times more potent than morphine has only 20 times morphine's affinity for the receptor. However, etorphine is 300 times more soluble in lipid, so is correspondingly more efficient

in penetrating the blood-brain barrier.[17] The combination of 20 fold greater affinity coupled with 300 fold greater penetration can therefore account for etorphine's 6 000 fold greater potency.

The discovery of the enkephalins by Hughes and Kosterlitz[18] in 1975 has opened up a whole new field of neurochemistry. These indigenous opiates are pentapeptides and were isolated from homogenised pig brain in the ratio, methionine enkephalin (15) to leucine enkephalin (16), 3:1. It has been shown that these peptides bind competitively at the same receptor sites in the central nervous system as morphine alkaloids and can be inhibited in their analgesic action by naloxone[8,17].

Although methionine enkephalin and the highly potent 6,14-bridged alkaloid (13) appear at first to be geometrically very different, it was shown that models of the two compounds may adopt very similar shapes. In addition, the main hydrophilic and hydrophobic regions of both molecules can be superimposed.

The aim of this project was to find an efficient and flexible synthetic route to the 14β-acylaminocodeinones (17; R = various alkyl and aryl groups) and to study their analgesic potency. These compounds contain a hydrophilic nitrogen substituent at the 14β-position (cf. the 14-hydroxy-series) and a hydrophobic alkyl or aryl group attached to ring C, and should therefore be highly potent analgesics.



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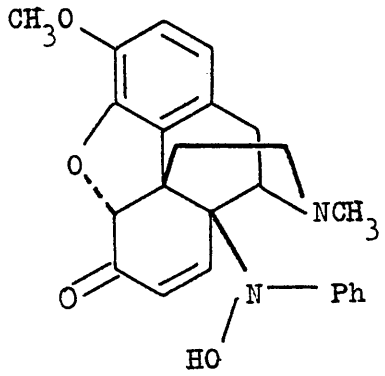

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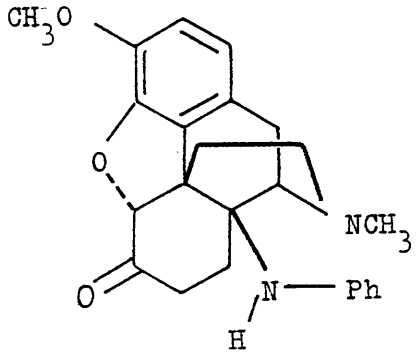

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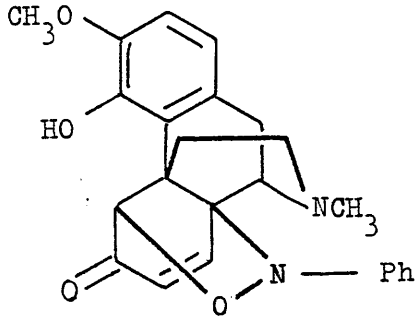

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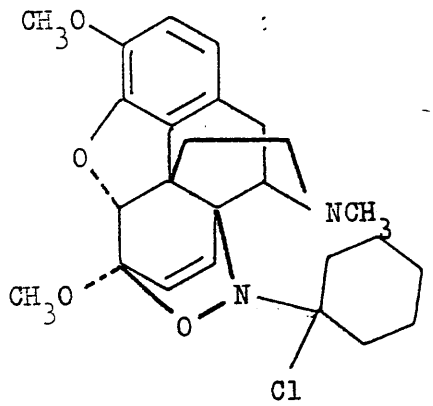

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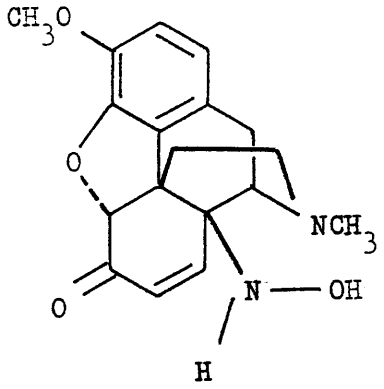

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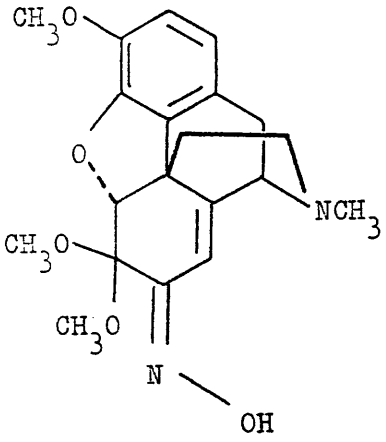
1.2 14-Nitrogen Substituted Derivatives of the Morphine Alkaloids

The introduction of nitrogen into an organic molecule is often achieved *via* nucleophilic attack by a nitrogen atom at an electron deficient centre. However, the 14-position of thebaine is electron rich due to the methoxy-diene system of ring C so nucleophilic attack at this position is precluded. The methods that have been used successfully fall into two categories; either Diels-Alder addition with a nitrogen containing dienophile, or nitration with a mild nitrating agent.

Diels-Alder reactions have been exploited in several different ways to functionalise the diene system of ring C. The first dienophiles to be utilised were nitroso-arenes[15,16,19,20] and it was found that nitrosobenzene readily formed the cyclic adduct (18) at room temperature. This reaction was found to be reversible, with slight dissociation of the adduct back to thebaine and nitrosobenzene. Trituration of the adduct (18) with 1 N hydrochloric acid gave 14β-(*N*-hydroxyphenylamino)-codeinone (19) which could be either catalytically hydrogenated to 14β-phenylaminodihydrocodeinone (20) or re-cyclised with sodium ethoxide in ethanol to give the 5,14-bridged phenol (21).

The capability of nitroso-alkanes to act as dienophiles in Diels-Alder reactions has been demonstrated by the addition



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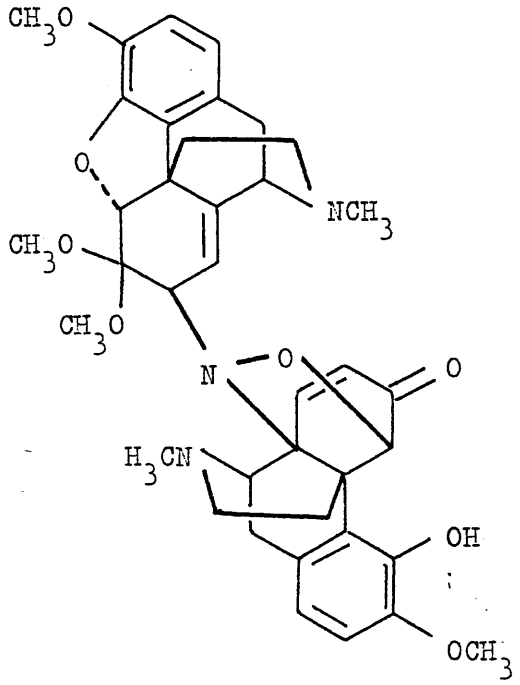

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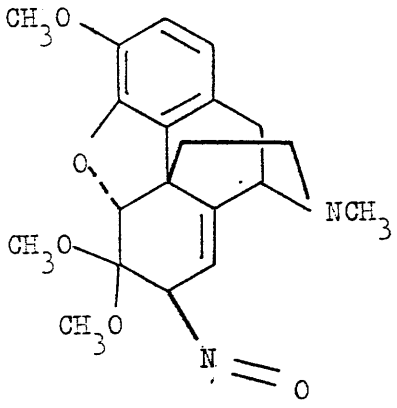

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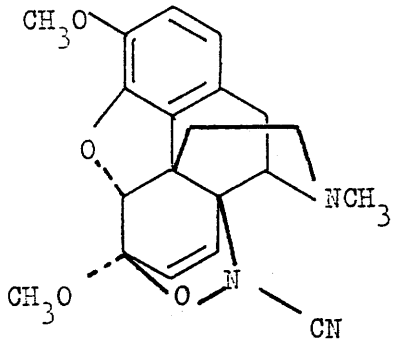

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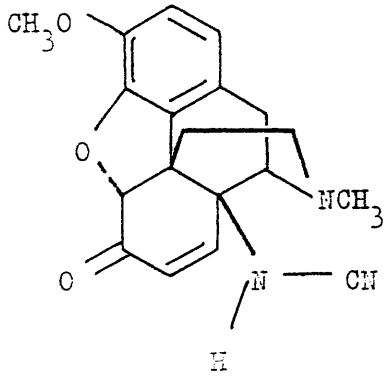

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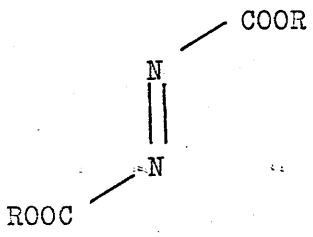


R = CH_3, C_2H_5, CH_2Ph

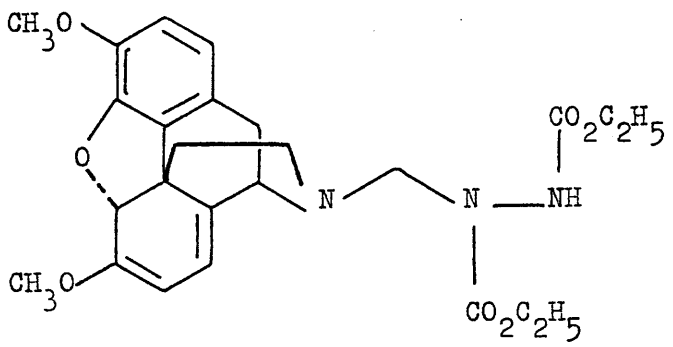
(29)

of 1-chloronitrosocyclohexane to thebaine hydrochloride in ethanol[21]. In this case, the cyclic adduct (22) was not isolated and the product of the reaction was 14β-hydroxyaminocodeinone (23), presumably formed by acid catalysed hydrolysis of the adduct (22).

Electrophilic attack by halogens on the methoxy-diene system of thebaine yielded 14-bromo- or 14-chloro-codeinone[22]. By analogy, nitrosation was expected to yield 14β-nitroso-codeinone, but the product obtained from the reaction of thebaine with nitrosyl chloride in methanol was the 7-substituted neopinone derivative (24)[23,24]. An interesting by-product of these nitrosation experiments was the ketonic dimer (25), presumably formed by the intermediate 7-nitroso-compound (26) effecting a Diels-Alder addition with thebaine to form a 6,14-adduct, which rearranged to the 5,14-bridged phenol (25).

The ability of thebaine to form 6,14-adducts with dienophiles has been used to provide evidence for the existence of the reactive species, nitrosyl cyanide[25]. Thus, thebaine, in the presence of silver cyanide and nitrosyl chloride formed the N-cyano-3,6-dihydro-2H-1,2-oxazine (27), which was hydrogenated with platinum oxide in methanol to the cyanamide (28). This reaction only took place in low yield and was therefore not synthetically useful.

The use of azo-compounds as dienophiles has been explored by several groups of workers. Merz and Pook[26] chose dialkyl azadicarboxylates (29) as their dienophiles and found that,



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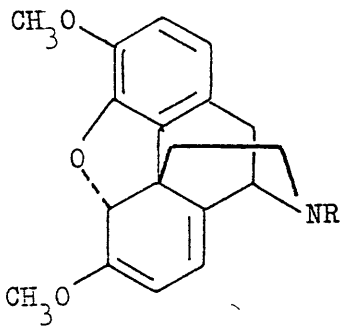

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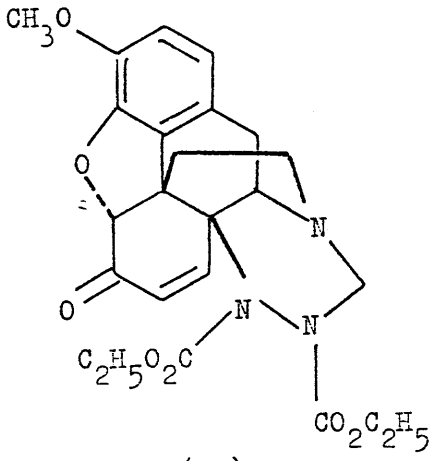

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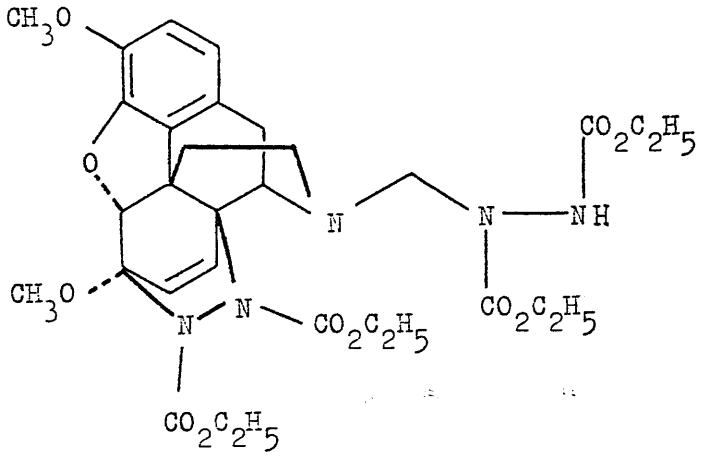

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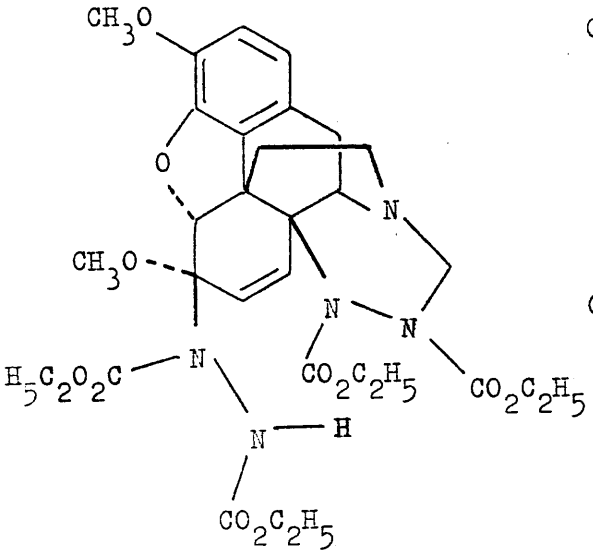
instead of the expected 6,14-cyclic adducts, they obtained, with equimolar amounts of thebaine and diethyl azodicarboxylate, N-(NN'-diethoxycarbonylhydrazinomethyl)northebaine (30), which was readily hydrolysed to northebaine (31; R = H). When thebaine was treated with two molar equivalents of diethyl azodicarboxylate, the product was the codeinone derivative (32). The mechanism postulated for this process proposed initial formation of the N-methyl substituted compound (30) which then reacted with a further molecule of diethyl azodicarboxylate to form the 6,14-adduct (33). Rearrangement of (33) to (34) followed by hydrolysis then yielded compound (32). In contrast, the reaction of N-trifluoroacetylnorthebaine (31; R = $COCF_3$) with one molar equivalent of diethyl azodicarboxylate afforded the adduct (35) which could be hydrolysed to the norcodeinone (36).

As the dialkyl azodicarboxylates only acted as weak dienophiles, it was postulated that this was due to their predominantly transoid geometry. Cyclic azo-compounds would have cisoid geometry, would be less hindered and consequently act as more powerful dienophiles. Several cyclic azo-compounds (37, 38, 39, 40, and 41) have been used to form thebaine adducts[27]. The reactions of "Cookson's Dienophile", 4-phenyl-1,2,4-triazoline-3,5-dione (41)[28] with thebaine have been studied extensively by Ginsburg and co-workers[29]. Formation of the adduct (42) occurred in high yield but attempted formation of the hydrochloride of (42) afforded a



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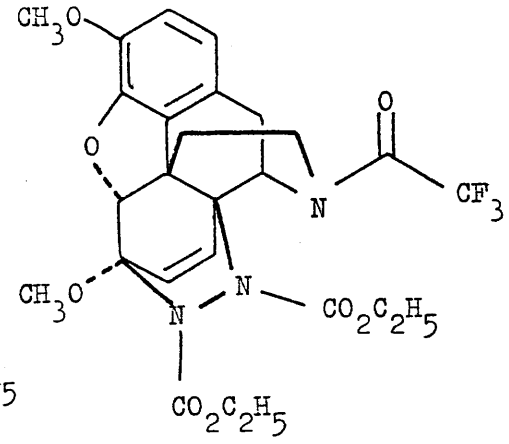

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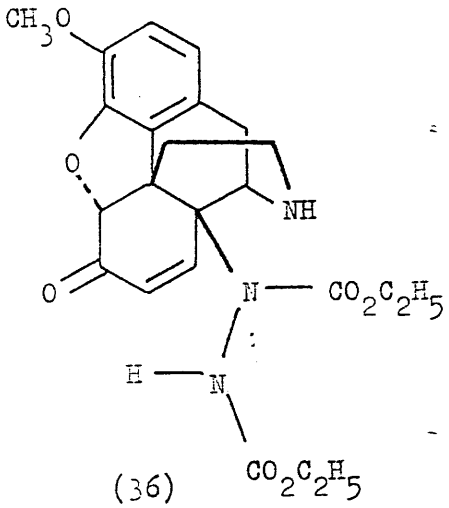

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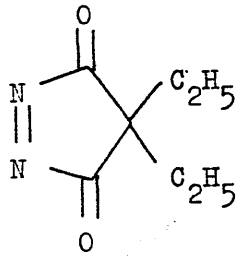

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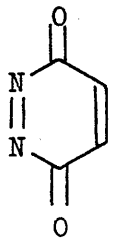

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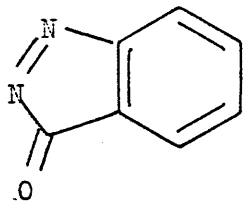

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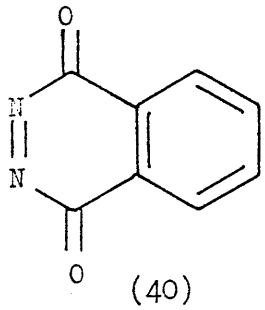

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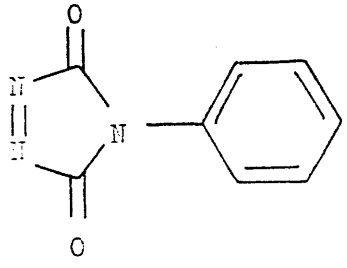

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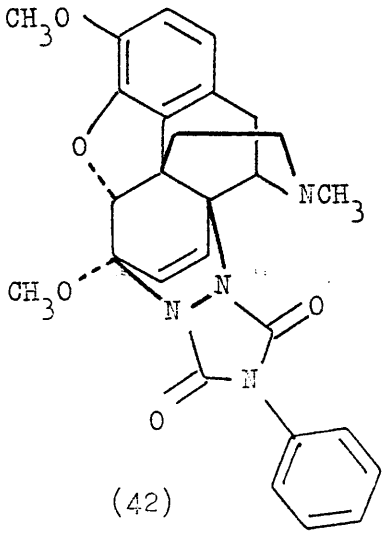

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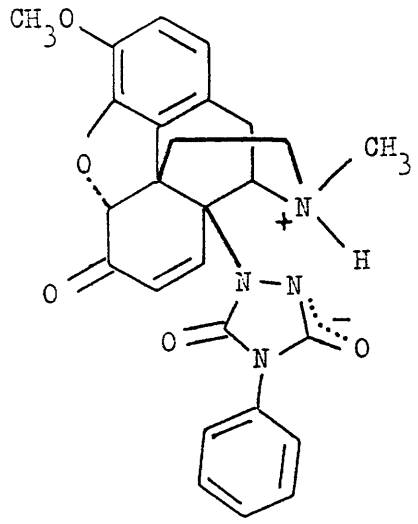

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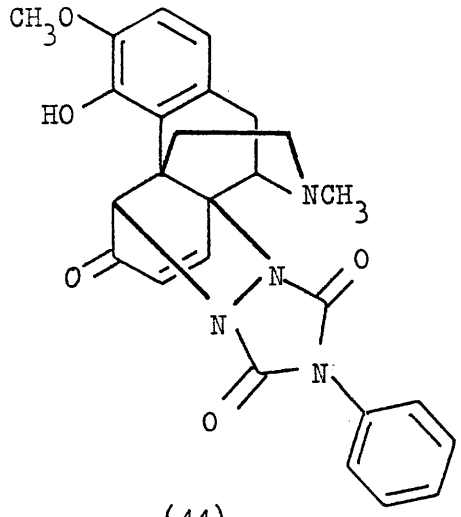

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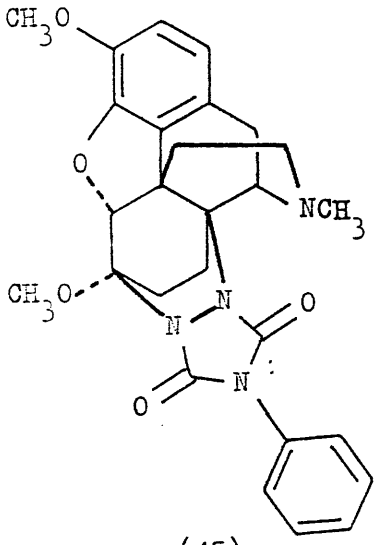

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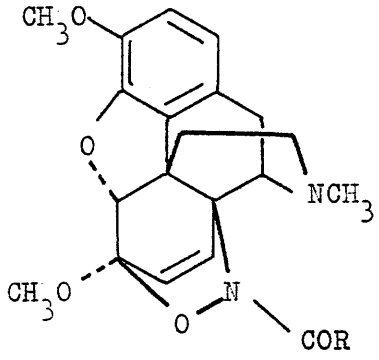

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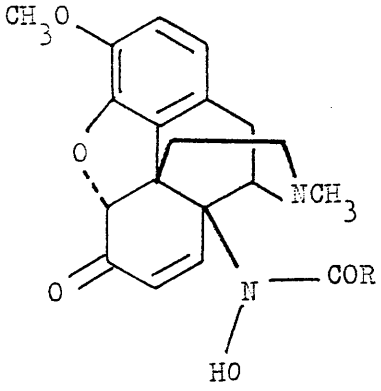

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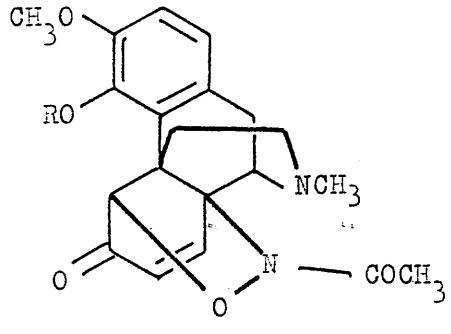
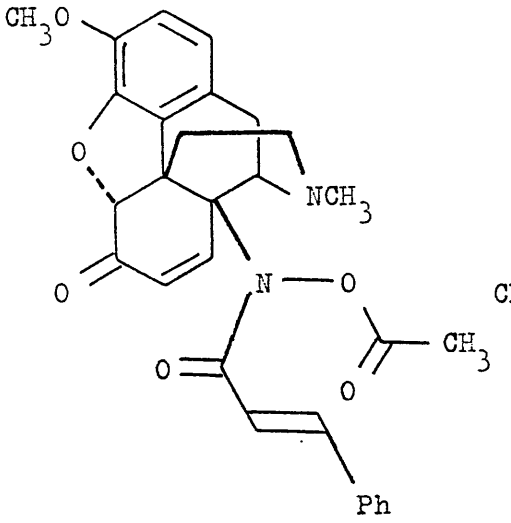


(48)

compound, the free base of which was shown, at least in the solid state, to have the betaine structure (43). This compound readily re-cyclised to the 5,14-bridged phenol (44) upon treatment with pyridine and water. Reduction of the adduct (42) with diimide yielded the dihydro adduct (45) which formed a normal hydrochloride.

The reaction of activated C-nitroso-compounds with thebaine has proved to be the most versatile method of introducing nitrogen at the 14-position of thebaine.[19] Nitrosocarbonyl compounds were first postulated by Beckwith and Evans[30] in 1962 as intermediates in the pyrolysis of alkyl nitrites, but their simplest method of preparation is by the oxidation of hydroxamic acids. Sklarz and Al-Sayyab[31] postulated that the then hypothetical nitrosocarbonyl compound was the active species responsible for acylation of primary aliphatic amines during the oxidation of hydroxamic acids with sodium periodate. Since then, several different oxidizing agents have been empoyed including bromine[32], t-butylhypochlorite,[32] iodine,[33] and mercuric oxide[33]. Oliver and Walters[34] have since postulated that the structure of the species formed during potassium ferricyanide oxidations was the radical anion ($RCO-\dot{N}-\bar{O}$) as opposed to the nitrosocarbonyl compound (RCO-NO). The use of nitrosocarbonyl compounds and their derivatives in Diels-Alder chemistry has been reviewed recently[35,19].

Thebaine reacted with benzohydroxamic acid and acetohydroxamic acid in the presence of tetraethylammonium periodate to yield



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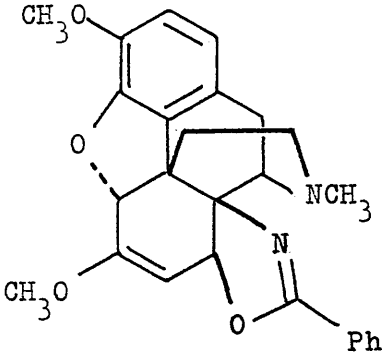

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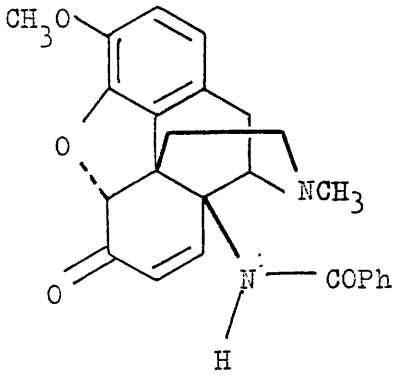

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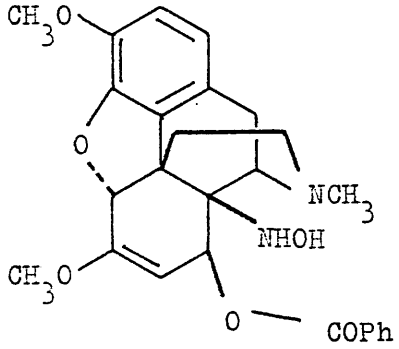

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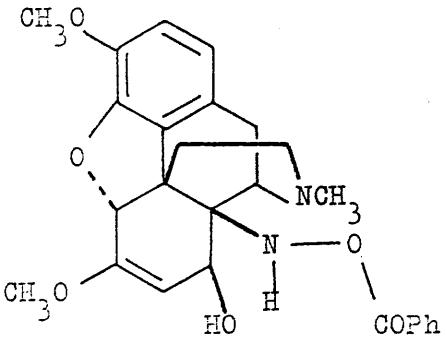

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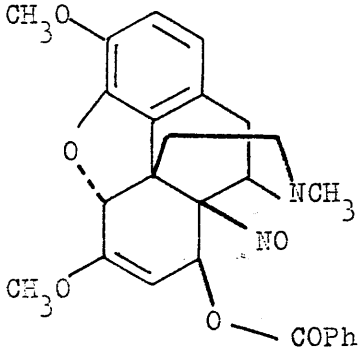
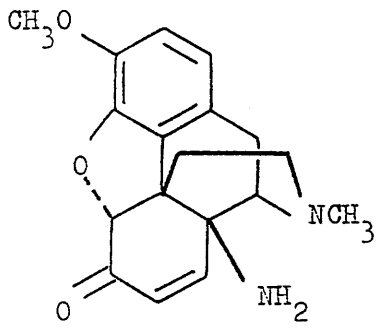


(54)

the nitrosocarbonylmethane and nitrosocarbonylbenzene adducts[36] (46; R = CH_3 or Ph). Hydrolysis of the nitrosocarbonylbenzene adduct (46; R = Ph) in refluxing aqueous methanolic hydrogen chloride yielded 14β-hydroxyaminocodeinone (23), while acid catalysed hydrolysis of the nitrosocarbonylmethane adduct (46; R = CH_3) at 0 °C afforded the enone (47; R = CH_3) which, upon treatment with sodium methoxide in methanol cyclised to the 5,14-bridged phenol (48; R = H)

The adduct (46; R = CH=CHPh) formed from thebaine and cinnamoylhydroxamic acid was prepared by D. McDougal[37], then hydrolysed to the codeinone (47; R = CH=CHPh). Acetylation then yielded the acetate (49). Further studies[37] on the adduct (46; R = Ph) showed that reduction with zinc in acetic acid led, in low yield, to the oxazoline (50) which readily hydrolysed under acidic conditions to yield N-benzoyl-14β-aminocodeinone (51). The adduct (46; R = Ph) was also hydrolysed under mild conditions to yield 8,14-dihydro-8β-benzoyloxy-14β-hydroxy-aminothebaine (52), which could either be hydrolysed to 14β-hydroxyaminocodeinone (23), isomerised to 14β-benzoyloxy-amino-8,14-dihydro-8β-hydroxythebaine (53) or oxidised with manganese dioxide to 8,14-dihydro-8β-benzoyloxy-14β-nitrosothebaine (54). However, these reactions, though extending the knowledge of thebaine chemistry did not provide a simple method of preparing 14β-aminocodeinones.

An efficient synthesis of 14β-aminocodeinone (55) has



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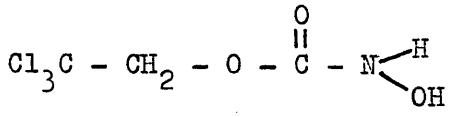

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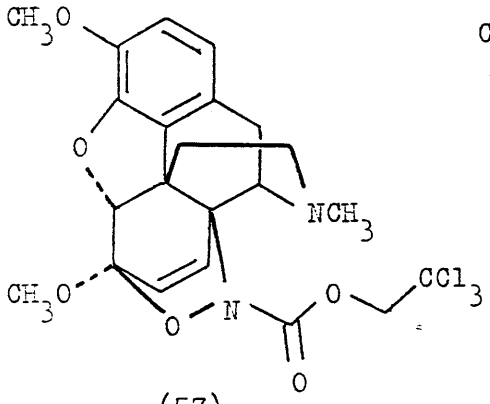

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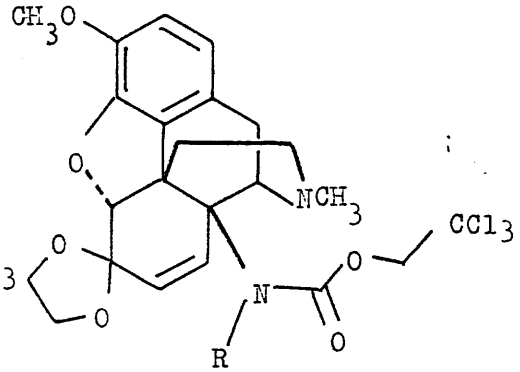

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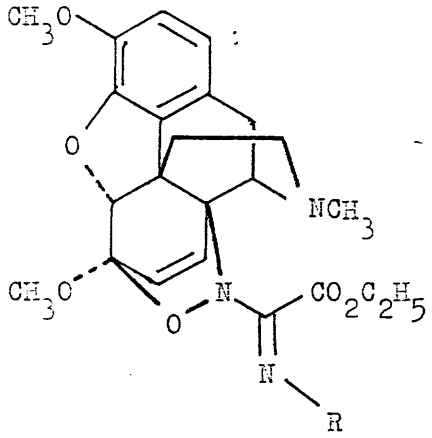
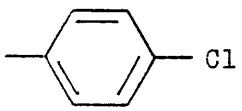
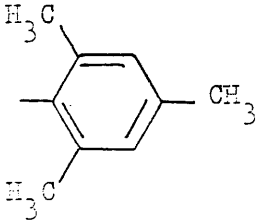
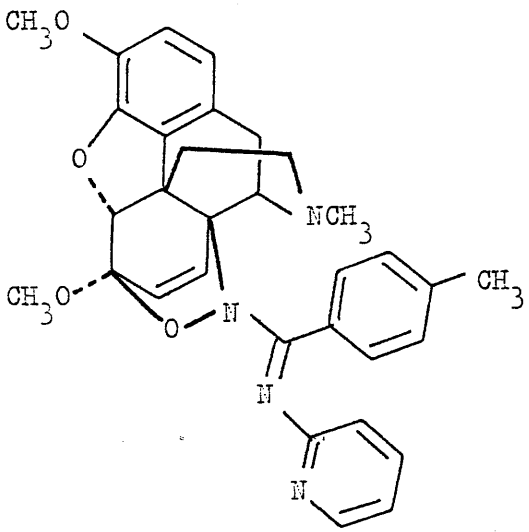


(59) R = 

(60) R = 



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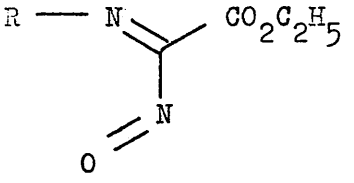

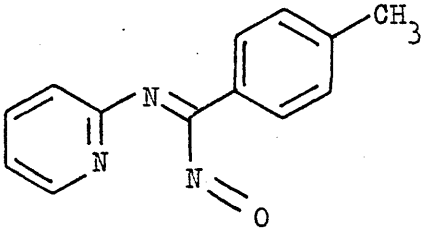

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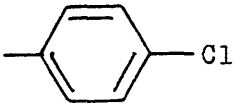
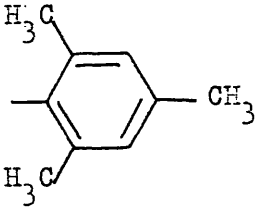
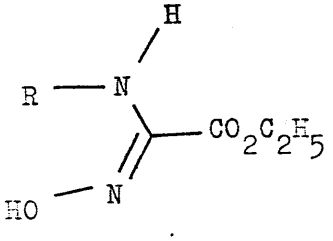
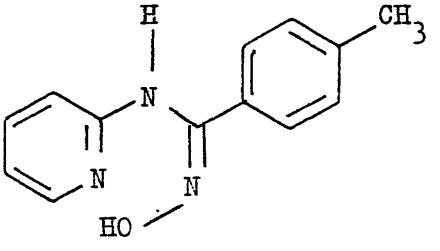
(62) R = 

(63) R = 





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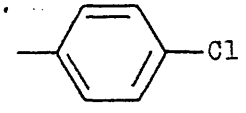
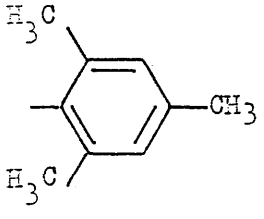
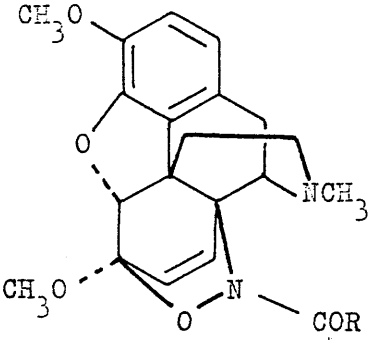
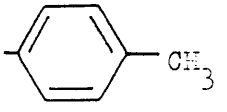
(65) R = 

(66) R = 



(68) R = OCH_2Ph

(69) R = $OC(CH_3)_3$

(70) R = $O(CH_2)_2SO_2$ 

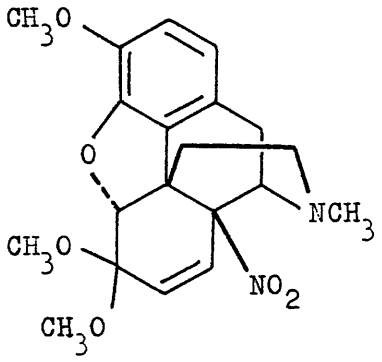
(71) R = NHPh

recently been achieved by D.MacLean[38]. In this example, thebaine and N-(2,2,2-trichloroethoxycarbonyl)hydroxylamine[35] (56) in the presence of sodium periodate, formed the adduct (57) which was converted into the protected N-hydroxycodeinone derivative (58; R = OH) by the action of anhydrous glycolic hydrogen chloride. Reduction with zinc in ammonium chloride ~~to (58; R = H)~~, followed by acidic hydrolysis then yielded 14β-aminocodeinone (55) in ca. 60% from thebaine.

Nitrosoimines have also been used in Diels-Alder reactions with thebaine[39,40]. Thus, the adducts (59,60, and 61) have been prepared from thebaine and the corresponding nitrosimines (62, 63, and 64), which were in turn generated from the corresponding amidoximes (65, 66, and 67) by lead tetra-acetate oxidation.

Nitrosoformates and nitrosoformamides have been prepared by J.MacKinnon[35] and their thebaine adducts studied. Thus benzyl N-hydroxycarbamate was oxidised with tetraethylammonium periodate in the presence of thebaine to yield the thebaine/benzyl nitrosoformate adduct (68); t-butyl N-hydroxycarbamate similarly yielded the adduct (69), and 2-toluene-p-sulphonyl-ethyl N-hydroxycarbamate gave the adduct (70). The analogous reaction of N-hydroxy-N'-phenylurea afforded the thebaine/N-phenylnitrosoformamide adduct (71).

The nitration of thebaine with tetranitromethane provides a method of obtaining 14β-aminocodeinone derivatives. This reaction was first studied by R.Allen[41] who reported that the



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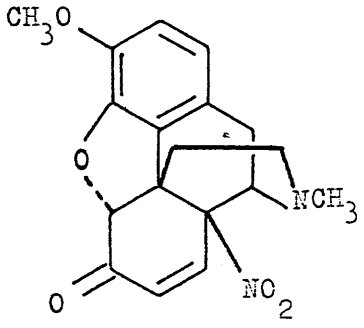

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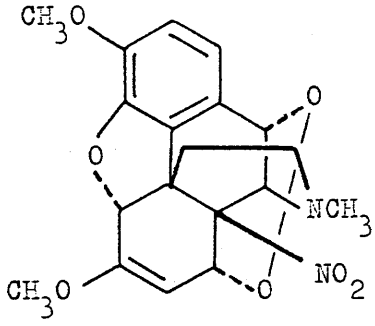

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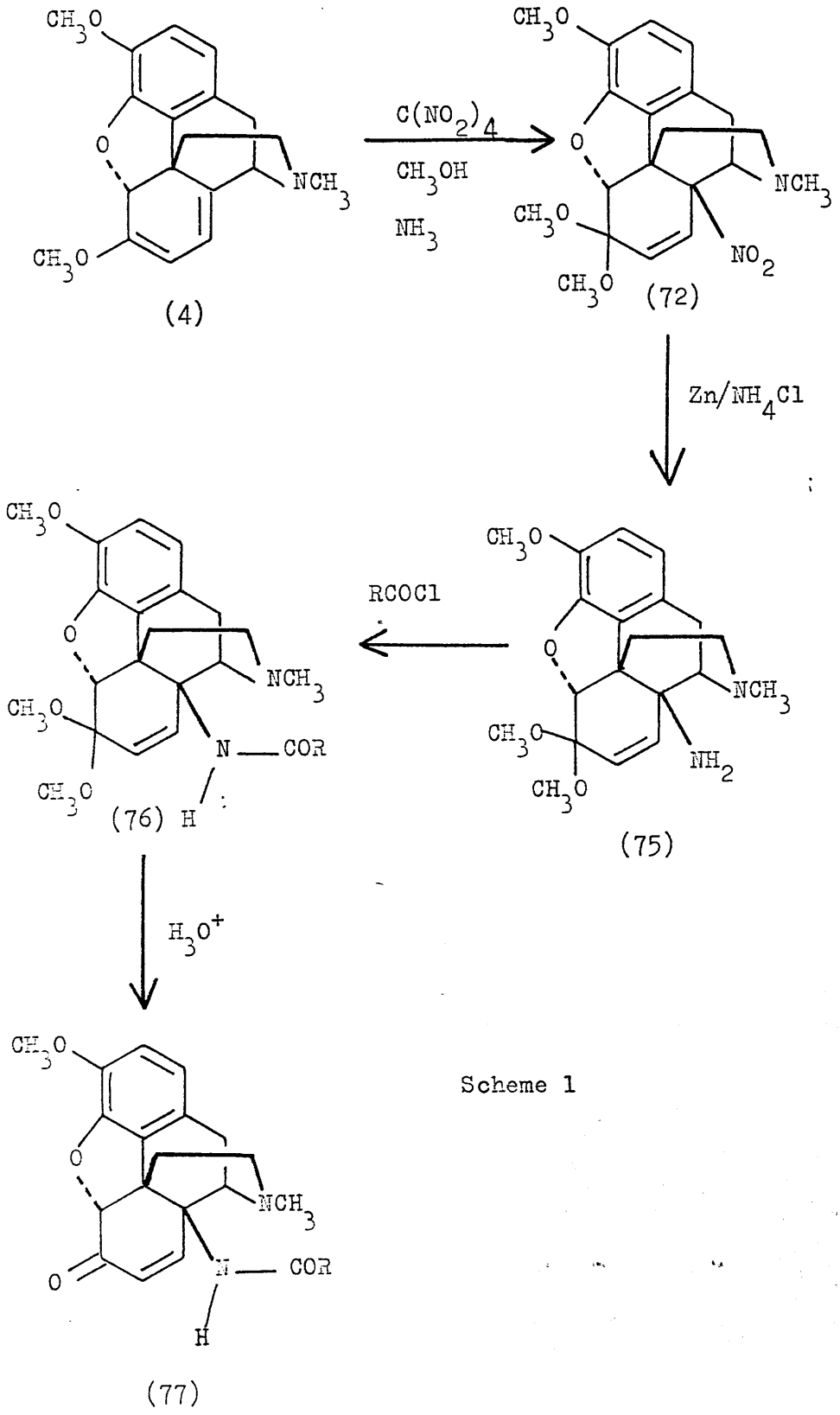
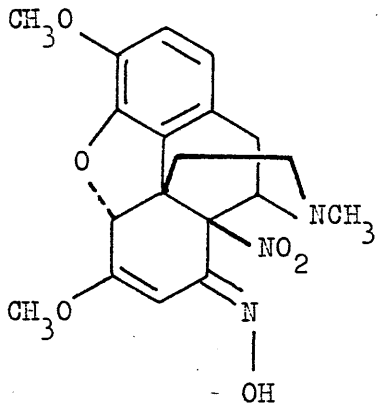

CH3O
O
NCH3
CH3O
(4)
C(NO2)4
CH3OH
NH3
CH3O
O
NCH3
CH3O
NO2
CH3O
(72)
Zn/NH4Cl
CH3O
O
NCH3
CH3O
NH2
CH3O
(75)
RCOCl
CH3O
O
NCH3
CH3O
N—COR
CH3O
(76) H
H3O+
CH3O
O
NCH3
O
N—COR
H
(77)

Scheme 1

major product was the nitroform salt of thebaine (thebaine H^+ $C(NO_2)_3^-$) with small amounts of 14β-nitrocodeinone dimethyl acetal (72), an unknown product which was chromatographically sililar to (72), and a trace of 14β-nitrocodeinone (73). Later work by D.McDougal[37] improved this reaction and identified the unknown product as 8α,10α-epidioxy-8,14-dihydro-14β-nitro-thebaine (74), although this compound did not give a satisfactory elemental analysis (vide infra).

This method has been developed[42] to provide a synthetic route to the 14β-acylaminocodeinones (scheme 1). Thebaine was first treated with tetranitromethane in methanol containing ammonia to yield the dimethyl acetal (72). Reduction with zinc and ammonium chloride to the amine (75), followed by acylation, then gave the 14β-aminocodeinone dimethyl acetals (76). Acid catalysed hydrolysis then gave the 14β-acylaminocodeinones (77). The main disadvantage in this route was that the nitration with tetranitromethane proceeded in only modsrate yield. Another more dangerous aspect of this reaction was the formation of ammonium nitroformate ($NH_4^+C(NO_2)_3^-$) as a by-product which was demonstrated to be a thermal and shock sensitive explosive. However, a large number of compounds have recently been prepared by this method[43,44].

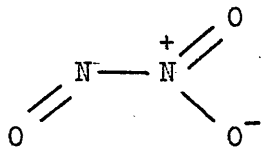
Nitration of thebaine has also been achieved with concentrated nitric acid[37], but the reaction proceeded in



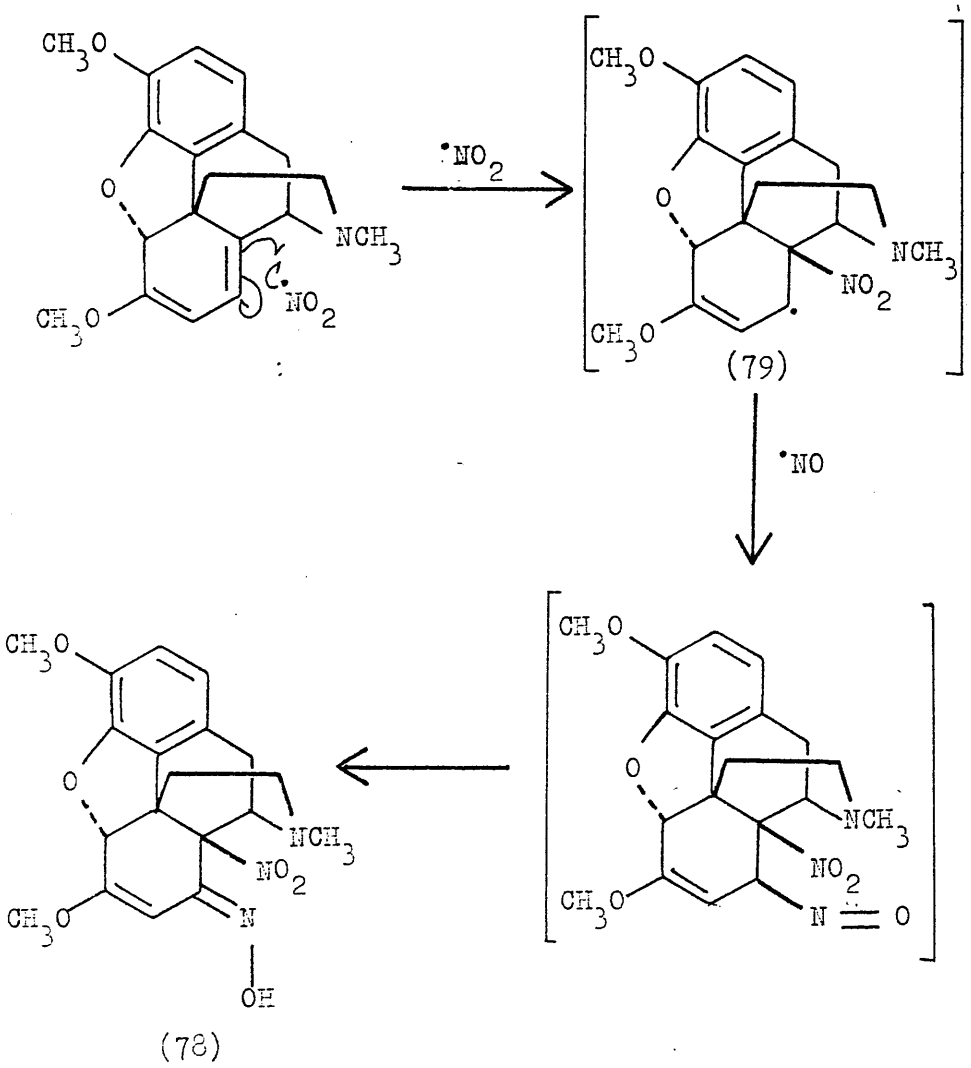
(78)

extremely low yield, presumably due to degradation of the starting material under the severe conditions. 14β-Nitrocodeinone (73) was obtained from this process in 9% yield, and 1-nitrothebaine in 4% yield.

Dinitrogen trioxide has also been used to nitrate thebaine[45]. This somewhat obscure reaction yielded 8,14-dihydro-14β-nitro-7-oximinothebaine (78) in low yield. Further work, vide infra, has explored the scope of this reaction and provided analytical data for compound (78).



(80)



(78)

Scheme 2

Chapter 2 DISCUSSION

2.1 The Reaction of Thebaine with Dinitrogen Trioxide

In preliminary studies on the reaction of thebaine with dinitrogen trioxide in benzene[45], a compound, tentatively assigned the structure (78) was isolated in low yield, The following studies were carried out to complete the characterisation of this product and to improve, if possible the yield.

The chemistry of dinitrogen trioxide has received considerable attention since its discovery by Gay-Lussac in 1816[46]. Dinitrogen trioxide exists as a bright blue solid which melts at ca. - 102 °C to form a deep blue liquid (b.p. 3.5 °C), and, in the liquid state has the nitro-nitroso structure (80)[47]. In the gaseous state however, it is highly dissociated to form a mixture of nitric oxide and nitrogen dioxide, but the chemistry is further complicated by the equilibrium between nitrogen dioxide and its dimer, dinitrogen tetroxide:

$$2NO_2 \rightleftharpoons N_2O_4$$

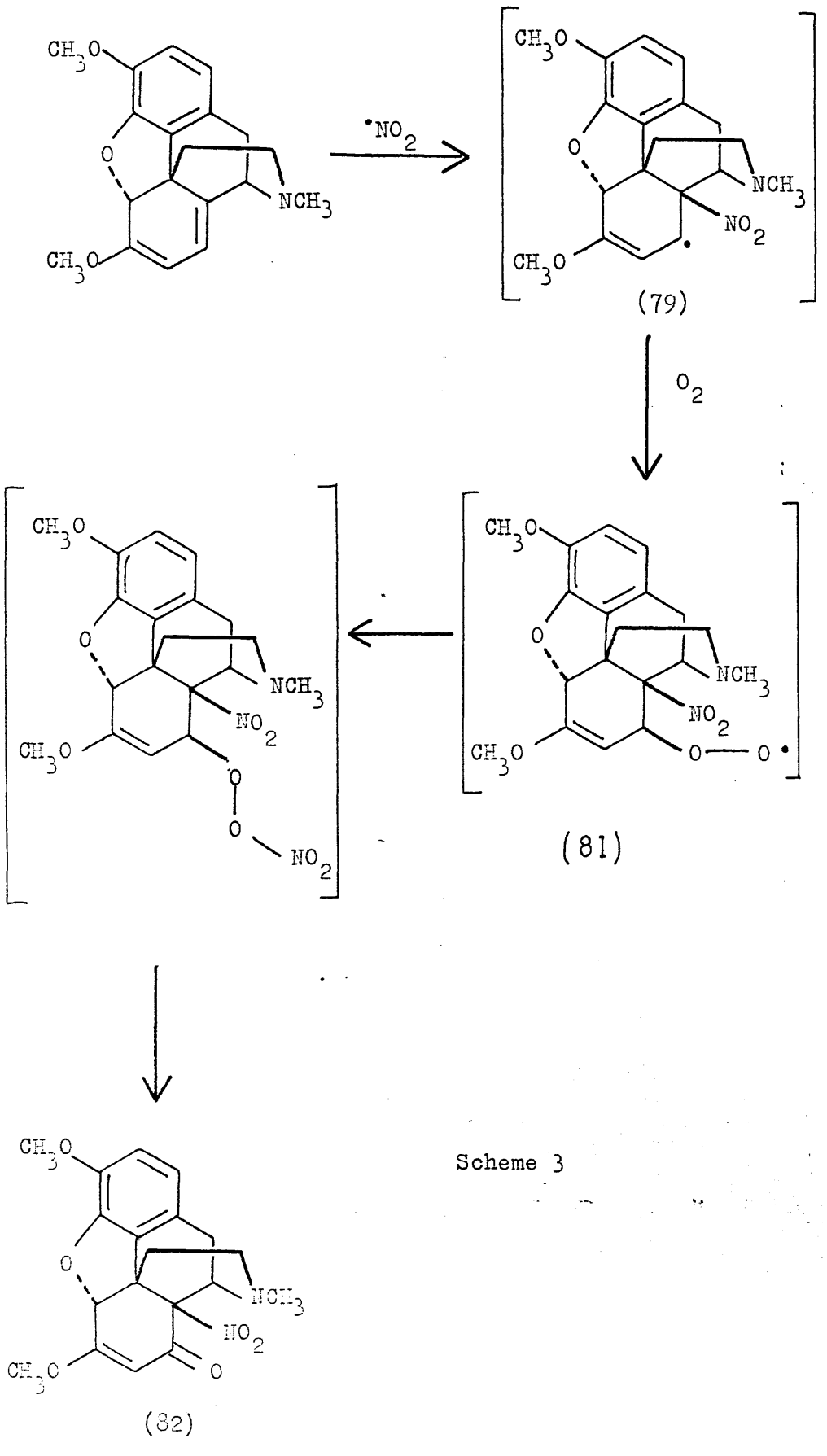
Thus,'nitrous fumes' consist of a complex mixture of nitrogen oxides, which exist in equilibrium.

The reaction of thebaine with dinitrogen trioxide to form the nitro-oxime (78) can best be considered as involving nitrogen dioxide and nitric oxide radicals as the reactive species. Scheme 2 shows a possible mechanistic pathway, in which the nitro-radical attacks the 14-position to form the stabilised

allylic radical (79) which in turn reacts with a nitroso radical to form the 14-nitro-8-nitroso compound, which tautomerises to form the oxime (78).

The i.r. spectrum of the oxime (78) showed the presence of an OH (3 280 cm^{-1}), a C=N (1 634 cm^{-1}) and an NO_2 group (1 550 and 1 373 cm^{-1}), while the u.v. spectrum was consistent with an $\alpha\beta$-unsaturated oxime (230 nm, ε 1.42 x 10^4). The n.m.r. spectrum gave three sharp singlets for the three methyl groups, and the broad doublet at δ 4.28 was assigned to H-9, which coupled to H-10α (J 7 Hz), but not to H-10β, as the dihedral angle H-9 :H-10β was ca. 90 °. The singlets at δ 5.31 and δ 5.76 were attributed to H-5 and H-7 respectively. The aromatic protons gave a double doublet centred at δ 6.77 with a coupling constant of 8 Hz. The upfield signal (δ 6.70) was assigned to H-1 due to the very slight broadening caused by the benzylic coupling (1 Hz) to the H-10 protons, and the D_2O exchangeable broad singlet at δ 11.70 was assigned to the N-OH proton. The mass spectrum showed the molecular ion at m/e 387, M-OH at 370 and M-NO_2 at 341.

Several experimental problems were encountered with this reaction, and all attempts to improve the process met with singular lack of success. The preparation of dry dinitrogen trioxide in the correct amounts for a specific experiment was difficult, and the apparatus for its generation evolved through several variants before the most successful design was constructed.



(79)

(81)

(82)

Scheme 3

A diagram of this apparatus is included in the experimental section.

The major by-product from this reaction was a thebaine salt which appeared as a voluminous yellow precipitate on addition of the dinitrogen trioxide to the solution of thebaine. This material was removed by filtration, and, upon treatment with dilute sodium hydroxide, followed by extraction with ethyl acetate, regenerated thebaine.

Various experimental parameters (eg. solvents, concentrations, reaction times, temperatures, rates of addition and amounts of dinitrogen trioxide) were altered in attempts to make formation of the nitro-oxime (78) more selective, but no increase in specificity was achieved. Attempts to improve the probability of capture of the allylic radical (79) by the addition of large excesses of nitric oxide gave no significant improvement.

As a variation of this experimental route, the addition of dinitrogen trioxide to thebaine was attempted in the presence of a large excess of oxygen. Thus, it was hoped that the intermediate stabilised allylic radical (79) would capture a molecule of oxygen to give the species (81), which might then form, for example, the 8-keto-4-nitro compound (82), as in scheme 3. This reaction was attempted with acetone as solvent to minimise precipitation of thebaine salts. During workup, evaporation of the solvent at ca. 30 ^{o}C/20 mm Hg resulted in the explosion of the total reaction mixture. Whether this was due

to thermal decomposition of a peroxide intermediate was never clearly established. In the hope that a peroxide had indeed been formed, the reaction was carefully repeated and the total reaction mixture treated with potassium iodide in acetic acid, to cleave any potential peroxide to an alcohol, but this procedure yielded no recognisable product.

The main disadvantage of this experimental route was the production of thebaine salts. It was decided that this problem could be readily overcome if thebaine was first converted into N-benzyloxycarbonylnorthebaine which would be incapable of salt formation. Thebaine was accordingly first converted into northebaine which was in turn reacted with benzylchloroformate to give N-benzyloxycarbonylnorthebaine.

The literature method for N-demethylation of thebaine is of interest, as it was discovered by Merz and Pook[26] during their attempt to carry out a Diels-Alder addition of diethyl azodicarboxylate to thebaine (see p10). Northebaine prepared by this method was then converted into N-benzyloxycarbonylnorthebaine.[48] The n.m.r. spectrum of this compound at 55 °C gave a sharp singlet (δ 5.16) for the two benzylic protons of the carbamate moiety, but on cooling to 0 °C, this singlet split into two signals separated by 0.03 ppm. In addition, at 55 °C, H-8 formed a sharp doublet at δ 5.61 (J 7 Hz), which became broader at 30 °C and finally formed a triplet centred at δ 5.62 at 0 °C. This behaviour was best explained

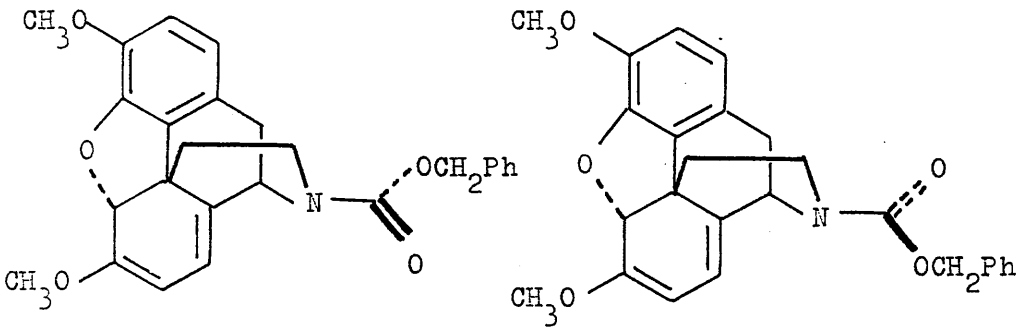
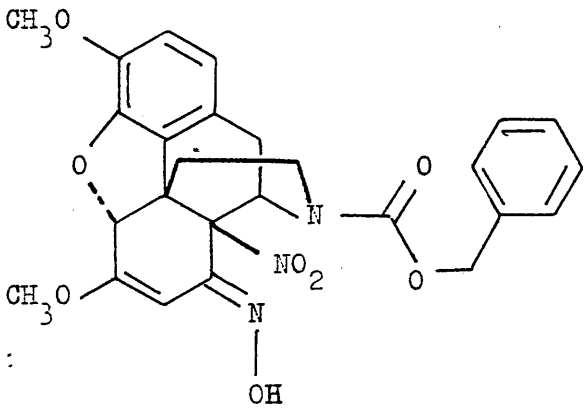
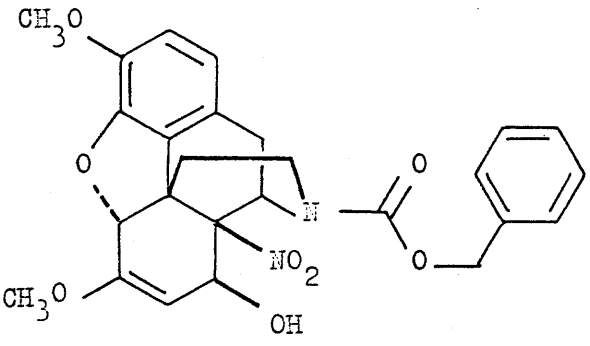


Figure 1



(83)



(84)

by the temperature dependent interconversion of the urethane rotamers, as shown in Fig. 1.

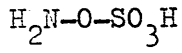
The reaction of N-benzyloxycarbonylnorthebaine with dinitrogen trioxide was studied under two different sets of experimental conditions: by passing gaseous dinitrogen trioxide into a solution of N-benzyloxycarbonylnorthebaine dissolved in a suitable solvent, or by adding a solution of N-benzyloxycarbonylnorthebaine directly to liquid dinitrogen trioxide at ca. 0 °C. Both these procedures yielded impure nitro-oxime (83), but although there was no precipitation of thebaine salts, the yields for both processes were still very low, with formation of several by-products.

The i.r. spectrum of the nitro-oxime (83) showed the presence of an OH (3 280 cm^{-1}), C=N (1 632 cm^{-1}), and an NO_2 group (1 549 and 1 372 cm^{-1}), and the u.v. spectrum was consistent with the presence of an $\alpha\beta$-unsaturated oxime (231 nm, ε 7.69 x 10^3). The n.m.r spectrum corresponded closely to that of the nitro-oxime (78) except for the loss of the N-methyl signal and replacement with the benzyl carbamate moiety showing singlets at δ 5.19 and δ 7.29 corresponding to the benzylic and aromatic protons respectively. The signal for H-9, though visible in the nitro-oxime (78) as a doublet at δ 4.28 was not visible in the spectrum of the oxime (83). This could have been due to a change in the chemical shift induced by the close proximity of the aromatic ring of the benzyl ester group causing the H-9

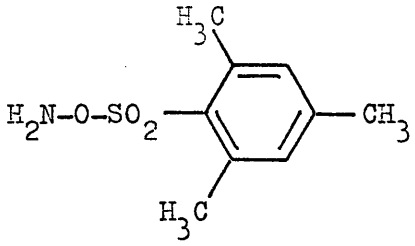
resonance to be masked by other signals. In addition, the presence of urethane rotamers, as observed with the starting material, could further complicate the spectrum.

Examination of the mass spectrum showed the molecular ion at m/e 507, M-NO_2 at 461, and M-$PhCH_2OH$ at 399. In addition, there appeared to be an extra molecular ion at m/e 494, and associated fragments, notably M-O at 478 and M-C_6H_5 at 417. A further molecular ion at 534 was also visible. The presence of these two contaminants explained the anomalous microanalytical data for the oxime (83) which was inconsistent with a molecular formula of $C_{26}H_{25}N_3O_8$, the result for carbon being 0.72% greater than the theoretical value. Close examination of this material by t.l.c. on silica showed that two compounds were indeed present, with somewhat similar chromatographic properties, but as the melting point of 199-201 °C was sharp, the oxime (83) was probably co-crystallising with impurities. The identity of the major impurity at m/e 494 remains unknown, but, with a possible molecular formula of $C_{26}H_{26}N_2O_8$, the alcohol (84) seems likely (see above).

Due to the experimental difficulties encountered in every aspect of the reactions of thebaine with dinitrogen trioxide, this strategy for introduction of nitrogen at the 14-position was abandoned.



(85)



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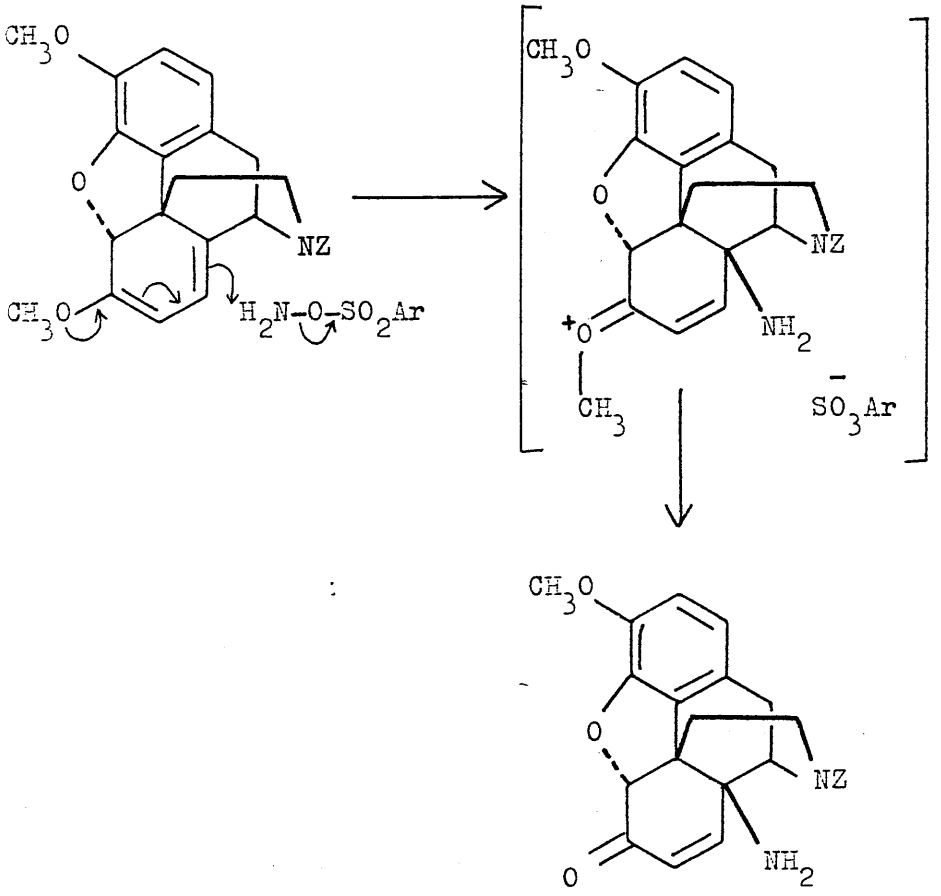
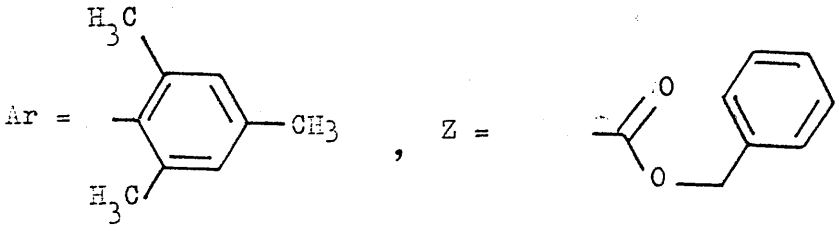
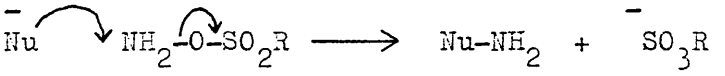




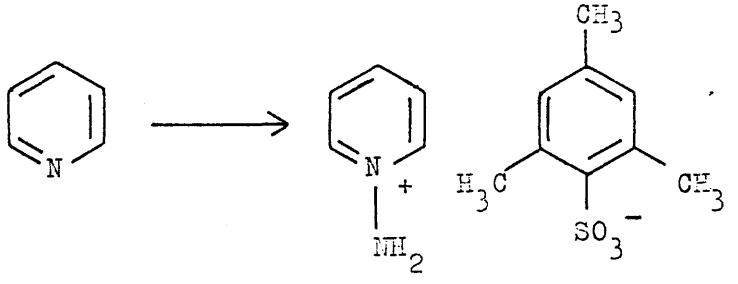
Scheme 4

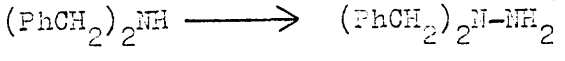
2.2 Attempts to Aminate Thebaine with Electrophilic Aminating Agents

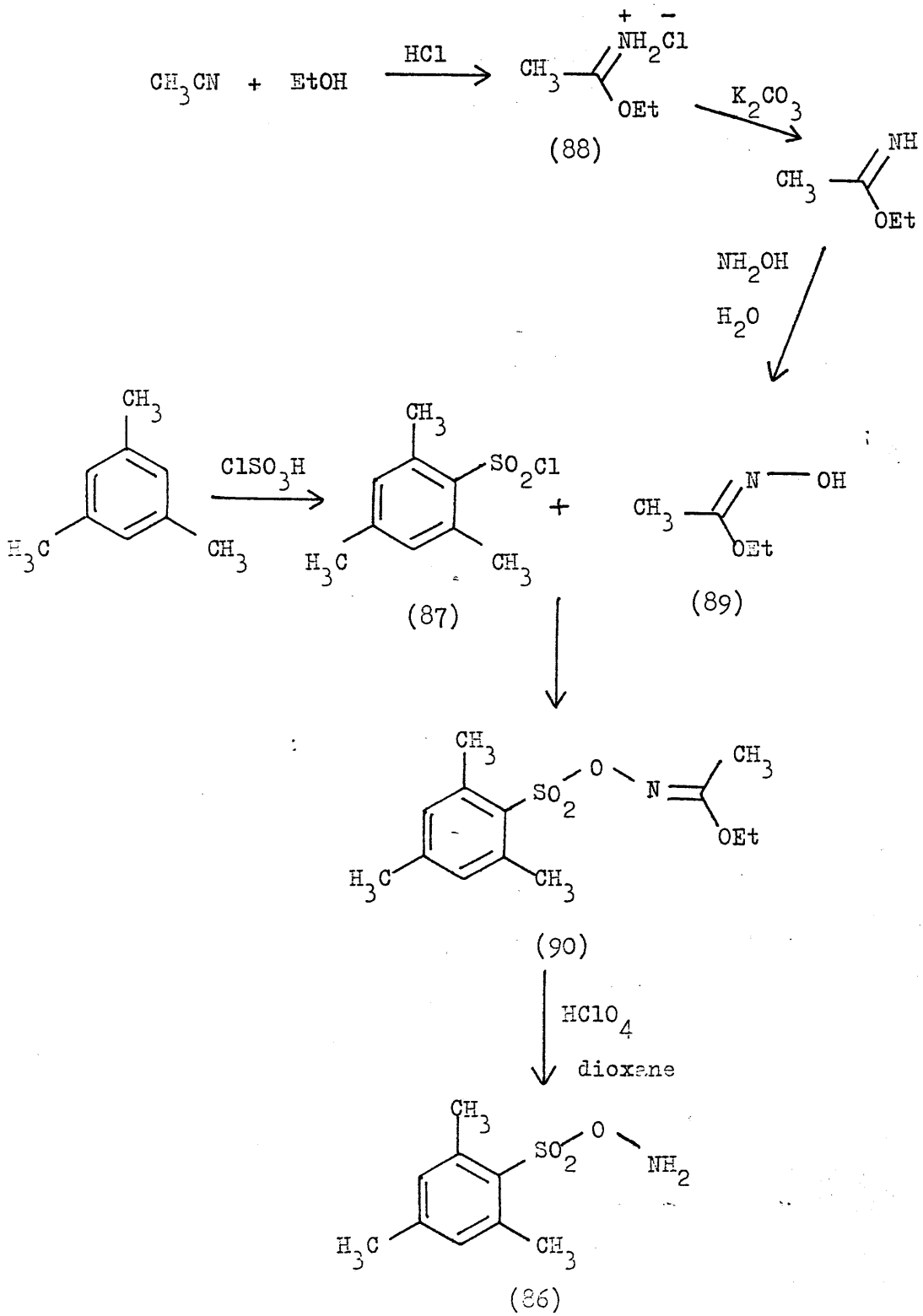
Most aminations proceed by nucleophilic attack of an amine at an electron deficient centre, but as the 14-position of thebaine is electron rich, aminations of this nature are precluded. The possibility of aminating thebaine directly with an electrophilic aminating agent of the general structure NH_2-X, where X is a leaving group was therefore considered. Reagents such as hydroxylamine-O-sulphonic acid (85) and aryl derivatives such as mesitylenesulphonylhydroxylamine (86)[49] fall into this category and react with nucleophiles as shown below.



Mesitylenesulphonylhydroxylamine is commonly used for the amination of amines such as pyridine, to form N-amino-pyridinium mesitylenesulphonate, and secondary amines to form substituted hydrazine derivatives.





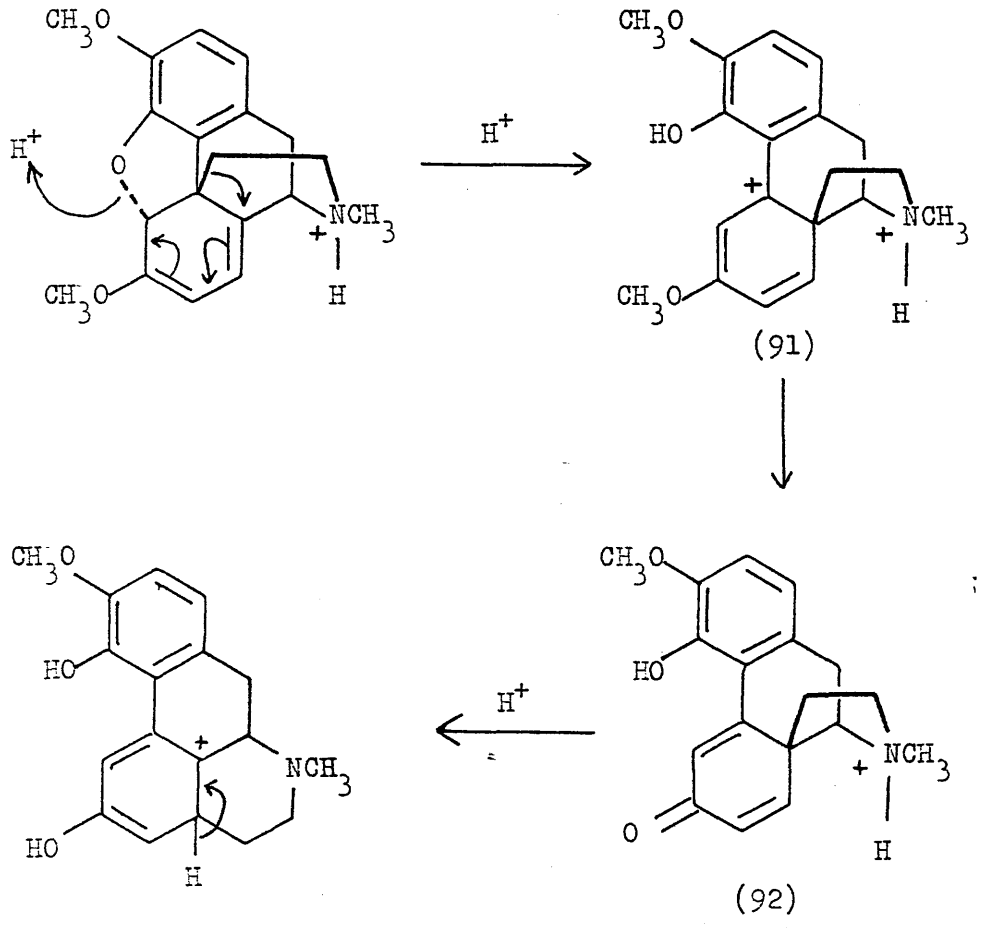

CH3CN + EtOH
HCl
(88)
K2CO3
NH2OH
H2O
ClSO3H
(87)
(89)
(90)
HClO4
dioxane
(86)

Scheme 5

The reaction of mesitylenesulphonylhydroxylamine with activated dienes, as is the case with thebaine, is unknown, but the advantage of this strategy, if successful, would be formation of the 14 -aminocodeinone from N-benzyloxycarbonyl-northebaine in one step, as shown in scheme 4. Thebaine itself, due to the presence of the tertiary amino-group might react preferentially at the nitrogen atom, forming a salt, and therefore must be protected as the urethane, N-benzyloxycarbonyl-northebaine.

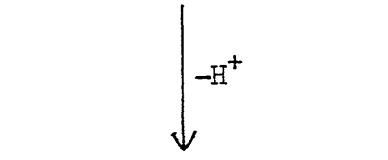
Mesitylenesulphonylhydroxylamine was prepared with difficulty by the literature method as described in scheme 5. The reactivity of the final product was confirmed by the preparation of N-amino-pyridinium mesitylenesulphonate from pyridine. This material had m.p. 123-124 °C, which agreed with the literature value[49] of 125-126 °C.

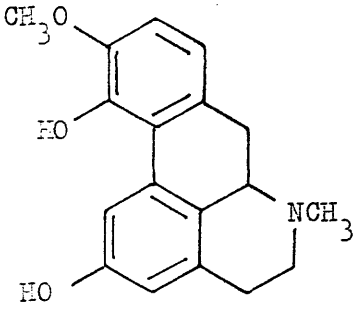
The reaction of mesitylenesulphonylhydroxylamine with N-benzyloxycarbonylnorthebaine unfortunately yielded no aminated products. N.m.r. spectroscopy was used to monitor the reaction progress and this indicated that no reaction occurred at 30 °C in deuteriochloroform for 10 h, after which the spectrum became progressively more complex. As the reaction of mesitylenesulphonylhydroxylamine with simple amines goes to completion within five minutes, the changes in the n.m.r. spectrum after 10 h were probably caused by degradation or rearrangement of the starting material as opposed to amination



(91)

(92)





(93)

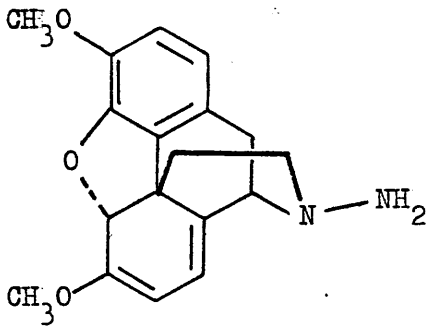
Scheme 6

The 14-position was therefore either not sufficiently strongly nucleophilic, or, the steric blocking effect of the benzyloxycarbonyl group was hindering the approach of the mesitylenesulphonylhydroxylamine molecule.

The reaction of N-benzyloxycarbonylnorthebaine with hydroxylamine-O-sulphonic acid was also attempted and was again followed by n.m.r. spectroscopy. After 3 h, all the starting material had been consumed, and t.l.c. showed that predominently two compounds were present. Separation by preparative t.l.c. and examination of the solution i.r. spectra of the components indicated that neither compound exhibited an N-H stretching vibration in the region 3 500-3 300 cm^{-1}, therefore no amination had taken place.

Due to the acidity of the hydroxylamine-O-sulphonic acid (pH 1), it was postulated that both compounds were formed by acid catalysed rearrangement of N-benzyloxycarbonylnorthebaine, as opposed to amination. The acid catalysed rearrangement of thebaine is well known[50] and proceeds with opening of the ether bridge followed by migration of the side chain from C-13 to C-14 to yield the benzylic carbonium ion (91). Hydrolysis to the ketone (92) followed by migration of the side chain from C-14 to C-8 allows ring C to aromatise, and so form morphothebaine (93). This is represented in scheme 6.

Thus, it appeared that the reaction of N-benzyloxycarbonylnorthebaine with hydroxylamine-O-sulphonic acid might involve

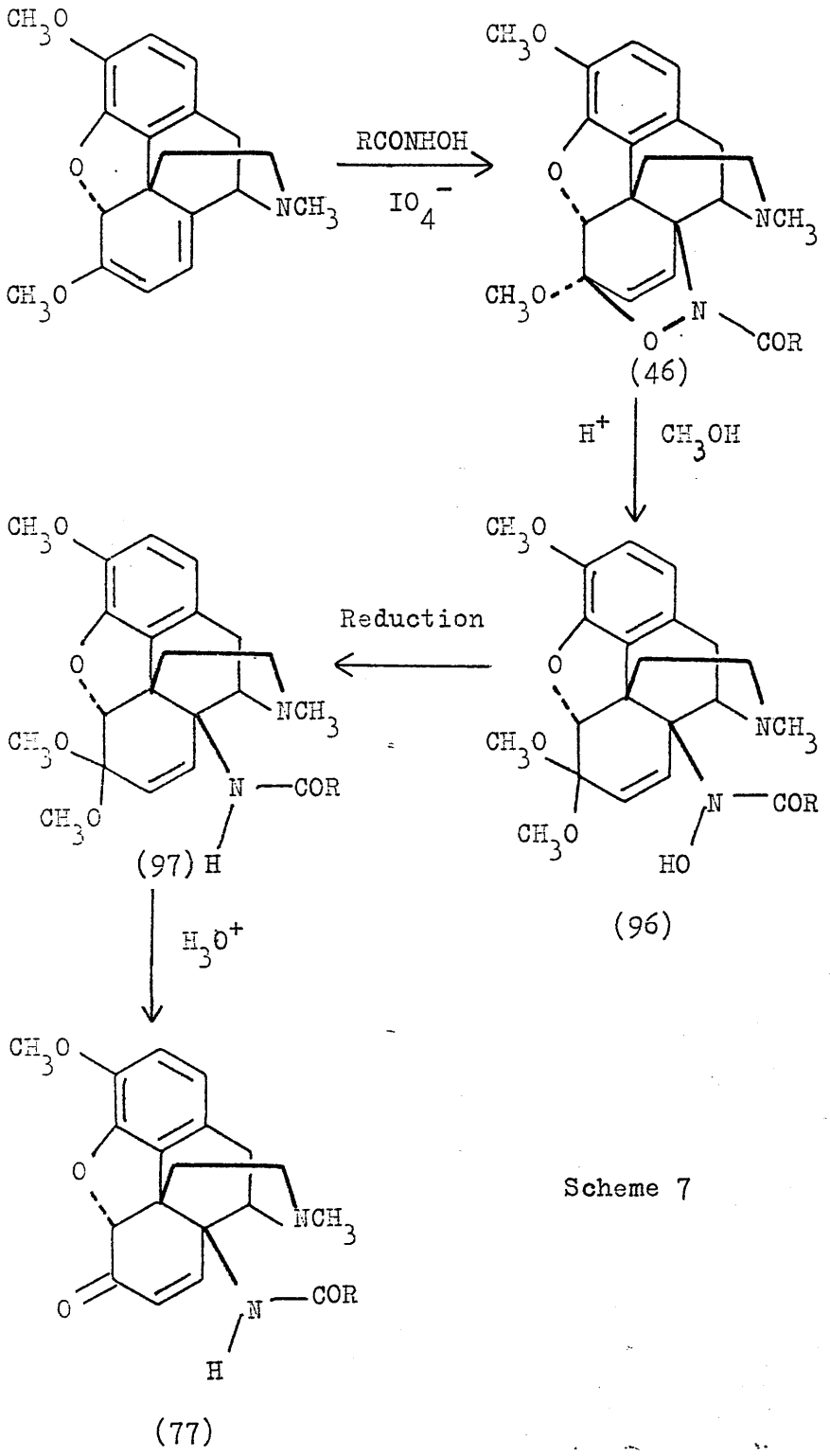


(95)

an acid catalysed rearrangement of the thebaine nucleus, and not an amination. Further evidence for this was obtained by the reaction of N-benzyloxycarbonylnorthebaine with a catalytic amount of hydroxylamine-O-sulphonic acid to give the same two products, and the rearrangement catalysed by concentrated hydrochloric acid in methanol gave two compounds, again separable by t.l.c. The major product (less polar) had the same n.m.r. spectrum as the unidentified product from the hydroxylamine-O-sulphonic acid rearrangement.

Although attempts to aminate N-benzyloxycarbonylnorthebaine directly in the 14-position had proved unsuccessful, it was decided that, since the reaction of mesitylenesulphonylhydroxylamine with secondary amines was well established, it would be worthwhile to attempt the preparation of the unknown N-aminonorthebaine. Northebaine was therefore treated with an equimolar amount of mesitylenesulphonylhydroxylamine in deuteriochloroform and the reaction progress followed by n.m.r. spectroscopy. Within 5 minutes, a compound had been formed which, though never isolated in a pure state, was provisionally assumed to be N-aminonorthebaine (95). The n.m.r. spectrum was very similar to that of northebaine, except for a downfield shift of the H-8 doublet by 0.3 ppm and the appearence of the H-9 doublet (δ 4.54), which previously had been masked by other resonances in the region δ 3.0 to 4.0.

The attempted N-amination of northebaine with hydroxylamine-



Scheme 7

O-sulphonic acid also proved unsuccessful with northebaine hydriodide being recovered in low yield. No N-amination was observed.

2.3 Preparation of 14β-Acylaminocodeinones via Nitrosocarbonyl Intermediates

The first improved route to the synthesis of 14β-acyl-aminocodeinones is shown in scheme 7. This work originated from the discovery that the activated diene system of thebaine reacted with nitrosocarbonyl compounds, formed by the oxidation of hydroxamic acids, to yield cyclo-adducts (46)[35].

It was postulated that treatment of the adduct (46) with methanol under acidic conditions would form the dimethyl acetal (96) which could be hydrolysed to the ketone at a later stage with dilute acid. In addition, the ether linkage at C-5 is now stable to reduction unlike that of the codeinone. Also, the likelihood of attack by the hydroxyl group attached to the nitrogen atom on C-5 forming the 5,14-bridged phenols (98) is reduced.

Reduction of the N-substituted hydroxamic acid (96) would then yield the amide (77) which could be readily hydrolysed to the codeinone (77). The amide (97), as well as being a potentially potent morphine agonist, may also be suitable for further structural modification of the side chain, due to the

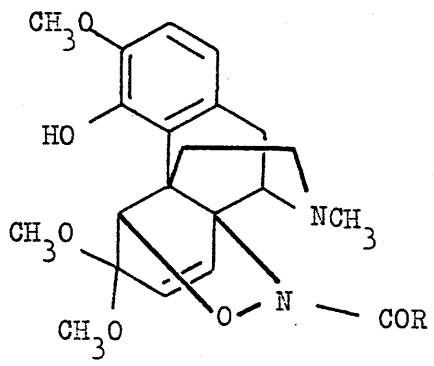
presence of the carbonyl function.

Extensive studies on this reaction pathway have shown that this method does indeed provide an efficient method of preparing 14β-acylaminocodeinones. The majority of the experimental effort was concentrated on the compounds with R = CH_2CH_2Ph, and after the reaction conditions had been established, the scope of the reaction pathway was extended to include compounds with several different R groups, for use in pharmacological screening experiments.

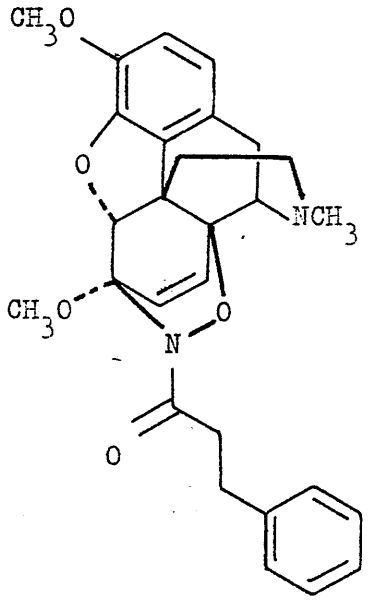
2.3 (i) Development of the Nitrosocarbonyl Route

The initial reaction shown in scheme 7 that is the formation of the thebaine-nitrosocarbonyl adduct has been carried out by other groups of workers[35,37] using either tetraethylammonium periodate or sodium periodate as the oxidiser. It was decided to confine our activities to the use of sodium periodate as it was more readily available and, provided rapid stirring was maintained, highly efficient at oxidising the hydroxamic acid.

The stoichiometry of this oxidation was studied by adding differing amounts of sodium periodate to acetohydroxamic acid in aqueous buffer at pH 6 and measuring the time taken for disappearance of the hydroxamic acid, as determined by a colour test with ferric chloride. It was found that one molar



(98)



(99)

equivalent of sodium periodate removed all the hydroxamic acid within 10 minutes, and a half molar equivalent removed the hydroxamic acid within 50 minutes. It was therefore decided to employ 1.5 equivalents each of hydroxamic acid and sodium periodate to each molar equivalent of thebaine.

The n.m.r spectrum of the adduct (46; R = CH_2CH_2Ph) showed in addition to the three methyl signals, a singlet for H-5 (δ 4.65) which was slightly broadened due to the very small W-type coupling of H-5 with H-7 (less than 1 Hz). The characteristic doublet for H-9 appeared at δ 4.90 with a coupling to H-10α of 7 Hz, and the olefinic protons H-7 (δ 6.00) and H-8 (δ 6.15) showed the normal mutual coupling of 9 Hz. Examination of the mass spectrum showed the molecular ion m/e 474, M-OH (457) and the base peak (311) due to thebaine, presumably formed by the retro-Diels-Alder reaction.

The adduct (46; R = CH_2CH_2Ph) was formed in effectively quantitative yield from thebaine, with no indication of formation of by-products arising from the three other possible Diels-Alder additions. Two of these can be ruled out on steric grounds as approach to the α face of ring C is hindered by aromatic ring A, however, formation of the hypothetical adduct (99) would seem possible. Although steric effects may exert a certain influence on the mode of addition, the more likely reason is electronic. Thus, with the 14-position of thebaine

being electron rich, and the nitrosocarbonyl species having a slight electron deficiency on the nitrogen atom, due to the electron withdrawing effect of the attached oxygen and carbonyl group, addition would take place to afford adduct (46) and not (99). It is also possible that the active nitrosocarbonyl-species is in fact the radical anion ($RCO-\dot{N}-O^{-}$), as was postulated by Oliver and Walters[34] as the species formed during the potassium ferricyanide oxidation of hydroxamic acids, and this radical anion would add to thebaine to give ultimately the observed adduct (46). Therefore, although formation of the cyclo-adducts is considered to be a Diels-Alder addition, a more complex mechanism cannot be ruled out.

Initial studies[51] on the conversion of the cyclic adducts (46) to the dimethyl acetals (96) were carried out with (46; R = CH_3 and OCH_2Ph), and indicated that 3 critical experimental conditions had to be obeyed before formation of the dimethyl acetals (96) was achieved. These were:-

a) The strength of the dry methanolic hydrogen chloride had to be about 0.1 M.

b) The temperature had to be maintained at 0 ^{o}C.

c) The workup conditions had to be anhydrous until all the hydrogen chloride had been neutralised.

Under these conditions, the dimethyl acetal (96; R = CH_3) formed in high yield, but the compound with R = OCH_2Ph attained

thermodynamic equilibrium with only 50% of the adduct being converted into the dimethyl acetal. This equilibrium was proved by submitting a sample of the acetal to the same reaction conditions and obtaining the same equilibrium mixture of adduct and acetal. Therefore the adducts (46) and acetals (96) were shown to be in thermodynamic equilibrium, the position of which was dependent on the nature of the side chain R.

The adduct (46; R = CH_2CH_2Ph), upon submission to essentially the same reaction conditions as above, gave the dimethyl acetal in high yield with none of the cyclo-adduct being visible in the n.m.r. spectrum of the total reaction mixture. This spectrum contained three singlets (δ 3.12, 3.50, and 3.90) assigned to the three methyl ether groups. The signal at δ 3.90 was assigned to the methoxy group at C-3, as it was the most deshielded due to the presence of the aromatic ring A. Comparison of the chemical shifts of the other two methoxy singlets with those of the analogous compounds with R = CH_3 and R = OCH_2Ph yielded the following information.

C-6 methyl ether chemical shifts (δ)

R = CH_3	3.23	3.50
R = OCH_2Ph	3.04	3.48
R = CH_2CH_2Ph	3.12	3.50

The chemical shift of the methoxy singlet at ca. δ 3.50 was essentially independent of the nature of the side chain R, while the signals from δ 3.04 to 3.23 showed a marked variation. It was therefore postulated that the signals at ca. δ 3.50 were furthest away from the side chain and were therefore assigned to the C-6α position. The signals that were dependent upon R were assumed to be on the same side of ring C as the side chain and were therefore assigned to C-6β.

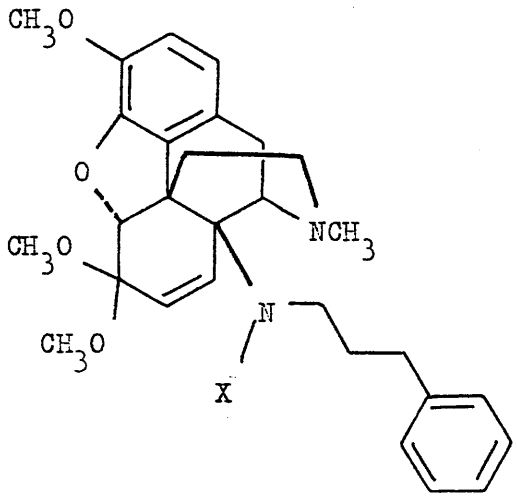
Comparison of chemical shifts of the H-9 doublet (δ 4.32) with the corresponding signal in the spectrum of the cyclic adduct (δ 4.90) implied that the H-9 proton was experiencing a larger shielding effect in the dimethyl acetal than it was in the cyclo-adduct. Examination of models showed that, in the dimethyl acetal, both the carbonyl and N-OH groups were considerably nearer to the H-9 proton and this would therefore explain the shielding effect. It was also considered possible that this effect was caused by the closer proximity of the benzene ring of the side chain in the dimethyl acetal, but this was discounted as a similar change of chemical shift was seen with the compounds with R = CH_3.

The mass spectrum of the dimethyl acetal (96; R = CH_2CH_2Ph) showed only a weak molecular ion at m/e 506, but M-OH (489) and M-CH_3OH (474) were clearly visible. Comparison with the mass spectrum of the cyclic adduct showed that the fragment M-CH_3OH (corresponding to the cyclic adduct) fragmented in

the same manner as before, giving a peak at M-CH_3OH-OH at 457 and the base peak at 311 due to thebaine, formed by loss of CH_3OH followed by a retro-Diels-Alder reaction.

The reduction of the dimethyl acetal (96; R = CH_2CH_2Ph) to the acetal (97; R = CH_2CH_2Ph) appeared in principle to be simple but, in fact, accounted for the majority of the experimental effort expended on the development of this synthetic route. It was initially thought that this reduction could be accomplished using zinc in acetic acid. This reaction was attempted and formed, instead of the reduced dimethyl acetal, the cyclo-adduct (46). The same reaction was found to proceed without the presence of zinc, so the reaction that was being observed was merely acetic acid catalysed cyclisation of (96) to (46). Attempted reduction using zinc in ammonium acetate afforded high recovery of starting material, but the reaction of zinc and ammonium chloride yielded four unknown products, plus some unreacted starting material.

The reduction of the dimethyl acetal (96; R = CH_2CH_2Ph) with lithium aluminium hydride yielded predominantly one compound, but this material was never positively identified. It was postulated that initially the carbonyl group would be reduced, so converting the side chain from a hydroxamic acid into a hydroxylamine. Whether further reaction converted the hydroxylamine to the amine was never established. The i.r.



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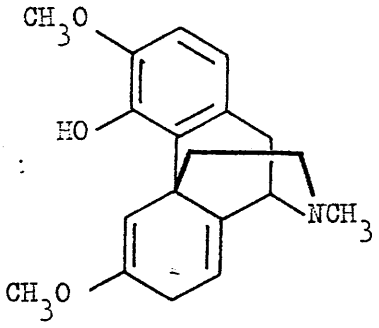
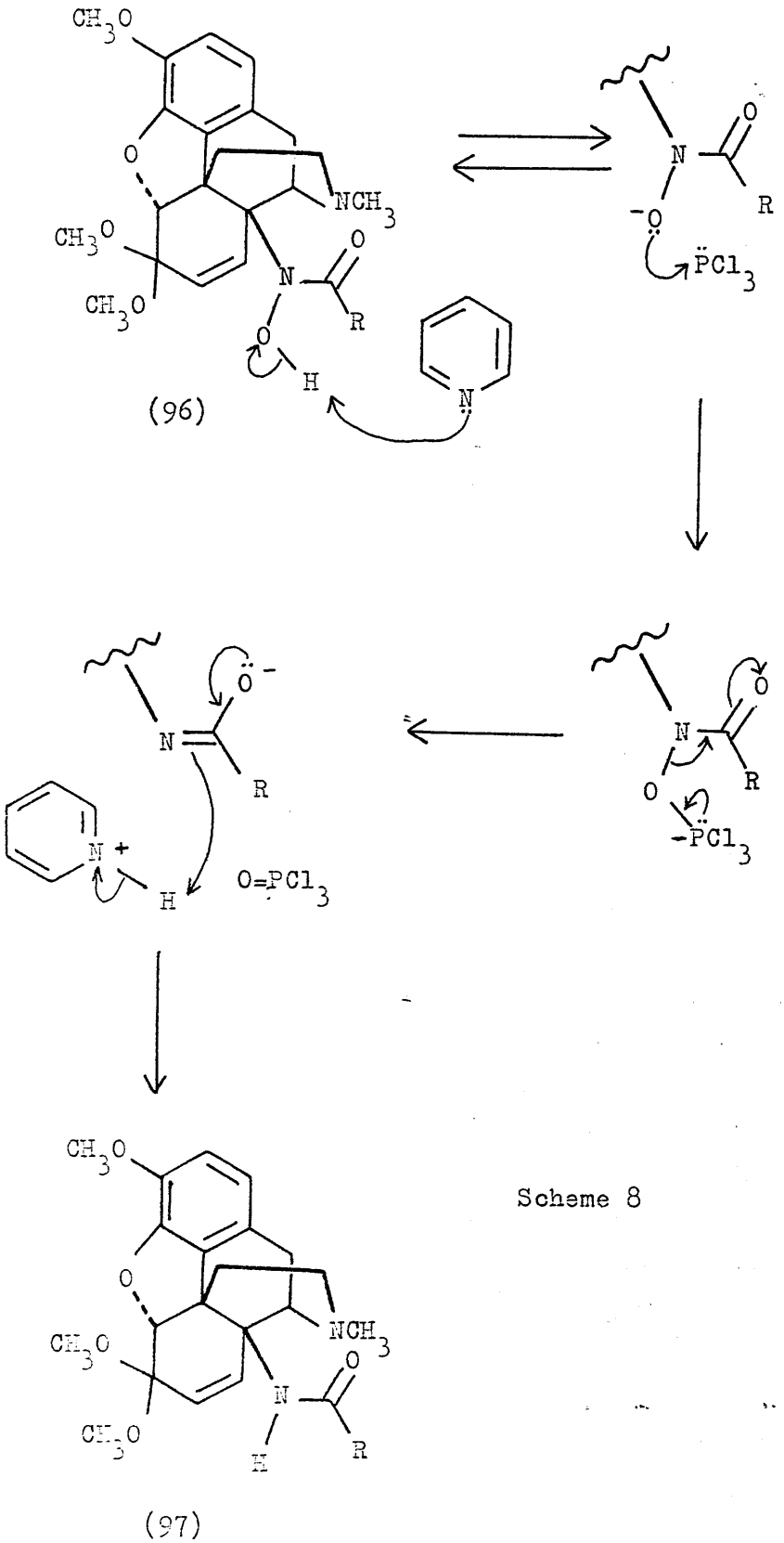


(101)

spectrum in chloroform did not show any carbonyl absorption, and a broad absorption centred at 3 200 cm^{-1} was indicative of the presence of an OH rather than an NH group. The n.m.r. spectrum was broadly similar to that of the starting material, except for the apparent upfield shift of the H-9 resonance and an upfield shift of 0.7 ppm for the H-8 doublet. This compound was tentatively assigned the structure (100; X = OH), but all attempts at purification were thwarted by its apparent instability when in contact with silica. Although the n.m.r. spectrum showed that predominantly one compound was present, t.l.c. showed the presence of multiple products.

The reduction of the dimethyl acetal (96; R = CH_2CH_2Ph) was attempted with sodium and lithium in liquid ammonia, but the only recognisable product from these reactions was dihydrothebaine-ø (101). As this compound is the major product of the Birch reduction of thebaine, the dimethyl acetal must first have been reduced to thebaine, which was then further reduced to dihydrothebaine-ø.

Chromium II species have also been investigated as potential reducing agents. Chromous acetate did not react with the dimethyl acetal (96) at room temperature but, at 85 °C this reaction yielded several products, none of which was identified. Similarly, multiple products were formed with chromous chloride. Attempts to reduce the acetal (96)



(96)

(97)

Scheme 8

catalytically with hydrogen also failed with palladium and copper chromite catalysts being equally unsuccessful. There was also little or no apparent reaction of the acetal (96) with sodium amalgam, sodium in ethanol, and sodium sulphite/sodium metabisulphite, while sodium dithionite yielded two compounds that were never identified. An attempt to reduce the cyclo-adduct (46) directly to the acetal (97) using titanium trichloride in dry acidic methanol also met with no success, yielding only impure acetal (96).

The reduction of the acetal (96) to the acetal (97) was finally achieved with phosphorus trichloride, which had been used previously by Ochiai[52] in 1953 to effect the transformation of 4-nitropyridine-N-oxide to 4-nitropyridine. The postulated reaction mechanism shown in scheme 8 involves initial removal of the hydroxamic acid proton by pyridine, then attack of the resulting anion at the phosphorus atom. Change in oxidation state of the phosphorus from III to V, with the formation of the phosphorus/oxygen double bond then forms phosphorus oxychloride and protonation of the amide residue affords the reduced dimethyl acetal (97).

The i.r. spectrum of the reduced dimethyl acetal (97; R = CH_2CH_2Ph) showed an absorbance at 3 460 cm^{-1} associated with an NH stretching vibration. Examination of the n.m.r. spectrum showed it to be similar to that of the starting material but several small changes were visible. The N-methyl and 3

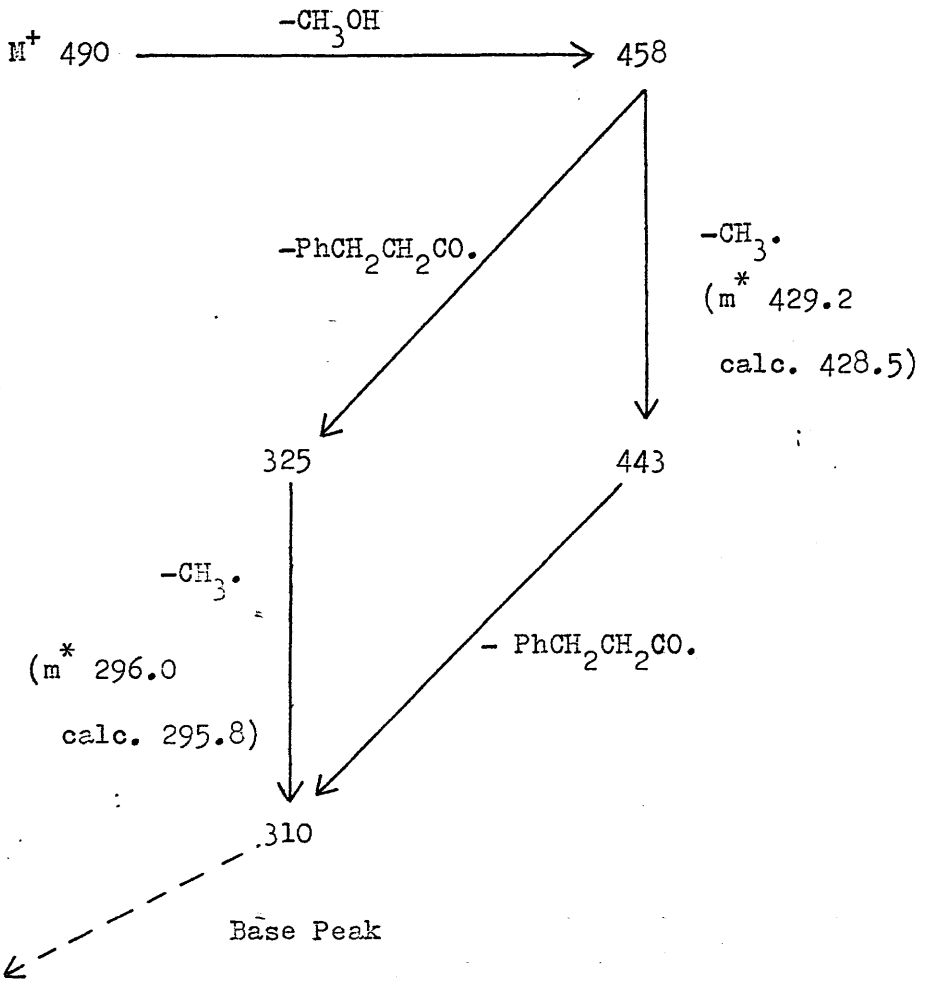

M+ 490
-CH3OH
458
-PhCH2CH2CO.
-CH3.
(m* 429.2
calc. 428.5)
325
443
-CH3.
(m* 296.0
calc. 295.8)
- PhCH2CH2CO.
310
Base Peak

Figure 2

O-methyl resonances were in approximately the same positions but the signal for H-5 had moved slightly upfield (from δ 4.86 to 4.62) and the small W coupling of H-5 to H-7 (ca. 1 Hz) was now visible. The doublet for H-9, formerly at δ 4.32 had moved upfield to δ 4.10, but the signal for H-8. which was expected to show some chemical shift variation only moved upfield by 0.1 ppm (from δ 6.40 to 6.28). The broad singlet exchangeable with D_2O at δ 6.22 was assigned to the NH proton.

The mass spectrum of the reduced acetal (97; R = CH_2CH_2Ph) showed peaks for the molecular ion (m/e 490) and M-CH_3OH (458). This fragment (458) appeared to fragment further by at least two different pathways; by loss of the side chain $PhCH_2CH_2CO$ to yield a fragment at 325, or by loss of a methyl group to afford a fragment at 443. The latter transformation (458-443) was supported by a metastable peak observed at 429,2 (calc. 428.5). The fragment (325) then lost a methyl group to yield the base peak at 310 with a metastable peak observed at 296.0 (calc. 295.8), while the fragment (443), upon loss of the side chain ($PhCH_2CH_2CO$), was also capable of affording the base peak fragment (310). Fig. 2 shows a schematic diagram for this postulated fragmentation process.

The mass spectrum also showed that a trace of chlorinated impurity was present. A double molecular ion at 524 and 526 indicated that substitution of a proton with a chlorine to form this compound had taken place. The structure of this

compound was never established, but, although the microanalytical data for the reduced dimethyl acetal was very close to the theoretical data, t.l.c. on silica (methanol–chloroform, 2:8) appeared to show the presence of this impurity (R_F 0.52) running just below the pure compound (R_F 0.59).

The final step in the synthetic sequence shown in scheme 7 is the hydrolysis of the reduced dimethyl acetal to the codeinone (77; R = CH_2CH_2Ph). This reaction was readily achieved by warming the acetal in dilute hydrochloric acid and methanol for 30 minutes. The i.r. spectrum showed the NH and $\alpha\beta$-unsaturated ketone carbonyl stretching vibrations (3 360 and 1 680 cm^{-1}) while the n.m.r. spectrum showed loss of the dimethyl acetal group. In addition, the H-7 and H-8 doublets had moved much closer together (δ 6.08 and 6.20) and the H-9 doublet was no longer visible, having presumably moved upfield to be masked by other resonances. H-5, having shown a weak W coupling to H-7 in the dimethyl acetal, now gave a sharper signal. The mass spectrum showed the molecular ion peak (444), the base peak (229), and the peak at 311 which was attributed to M-$PhCH_2CH_2CO$. The mass spectrum also showed that the trace of chorinated impurity, formed as a by-product of the phosphorus trichloride reaction, had also been hydrolysed and gave a low intensity double molecular ion at 478 and 480. Again the microanalytical data did not appear to be influenced by this trace impurity.

2.3 (ii) Preparation of Samples for Pharmacological Testing

Having ascertained that the synthetic pathway shown in scheme 7 was capable of affording the 14β-acylaminocodeinone (97; R = CH_2CH_2Ph), it was decided to use this sequence with other hydroxamic acids to prepare a series of analogous compounds with differing R groups, some of which would be used in pharmacological testing experiments. The hydroxamic acids, RCONHOH, where R = CH_3, Ph, CH_2Ph, $(CH_2)_3Ph$ and $(CH_2)_4CH_3$ were therefore prepared by the reaction of the ethyl esters of the relevant carboxylic acids with hydroxylamine hydrochloride.

The Compounds (46, 96, 97, and 77; R = CH_3)

The compounds (46 and 96; R = CH_3) had previously been prepared[51] so it was decided to attempt the reduction of (96; R = CH_3) with phosphorus trichloride. The reduction readily afforded the reduced dimethyl acetal (97; R = CH_3) but as with compound (97; R = CH_2CH_2Ph), a chlorinated impurity was observed in the mass spectrum. It was considered that as this reaction had been attempted on a much larger scale than the previous reduction, the exothermic nature of the reaction had caused local overheating, and this had favoured the substitution of chlorine somewhere in the alkaloid molecule. The reaction was therefore repeated with the temperature maintained at 10 °C

during the addition of the phosphorus trichloride, then the temperature was allowed to rise to 20 °C over 10 minutes. This procedure gave a much purer product with only an extremely small amount of the chlorinated impurity being visible in the mass spectrum. The mass spectrum of the reduced dimethyl acetal (97; R = CH_3) exhibited a slightly different fragmentation pattern when compared to (97; R = CH_2CH_2Ph), with peaks for M-15 (385), due presumably to loss of a methyl group, and M-31 (369) due to loss of a methoxy group now being visible, in addition to the peaks previously cited.

Hydrolysis of this compound gave the codeinone (77; R = CH_3) which again was contaminated by a chlorinated impurity. The starting material for this reaction had not been prepared by the low temperature method and consequently the by-product of the phosphorus trichloride reduction had been hydrolysed to a chlorinated codeinone (M^+ 388 and 390) that was not identified.

The compounds (46, 96, 97, and 77: R = Ph)

The adduct (46; R = Ph) had been previously prepared[37] and was formed in high yield from thebaine. The literature m.p. of this compound, crystallised from benzene-petrol was 170-172 °C, while the experimentally determined value for this material, crystallised from ethyl acetate, was 162-163 °C. As the n.m.r., i.r., and mass spectral data agreed with those of the literature, this discrepancy in melting point was considered to reflect the occurrence of two different crystalline forms of the same compound.

The conversion of the adduct (46; R = Ph) into the dimethyl acetal (96; R = Ph) proved to be extremely difficult. Although equilibrium was attained with ca. 37% cyclo-adduct and ca. 63% dimethyl acetal, all attempts to separate these compounds by fractional crystallisation proved unsuccessful. Several chromatographic systems were employed in attempts to separate the compounds, and eventually preparative t.l.c. on alumina proved successful, but the recovery of the acetal (96; R = Ph) from this system was disappointingly low.

As a sample of the isolated dimethyl acetal (96; R = Ph) was initially unavailable for reduction to (97: R = Ph), this reaction was attempted on a mixture of cyclic adduct and dimethyl acetal. The procedure proved effective, with the phosphorus trichloride reacting only with the dimethyl acetal (96; R = Ph) to yield the reduced species (97; R = Ph) without interfering with the cyclic adduct. Separation of the unreacted cyclo-adduct and reduced dimethyl acetal was easily achieved by fractional crystallisation, yielding the reduced dimethyl acetal in pure form with no trace of any chlorinated by-product being observed in the mass spectrum. Acidic hydrolysis then yielded the codeinone.

The Compounds (46, 96, 97, and 77; R = CH_2Ph)

The adduct (46; R = CH_2Ph) was formed in high yield from thebaine but this material, though pure by n.m.r. spectroscopy

proved to be very difficult to crystallise. A specimen, abandoned in the refrigerator at 0 °C for 14 months in ethyl acetate - di-isopropyl ether finally crystallised to yield the pure compound.

Opening of this adduct to the dimethyl acetal (96; R = CH_2Ph) occurred easily with the equilibrium mixture containing only ca. 10% of the cyclo-adduct. The molecular ion (492) in the mass spectrum was hardly visible, but the characteristic cracking pattern, M-17, M-32, and M-49 was present.

Reduction of this compound yielded the reduced dimethyl acetal (97; R = CH_2Ph), which again proved difficult to crystallise. Crystallisation was successful after passing the crude material through an alumina column, but the microanalysis of this compound showed that it had crystallised apparently as the half hydrate. Some evidence in favour of this idea was that although this compound melted at 164 to 165 °C, darkening of the crystals occurred at 92-93 °C possibly as a result of loss of water from the crystal lattice.

Hydrolysis of the reduced dimethyl acetal to the codeinone (77; R = CH_2Ph) was successful, but again problems were encountered in crystallisation and therefore the yield for this step was only 35%. The m.p. of this compound was not sharp with crystal growth occurring above 207 °C until the compound finally melted at 237-240 °C.

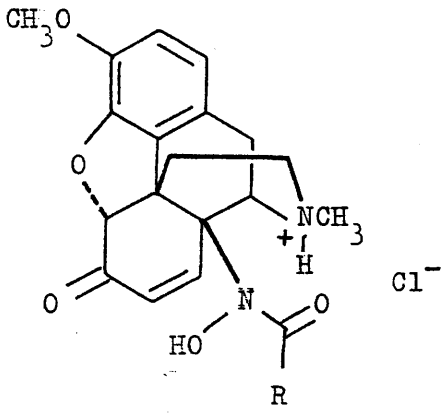
The Compounds (46, 96, 97, and 77; R = $(CH_2)_3Ph$)

Formation of the adduct (46; R = $(CH_2)_3Ph$) proceeded normally, but the conversion of this adduct into the dimethyl acetal was hampered by the unfavourable equilibrium of ca. 40% cyclic adduct to 60% dimethyl acetal. Separation was however achieved by fractional crystallisation.

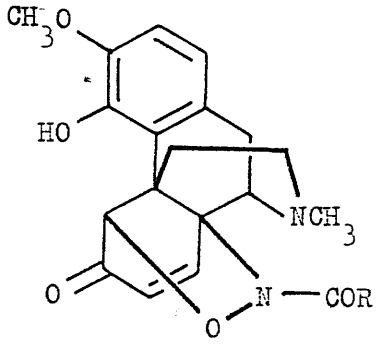
The reduction of the dimethyl acetal gave no chlorinated by-product, as seen by mass spectrometry, but t.l.c. did indicate that another impurity was present. This compound was not identified but its presence accounted for the failure of the microanalysis result to agree with the theoretical value. Attempts to remove this impurity by fractional crystallisation proved to be unsuccessful. Hydrolysis of the reduced dimethyl acetal gave the codeinone in high yield and the by-product from the phosphorus reduction appeared to remain in solution during the crystallisation of the final product.

The compounds (46, 96, 97, and 77; R = $(CH_2)_4CH_3$)

The adduct (46; R = $(CH_2)_4CH_3$) formed in high yield, but all attempts at crystallisation proved unsuccessful. Formation of the dimethyl acetal occurred normally with equilibrium being reached at ca. 30% cyclo-adduct, 70% dimethyl acetal, the dimethyl acetal being separable by fractional crystallisation.



(102)



(103)

As was the case with the dimethyl acetal (96; R = $(CH_2)_3Ph$) an impurity appeared to be formed during the reduction which was not separable by crystallisation, nor did it appear in the mass spectrum as a chlorinated compound. Hydrolysis of the reduced dimethyl acetal (97; R = $(CH_2)_4CH_3$) was carried out successfully and the impurity from the reduction step remained in solution during crystallisation. A pure sample of the codeinone was therefore obtained.

2.4 Some Reactions of Thebaine Cyclo-adducts

During the development of the nitrosocarbonyl route to 14β-acylaminocodeinones, several reactions were studied which though not directly involved in the synthesis outlined in scheme 7, were relevant to an understanding of the chemistry of the cyclo-adducts (46).

The thebaine adduct (46; R = CH_2CH_2Ph) was hydrolysed in dilute acid at 0 °C to give the N-hydroxycodeinone hydrochloride (102; R = CH_2CH_2Ph). The n.m.r. spectrum was recorded in deuterioacetone at 50 °C due to solubility problems, and, as expected showed a significant change in the chemical shift of the signal assigned to the $\underline{N}$-CH_3 protons. Quaternisation of the nitrogen had moved this resonance from its more usual position of δ 2.40, as observed with the dimethyl acetal (96; R = CH_2CH_2Ph), to δ 2.89 where it appeared as a broad signal. The adjacent sharp singlet at δ 3.07 was attributed

to the presence of water in the deuterioacetone. A signal for H-5 appeared at δ 5.08 and did not exhibit significant W coupling to H-7, while the olefinic protons H-7 and H-8 resonated at δ 6.10 and δ 6.78 respectively with a coupling of 10 Hz. The broad signal at δ 5.31 was assigned to the N-OH proton.

Examination of the mass spectrum showed a strong molecular ion at m/e 460, corresponding to the free base. This compound appeared to lose oxygen to give the fragment M-16 (444) and the side chain ($PhCH_2CH_2CO$) was also lost to give a fragment at 327. This conclusion was reinforced by the occurrence of a metastable peak at 232.5 (calc. for 460 → 327, m/e 232.6). additional peaks were observed for M-30, M-29, and M-57.

Because of the close proximity of the ammonium proton and the two oxygen atoms on the side chain, various possibilities existed for the intramolecular hydrogen bonding, and the presence of a free OH (3 575 cm^{-1}) and hydrogen bonded OH (3 300 - 3 500 cm^{-1}) vibrations in the i.r. spectrum confirmed this. In addition, there appeared to be two carbonyl vibrations at 1 679 and 1 688 cm^{-1} of roughly equal intensity. This information tended to show that it was the N-OH that contributed more to the hydrogen bonding with the ammonium proton <u>via</u> a 6-membered ring favoured perhaps by steric considerations.

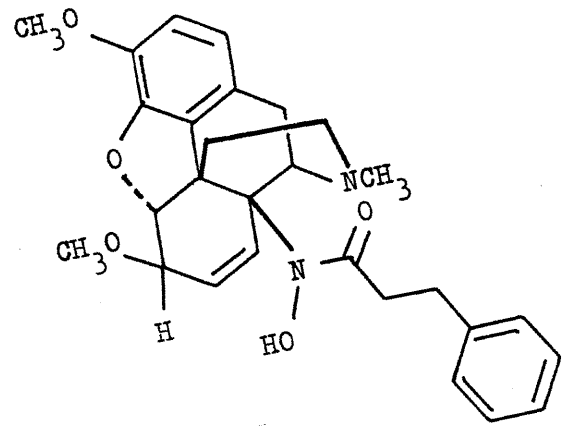
An attempt to form the free base by treating (102: R = CH_2CH_2Ph)

with sodium hydrogen carbonate at room temperature for one minute, followed by extraction with chloroform, gave a mixture of the free base (50%) and the phenol (103; R = CH_2CH_2Ph)(50%).

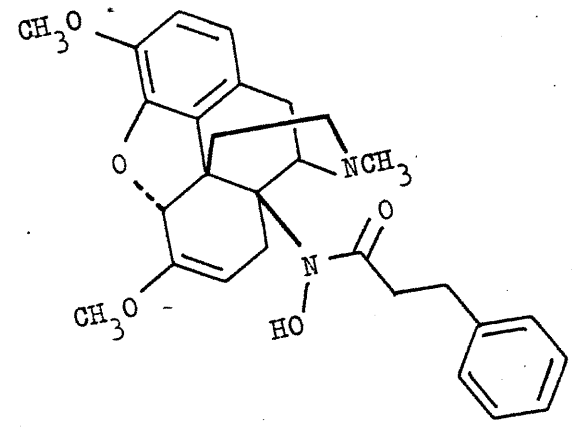
A more efficient synthesis of the 5,14-bridged phenol (103) was effected by treating the codeinone (102; R = CH_2CH_2Ph) with sodium ethoxide in ethanol at room temperature. The i.r. spectrum of the product showed the presence of a hydrogen bonded OH (3 300 - 3 600 cm^{-1}) and an intense carbonyl vibration (1 600 - 1 680 cm^{-1}) showed that both carbonyl groups were still present. The mass spectrum was identical to that of the hydroxycodeinone hydrochloride (102; R = CH_2CH_2Ph) with the molecular ion (460) forming the base peak. This implied that the compounds (102; R = CH_2CH_2Ph), after loss of hydrogen chloride and (103; R = CH_2CH_2Ph) were interconvertable in the mass spectrometer.

The n.m.r. spectrum of (103; R = CH_2CH_2Ph) contained the characteristic H-9 doublet (δ 4.28) with the coupling to H-10α of 6 Hz. H-5 and H-7 (δ 5.20 and 5.95) showed the weak W coupling of 1 Hz. The olefinic protons (H-7 and H-8) exhibited their normal coupling of 9 Hz, but the hydroxyl proton attached to C-4 was not observed, either because of masking by other signals, or due to the fact that it was very broad.

It was decided to prepare the corresponding compound with



(104)

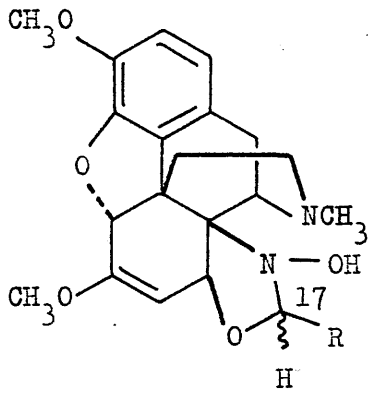


(105)

the dimethyl acetal functionality at C-6. It was expected that this reaction would be considerably harder to effect as there was now no stabilisation of developing negative charge at the 5-position, which was formerly α to the C-6 ketone carbonyl. Indeed this was one of the reasons why it was considered desirable to protect the C-6 ketone carbonyl as the dimethyl acetal. All attempts to induce this cyclisation met with failure. Several bases were used but, even at elevated temperature, the dimethyl acetal (96; R = CH_2CH_2Ph) was stable under basic conditions. The compound (98; R = CH_2CH_2Ph) was therefore never prepared.

One of the drawbacks of the nitrosocarbonyl route was the existence of the equilibrium between the cyclo-adducts (46) and dimethyl acetals (96). As a method of overcoming this, it was decided to react the cyclo-adduct (46) in the presence of acidic methanol with sodium cyanoborohydride[53]. This reagent was known to reduce dimethyl acetals to methyl ethers under acidic conditions[54], and it was considered that formation of compounds (104) or (105) was likely. It was also considered possible that this reducing agent could attack the substituted hydroxamic acid side chain to yield a variety of reduced species. Therefore, as a highly speculative experiment, the cyclo-adduct (46; R = CH_2CH_2Ph) in methanolic hydrogen chloride was treated with sodium cyanoborohydride.

The n.m.r. spectrum of the total reaction mixture indicated that the dimethyl acetal (96; R = CH_2CH_2Ph) had

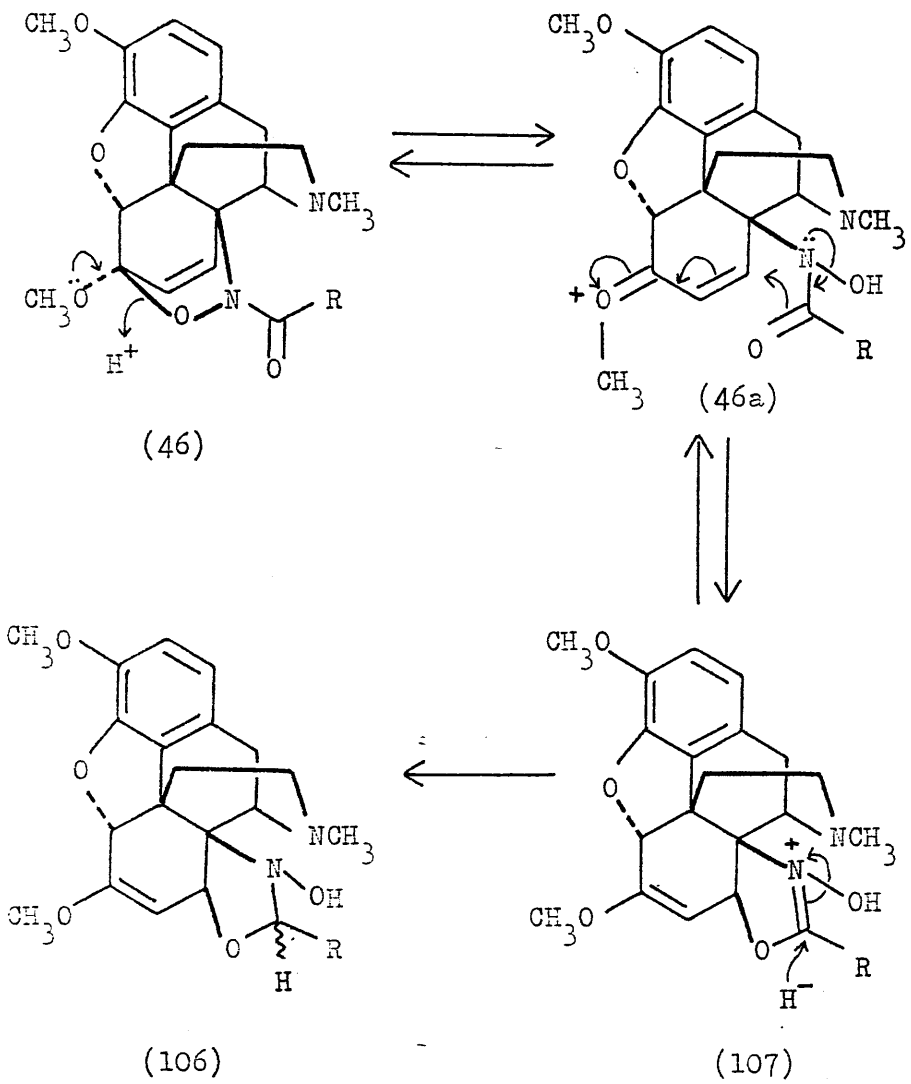


(106)

formed in ca. 50% yield, along with an unknown compound. Several attempts to improve this reaction met with no success, and it was concluded that the nucleophilic character of the methanol was responsible for the formation of the dimethyl acetal in preference to the unknown reduction product. Accordingly, this reaction was repeated at pH 3 using tetrahydrofuran as the solvent and proved to be immediately successful, with the unknown compound forming in high yield. This compound was shown to have the structure (106; R = CH_2CH_2Ph).

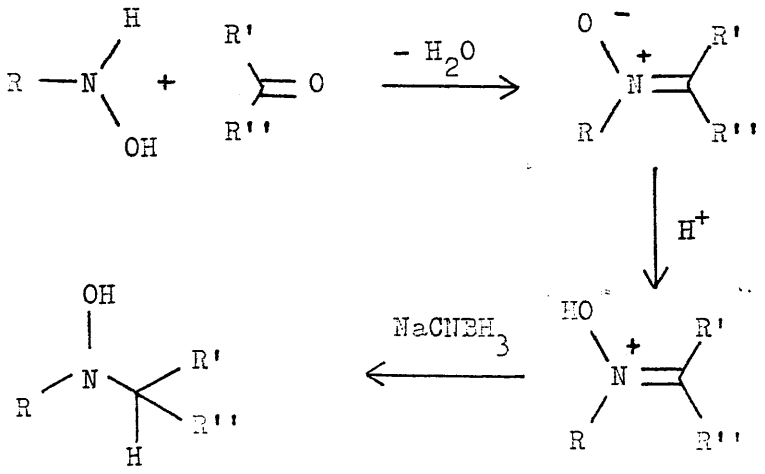
The i.r. spectrum of the oxazolidine (106; R = CH_2CH_2Ph) showed that an OH was present (3 288 cm^{-1}) but the carbonyl vibration was absent. The medium intensity vibration at 1 659 cm^{-1} was attributed to C=C. In the mass spectrum, the molecular ion appeared at m/e 476 and the base peak was observed at M-18 (458), presumably formed by loss of water. A peak was observed at M-2 (474) and thereafter, several fragments appeared separated by two mass units. For example, M-31 (445), (M-2)-31 (443) corresponding to loss of CH_3O and M-121 (355),(M-2)-121 (353). In addition a peak was observed at M-17 (459) corresponding to loss of OH and the base peak (458) appeared to fragment to a peak at 402. This was supported by a metastable ion observed at 353.0 (calc. 352.9).

The n.m.r. spectrum contained three resonances due to the methyl groups, the N-methyl at δ 2.39 and the O-methyls at δ 3.52 and 3.83. The signal for H-7 appeared at δ 4.26 as a



(46) (46a) (106) (107)

Scheme 9



R = R' = H or Alkyl

R'' = Alkyl

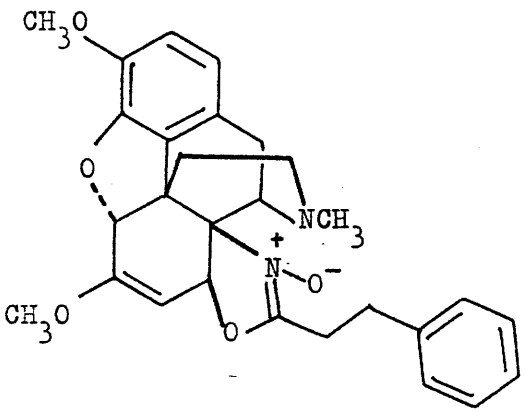
Ref. 55

Scheme 10

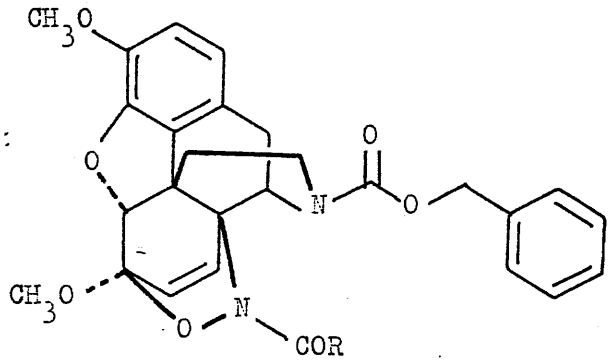
double doublet with a coupling of 2 Hz to H-8 and ca. 1 Hz to H-5. Irradiation of H-5 (δ 4.95) caused this signal to sharpen to a doublet (J = 2 Hz) and similarly, irradiation of H-7 removed the 1 Hz coupling in the signal for H-5. The doublet at δ 4.58 was assigned to H-8, which coupled to H-7 by 2 Hz. H-17 gave a quartet centred at δ 4.74 with a coupling of 4 Hz and 7 Hz to the two adjacent protons at C-18. An additional small coupling of less than 1 Hz was observed between H-17 and H-8. This was confirmed by irradiation of H-8 causing a sharpening of the H-17 quartet. The H-9 doublet was not observed being masked by other resonances in the region of δ 3.0, and the broad singlet at δ 6.47 was assigned to the N-OH proton.

The proposed mechanism for this reaction is shown in scheme 9. Thus the reductive step probably occurred by attack of a hydride ion at the intermediate (107; R = CH_2CH_2Ph). In the original experiments conducted in acidic methanol attack of methanol at the 6-position of (46a; R = CH_2CH_2Ph) would explain the formation of the dimethyl acetal (96; R = CH_2CH_2Ph). A Search of the literature revealed[55] that the reaction of sodium cyanoborohydride with protonated nitrones, as shown in scheme 10 was known, so lending credibility to the mechanism shown in scheme 9.

The stereochemistry at C-17 of the oxazolidine (106; R = CH_2CH_2Ph) was not determined, but the sharp nature of the



(108)



(108a)

peaks for H-17 in the n.m.r. spectrum indicated that one isomer had been formed. The attack of the hydride ion at the intermediate (107; R = CH_2CH_2Ph) in scheme 9 could occur from either side of the oxazolidine ring and presumably, attack from the less hindered side yielded the product observed by n.m.r. spectroscopy. However, examination of models did not clarify this problem, so the stereochemistry remained undecided.

The mechanism shown in scheme 9 involves formation of the intermediate (107; R = CH_2CH_2Ph) as the initial step. In an attempt to verify if this rearrangement could be observed spectroscopically, the cyclic adduct (46; R = CH_2CH_2Ph) was dissolved in trifluoroacetic acid containing 1% concentrated sulphuric acid and the n.m.r. spectrum recorded. The spectrum suggested that one compound had been formed which was either the nitrone (108) of its trifluoroacetate salt. This compound degraded rapidly in the n.m.r. spectrometer, and by-products were visible within 15 minutes. The salient features of this spectrum were the doublets for H-7 (δ 4.72) and H-8 (δ 5.69), showing a coupling constant of 3 Hz. H-5 appeared as a slightly broadened singlet at δ 5.40. The 3 Hz coupling between H-7 and H-8 was very close to that observed for the oxazolidine (106; R = CH_2CH_2Ph) (2 Hz), implying that both compounds had a similar angular relationship between H-7 and H-8.

An attempt was made to remove the OH group of the N-hydroxy-oxazolidine (106; R = CH_2CH_2Ph) by reduction with lithium

aluminium hydride. This reaction gave four products as seen by t.l.c., and preparative t.l.c. was used to separate the major component. A crystalline compound was obtained in low yield from this reaction, m.p. 185-187 °C. The n.m.r. spectrum was reminiscent of the starting material but did not contain a signal due to the N-CH_3 protons. Several small signals in the region δ4.0 to 5.0 implied that the fused ring system was still intact, but the mass spectrum contained a molecular ion at m/e 476, the same as that of the starting material. No reduction could therefore have taken place, but a rearrangement to this unidentified product seemed likely.

During earlier work on the reactions of thebaine with dinitrogen trioxide and mesitylenesulphonylhydroxylamine, N-benxyloxycarbonylnorthebaine had been prepared (see chapters 2.1 and 2.2). It was decided to attempt the formation of some cyclo-adducts of N-benzyloxycarbonylnorthebaine (108a), to see if the extended aryl chain on the nitrogen atom blocked the approach of the nitrosocarbonyl-species.

The reaction of N-benzyloxycarbonylnorthebaine with N-(3-phenylpropanoyl)hydroxylamine in the presence of sodium periodate formed the cyclo-adduct, analogous to (46; R = CH_2CH_2Ph). All attempts to crystallise this material failed, but the n.m.r. spectrum of the crude compound was similar to the adduct (46; R = CH_2CH_2Ph) except for the loss of the N-methyl signal, a change of chemical shift of H-9 and the shift of the signals due to

the carbamate moiety.

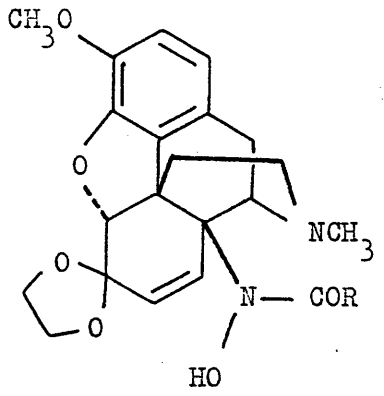
This reaction unfortunately did not prove to be general. The formation of the cyclo-adduct of N-benzyloxycarbonylnorthebaine and the nitrosocarbonyl species derived from acetohydroxamic acid was unsuccessful. Examination of the reaction progress by t.l.c. showed that only starting material was present. Large excesses of acetohydroxamic acid and sodium periodate were eventually added, but none of the desired cyclo-adduct was observed.

2.5 Improvements to the Nitrosocarbonyl Route

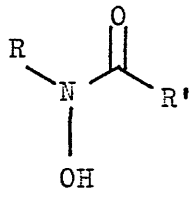
The nitrosocarbonyl route for the preparation of 14β-acylaminocodeinones as shown in scheme 7 suffered from two disadvantages, namely, the existence of the equilibrium between the adducts (46) and the dimethyl acetals (96), and formation of impurities during the phosphorus trichloride reduction. These problems have now both been overcome.

The problem of equilibration in the second step in the synthesis shown in scheme 7 was solved by converting the cyclo-adducts (46) into the ethylene ketals (109) rather than the dimethyl acetals (96). This idea stemmed from the work of D.Maclean[38] on the thebaine/2,2,2-trichloroethyl nitrosoformate adduct (57) (see p.20).

The cyclo-adducts (46; R = Ph and CH_2CH_2Ph), when treated



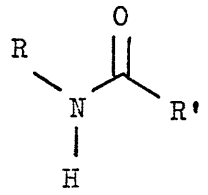
(109)



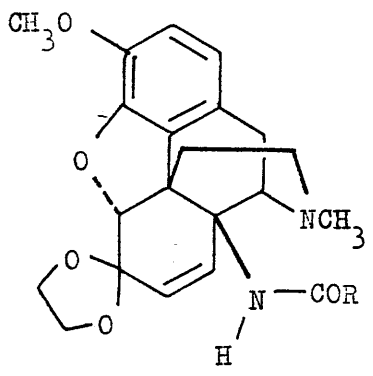
(110)

R and R' =

alkyl or aryl



(111)



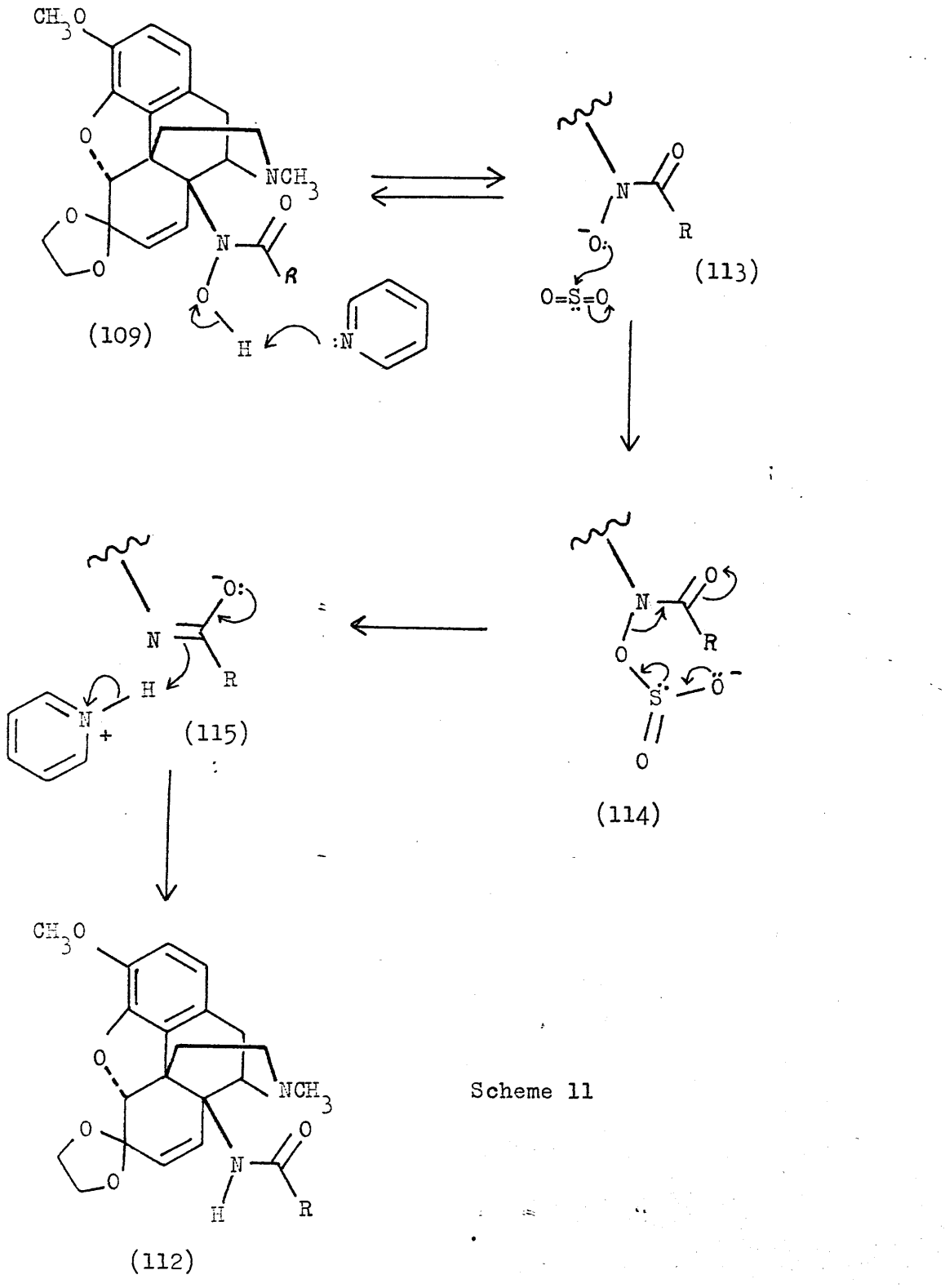
(112)

with anhydrous glycolic hydrogen chloride in methylene chloride at room temperature gave the ethylene ketals (109; R = Ph and CH_2CH_2Ph) in virtually quantitative yield. The following discussion of the spectral characteristics of the ethylene ketals (109) shall be confined to the compound with R = CH_2CH_2Ph. The compound with R = Ph behaved in a similar manner.

The i.r. spectrum of the ethylene ketal (109; R = CH_2CH_2Ph) showed the presence of an OH (3 270 cm^{-1}) and a carbonyl (1 639 cm^{-1}) group, while the n.m.r. spectrum was similar to that of the dimethyl acetal (96; R = CH_2CH_2Ph), except for the loss of the two sharp singlets assigned to the C-6 methoxy groups and the introduction of a multiplet, centred at δ 4.1, assigned to the protons of the ethylene ketal moiety. In addition, a small extra coupling was now observed between H-9 and H-10β of *ca.* 1 Hz, which was not distinguishable before. The mass spectrum contained a prominant molecular ion at m/e 504 and was considerably different from that of the dimethyl acetal (96; R = CH_2CH_2Ph). The spectrum of the dimethyl acetal was dominated by initial loss of methanol and recyclisation to the cyclo-adduct (46), which then underwent a retro-Diels-Alder reaction to form thebaine. This process was not possible with the ethylene ketal and the spectrum was consequently more complex, with peaks being observed at M-16, M-17, M-61 and M-74.

During studies on the reduction of model compounds (see p.89), it was discovered that the substituted hydroxamic acids (110) could be efficiently reduced to the amides (111) by dissolving them in pyridine saturated with sulphur dioxide and heating under reflux for one hour. Using this reducing system, the ethylene ketals (109; R = Ph and CH_2CH_2Ph) were reduced cleanly to the ketals (112; R = Ph and CH_2CH_2Ph). This reaction gave a purer product than did the phosphorus trichloride reduction, as observed by t.l.c.

The i.r.spectrum of the reduced ethylene ketal (112; R = CH_2CH_2Ph) contained bands for an NH (3 440 cm^{-1}) and an amide carbonyl (1 663 cm^{-1}) group. The n.m.r. spectrum was, as expected, similar to that of the dimethyl acetal (97; R = CH_2CH_2Ph) with the substitution of the multiplet due to the ethylene ketal group (δ 4.0) for the two C-6 methoxy singlets. The signal for H-9 had moved upfield from δ 4.10 to δ 3.41 and now showed additional coupling of ca. 1 Hz to H-10β and H-5 no longer showed the W coupling to H-7. Examination of the mass spectrum showed a strong molecular ion at m/e 488 with prominent peaks for M-$PhCH_2CH_2CO$ (355) and M-148 (340). The peak at 443 corresponding to M-45 could have been formed by loss of CH_3CH_2O. Spectroscopic details for the compound (112; R = Ph) were essentially the same, with the mass spectrum showing the loss of the fragments 105, 120, and 45.

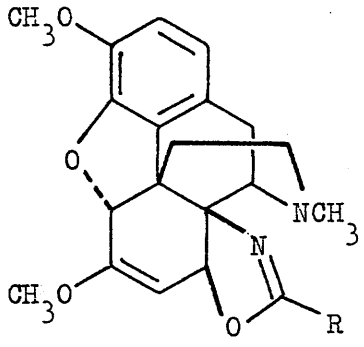


Scheme 11

The mechanism proposed for this reduction is shown in scheme 11, and is similar to that of the phosphorus trichloride/ pyridine reduction. After initial removal of the acidic proton by pyridine, the resulting anion (113) attacks the sulphur dioxide molecule to form the intermediate (114). Oxidation of sulphur dioxide to sulphur trioxide then ejects the amide residue (115) which captures a proton from pyridine hydrochloride to form the amide (112). A more complicated mechanism involving the formation of a sulphur dioxide/pyridine complex is also possible. This reaction only proceeded at elevated temperatures while the phosphorus trichloride reduction could be successfully carried out at 10 ^{o}C. A possible reason for this is the tendency for phosphorus to form a double bond with oxygen is considerably greater thanthat for formation of a sulphur/ oxygen double bond.

The reduction of the ethylene ketals (112; R = Ph and CH_2CH_2Ph) was also successfully carried out with the former reducing system of phosphorus trichoride in pyridine. In both cases, the product from the sulphur dioxide/pyridine reaction was of higher purity and the yield of reduced ethylene ketal was also greater.

Hydrolysis of the ethylene ketals (112; R = Ph and CH_2CH_2Ph) was effected using the same conditions as those for the hydrolysis of the dimethyl acetals (97) and yielded the

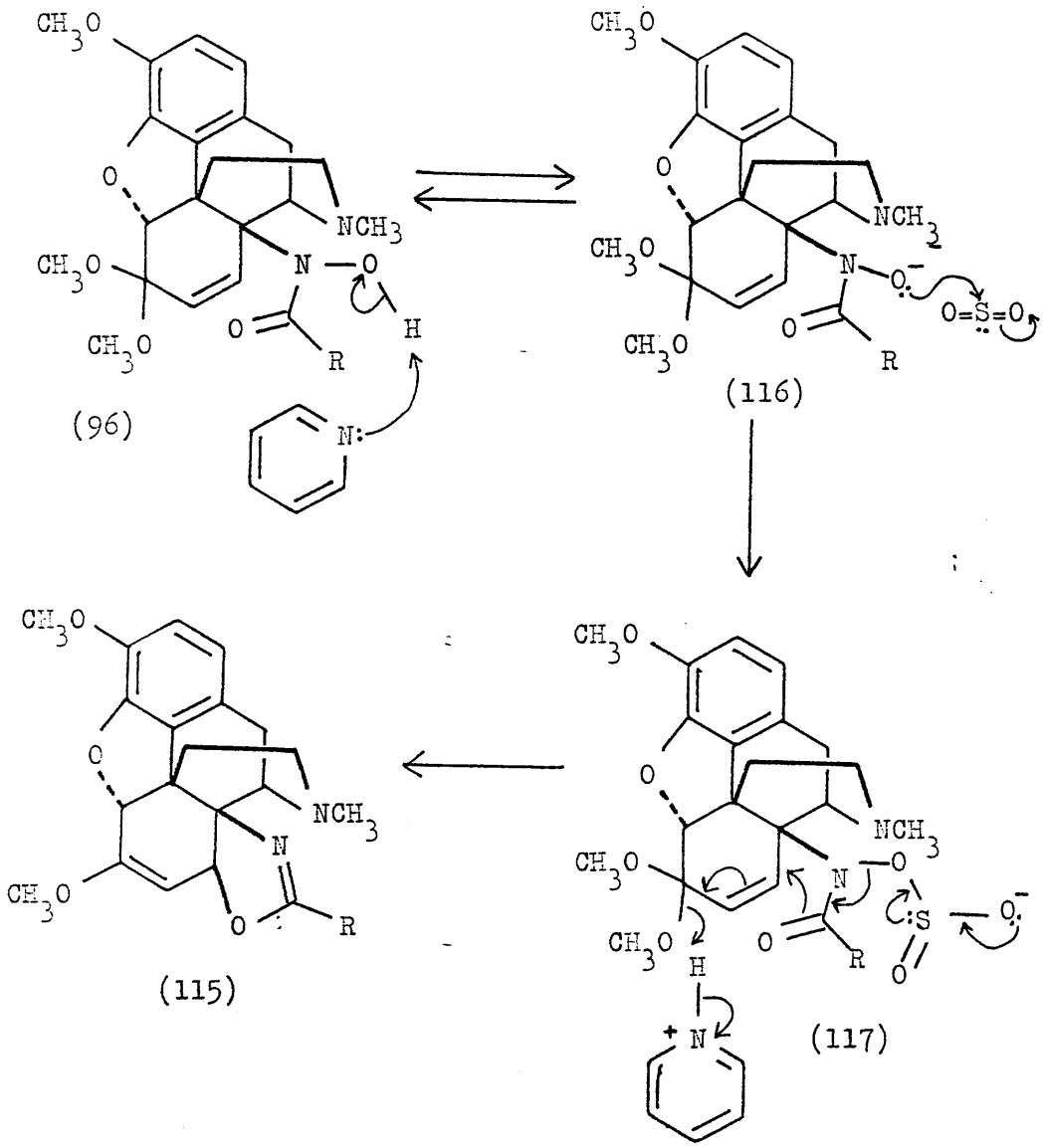


(115)

14β-acylaminocodeinones (77). Both these compounds were purer than those prepared by reduction of the dimethyl acetals with phosphorus trichloride, as demonstrated by their slightly higher melting points and lack of impurities visible by t.l.c.

The preparation of the 14β-acylaminocodeinones (77; R = Ph and CH_2CH_2Ph) was also carried out using this synthetic route without isolation of intermediates so as to maximise the overall yield for the reaction sequence. Accordingly the thebaine adducts (46) were formed and converted directly into the ethylene ketals (109) without prior crystallisation of the adducts (46). The crude ethylene ketals (109) were heated with sulphur dioxide in pyridine for 30 minutes, then, to this mixture was added dilute hydrochloric acid and the mixture was heated for a further 30 minutes. Thus, reduction, followed by hydrolysis to the codeinone had been combined into one step. The codeinones (77) were prepared by this method in greater than 60% yield from thebaine.

As the reducing system of sulphur dioxide in pyridine had proved so successful with the ethylene ketals, it was decided to attempt the reduction of the dimethyl acetals (96; R = Ph and CH_2CH_2Ph) with this reagent. The dimethyl acetal (96; R = CH_2CH_2Ph) was therefore heated with sulphur dioxide in pyridine but, surprisingly, it yielded the oxanoline (115; R = CH_2CH_2Ph) in high yield and not the reduced dimethyl acetal (97; R =



Scheme 12

CH_2CH_2Ph). Assignment of this structure was assisted by comparison of the spectral data with that of the compound (115; R = Ph), which had been prepared previously by D. McDougal[37] in low yield by the reduction of the cyclo-adduct (46; R = Ph) with zinc in acetic acid.

The oxazoline (115; R = CH_2CH_2Ph) exhibited bands in the i.r.spectrum associated with C=C and C=N (1 662 and 1 649 cm^{-1}) while the n.m.r. spectrum was reminiscent of the N-hydroxy-oxazolidine (106). The most striking feature of the n.m.r spectrum was the H-8 doublet at δ 4.45 coupled to H-7 by 3 Hz, and the H-7 doublet at δ 4.57 coupled to H-8 by 3 Hz, with an additional small allylic coupling to H-5 (δ 4.82) of less than 1 Hz. It was interesting to note that the oxazolines (115) were the only compounds in which H-7 was further downfield than H-8. The mass spectrum contained the molecular ion (m/e 458) and peaks at M-15, M-133, and M-148. A metastable peak observed at 231 corresponded to the loss of 133 ($PhCH_2CH_2CO$) from the molecular ion. To verify that this compound did indeed have the oxazolidine structure, reduction of the dimethyl acetal (96; R = Ph) was performed with sulphur dioxide in pyridine and yielded the oxazoline (115; R = Ph), the spectral data and melting point of which agreed with the literature[37].

The proposed mechanism of this reaction is shown in scheme 12. As before, the anion (116) attacks a molecule of sulphur

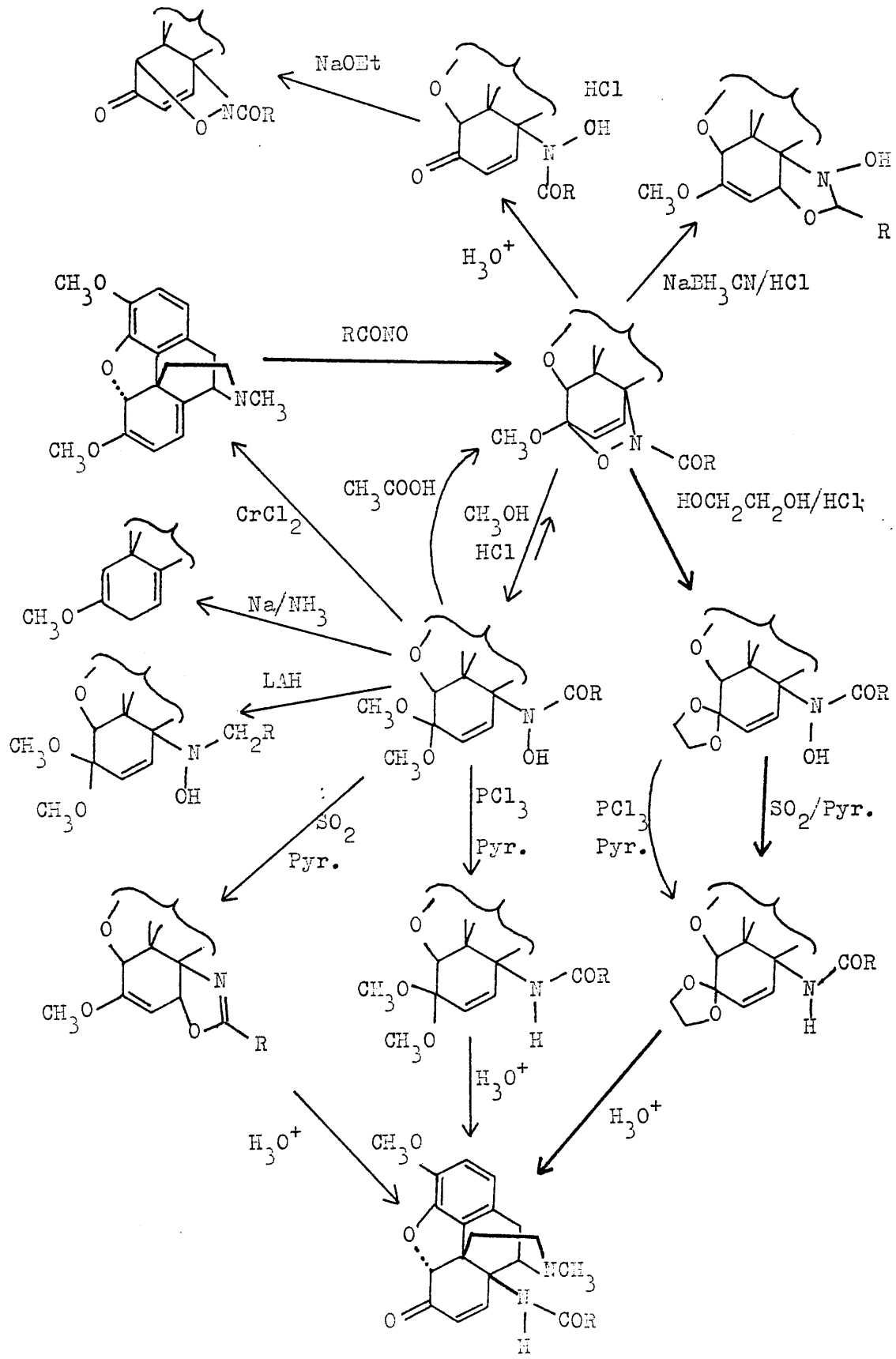

NaOEt
HCl
OH
COR
NCOR
H_3O^+
$NaBH_3CN/HCl$
RCONO
NCH_3
CH_3O
CH_3COOH
CH_3OH
HCl
$HOCH_2CH_2OH/HCl$
$CrCl_2$
Na/NH_3
LAH
CH_2R
PCl_3
Pyr.
SO_2
$SO_2/Pyr.$
R
H

Figure 3

dioxide to form the intermediate (117). Cyclisation of the compound (117) with consequent loss of methanol yields the oxazoline (115). With the ethylene ketals shown in scheme 11, it is not possible for the leaving group to detatch itself from the 6-position so re-cyclisation to the ethylene ketal with concomitant reopening of the oxazoline ring could occur. In addition, five membered ring ketals are slightly more stable than the dimethyl acetals and so this excess stability may be a contributary factor in the formation of reduced ethylene ketals (112) or oxazolines (115).

The oxazolines (115; R = Ph and CH_2CH_2Ph) were readily hydrolysed to the 14β-acylaminocodeinones (77), with the melting point and spectral data agreeing with the values already obtained for the same compounds prepared by different routes.

Figure 3 summarizes the reactions that have been studied based on the adducts of thebaine, with nitrosocarbonyl compounds.

2.6 Studies on Model Compounds

The key step in the nitroso-carbonyl route to 14β-acyl-aminocodeinones was the reduction of the dimethyl acetals (96) or ethylene ketals (109) with phosphorus trichloride or sulphur dioxide in pyridine. As these reductions were previously unknown, it was decided to apply these reducing systems to the reduction of some simple substituted hydroxamic acids, and so ascertain the generality and scope of the reagents.

The model compounds used were as shown in figure 4 and were chosen because of their different types of alkyl and aryl substituents and their ease of preparation. In addition, these hydroxamic acids were all crystalline solids and the corresponding amides were also easily prepared crystalline solids. Attempts to make cyclic hydroxamic acids such as 1-hydroxy-2-piperidone by the literature method[56] were unsuccessful.

Three different reagents were used for these reductions. Phosphorus trichloride in pyridine had been used successfully in the reduction of the dimethyl acetals (96), but sulphur dioxide in pyridine, previously used for the reduction of aromatic N-oxides[57] had never been applied to the problem of reducing hydroxamic acids. By analogy with the phosphorus trichloride reaction, sulphur dioxide was thought to be capable of performing this reduction. It was also decided to attempt

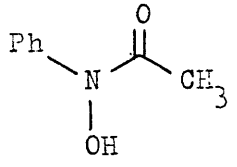
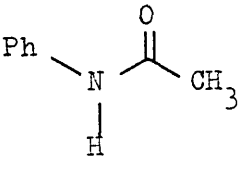
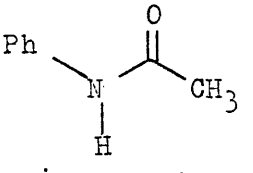
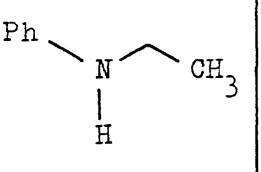
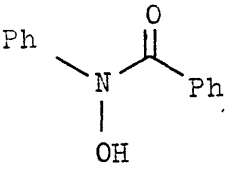
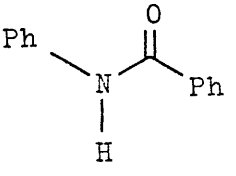
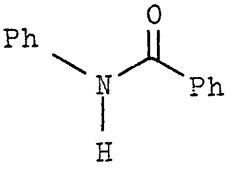
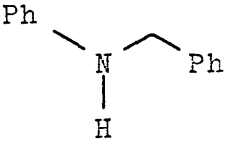
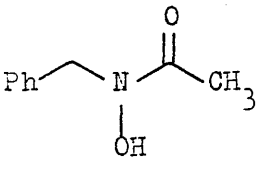
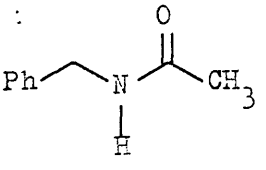
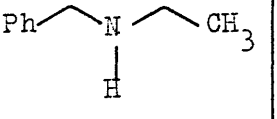
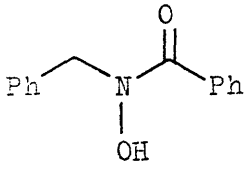
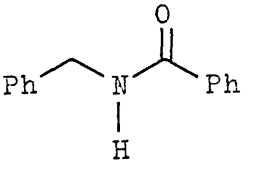
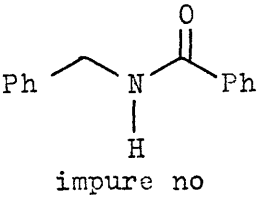
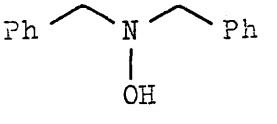
Compound \ Reagent	SO_2/Pyridine 115 °C	PCl_3/Pyridine 0 °C	BH_3/THF 68 °C
 (118)	 60%	 impure no crystallisation	 86%
 (119)	 64%	 impure 32%	 8%
 (120)	 18%	No Product	 48%
 (121)	 61%	 impure no Crystallisation	 24%

Figure 4

the reduction of the hydroxamic acids with borane in tetrahydrofuran.

The results of these experiments are shown in figure 4. It is immediately obvious that the most efficient method of reducing hydroxamic acids to amides utilised sulphur dioxide in pyridine under reflux. The only problem observed with these reductions was the low yield (18%) for the conversion of N-acetyl-N-benzylhydroxylamine (120) into benzylacetamide, even after 20 hours heating under reflux.

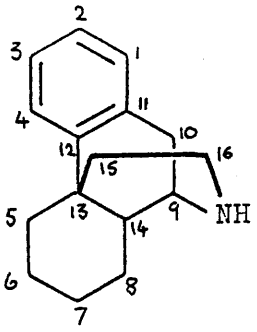
The reductions using phosphorus trichloride in pyridine gave disappointing results, with N-benzoyl-N-benzylhydroxylamine (119) being the only hydroxamic acid to yield a crystalline product. On addition of the phosphorus trichloride to the hydroxamic acid an immediate brown colouration was produced. It was interesting to note that N-acetyl-N-phenylhydroxylamine (120), though only partially reduced by sulphur dioxide in pyridine, was apparently not reduced by phosphorus trichloride in pyridine.

The reaction of hydroxamic acids with borane/tetrahydrofuran complex was also studied, but it was expected that the borane would initially reduce the carbonyl group to a methylene group. Whether the hydroxylamine would be reduced further to the amine was not known. The results shown in figure 4 were inconsistent in terms of product formed and yield, with the

only efficient reduction being that of N-acetyl-N-phenyl-hydroxylamine into N-ethylaniline. Reduction of both of the benzoylhydroxylamines only gave low yields of the benzylamines. The most puzzling example was that of the reduction of N-benzoyl-N-benzylhydroxylamine, which, by analogy with the three other borane reductions, was expected to give dibenzyl-amine (m.p. - 26 °C). The product from this reduction readily crystallised to yield colourless needles, m.p. 117-119 °C. This inconsistency was resolved when the mass spectrum of this compound showed a molecular ion at m/e 213 with a fragment at M-17, corresponding to loss of a hydroxyl. The compound was therefore assigned the structure of NN-dibenzylhydroxylamine (lit. m.p. 123 °C), which, when treated with more borane under the same conditions was not reduced further to the amine. A logical explanation for this was not obvious. Not shown in figure 4 was the reduction of N-acetyl-N-phenylhydroxylamine with zinc in acetic acid, which formed the desired amide, but in low yield.

The reduction of N-hydroxysuccinimide was also attempted. Phosphorus trichloride in pyridine successfully formed succinimide though in very low yield, but sulphur dioxide in pyridine did not appear to be effective, even after 24 hours under reflux.

Some speculative experiments on the reduction of N-acetyl-N-phenylhydroxylamine (118) were also attempted with silicon


2
3
1
11
4
10
12
16
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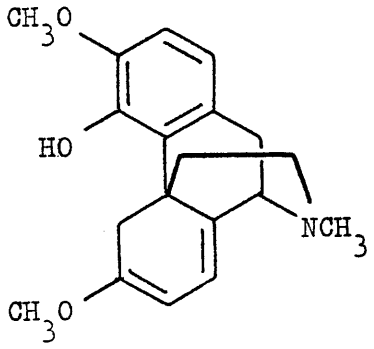
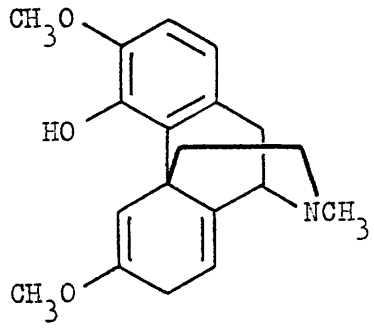
13
9
NH
14
6
8
7

(122)


CH3O
HO
NCH3
CH3O

(123)


CH3O
HO
NCH3
CH3O

(101)

containing reagents. No reaction was observed with trichlorosilane[58] in refluxing benzene, or with polymethylhydrosiloxane[59]. However, hexachlorodisilane, previously used for the reduction of aromatic amine oxides[60], reacted rapidly with N-acetyl-N-phenylhydroxylamine at room temperature in deuteriochloroform. The n.m.r. spectrum of the product indicated that reduction to acetanilide had not taken place, and t.l.c. showed there to be three compounds present in the total reaction mixture.

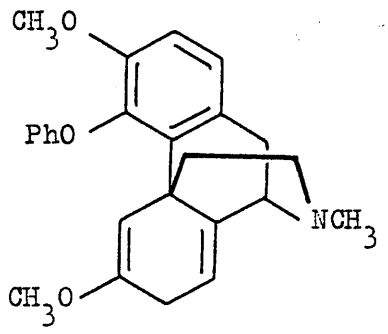
2.7 Some Reactions of Thebaine and its Derivatives with Tetranitromethane

The presence of the ether bridge linking C-3 and C-5 in the morphine alkaloids is not essential for pharmacological activity. Compounds based on the morphinan ring system (122), especially those containing a 3-hydroxyl substituent have been used as mild analgesics and considerable interest is therefore attached to the possibility of removing the ether bridge from thebaine, and introducing nitrogen containing groups at the 14β-position. It was therefore decided to carry out a preliminary investigation into the reactions of derivatives of β-dihydrothebaine (123) with tetranitromethane.

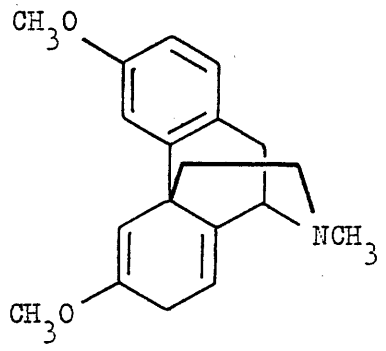
The reduction of thebaine with sodium in liquid ammonia has been studied by Bentley and co-workers[61] who reported that

the major product was dihydrothebaine-ϕ (101). More recent investigations[62] have shown that by varying the reaction conditions, or by using potassium instead of sodium, a certain amount of β-dihydrothebaine (123) can also be formed. We have found that by allowing the products of reduction with sodium in liquid ammonia to equilibrate for several hours in the presence of sodamide, the percentage of β-dihydrothebaine (123) in the total reaction mixture increases as a function of time, with, for example, a mixture of β-dihydrothebaine (65%) and dihydrothebaine-ϕ (35%) being obtained after 20 hours equilibration. The products were separated by fractional crystallisation, but n.m.r. spectroscopy showed that the β-dihydrothebaine was contaminated by a small amount of dihydrothebaine-ϕ.

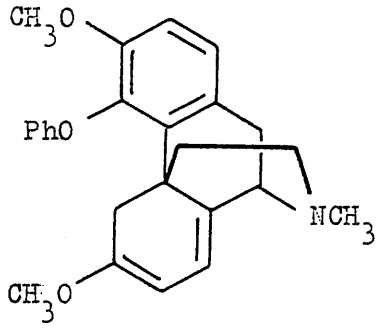
The presence of the hydroxyl group at the 4-position, as in β-dihydrothebaine was considered to be undesirable due to the activity imparted into the aromatic ring by the phenolic system. It was therefore decided to protect this hydroxyl group as the acetate, but several attempts to acylate β-dihydrothebaine with acetic anhydride in pyridine met with no success. Even under mild conditions (0 °C for 2 days) multiple products were formed, with a deep purple colour being produced. It was concluded that a rearrangement had preferentially taken place to produce a highly conjugated system, the nature of which was not established.



(125)



(126)



(127)

A search of the literature revealed that dihydrothebaine-Ø had been converted into the 4-phenyl ether (125) by an Ullmann reaction[63], and the 4-phenyl ether group had been subsequently removed by reduction with sodium in liquid ammonia to yield the substituted tetrahydromorphinan (126). This Ullmann reaction was repeated with β-dihydrothebaine and, after preparative t.l.c., the 4-phenyl ether (127) was obtained as an oil. All attempts to crystallise this material failed, but the compound was homogeneous by t.l.c., and the n.m.r. spectrum was consistent with the structure (127). This compound was used as the starting material for the nitration reactions with tetranitromethane.

The reaction of tetranitromethane with thebaine has been studied in depth[37] and it was decided to consolidate some of this earlier work before attempting the nitration of 4-phenyl ether (127).

Among the products obtained from the reaction of thebaine with tetranitromethane in benzene was a compound which was assumed to have the peroxide structure (74). Earlier combustion analysis of this compound had been unsatisfactory, but the structure had been determined by chemical degradation and n.m.r. spectroscopy. The literature method was therefore modified and the product, isolated by preparative t.l.c. on alumina followed by crystallisation from ethyl acetate was spectroscopically identical to the previously prepared material, with a specimen

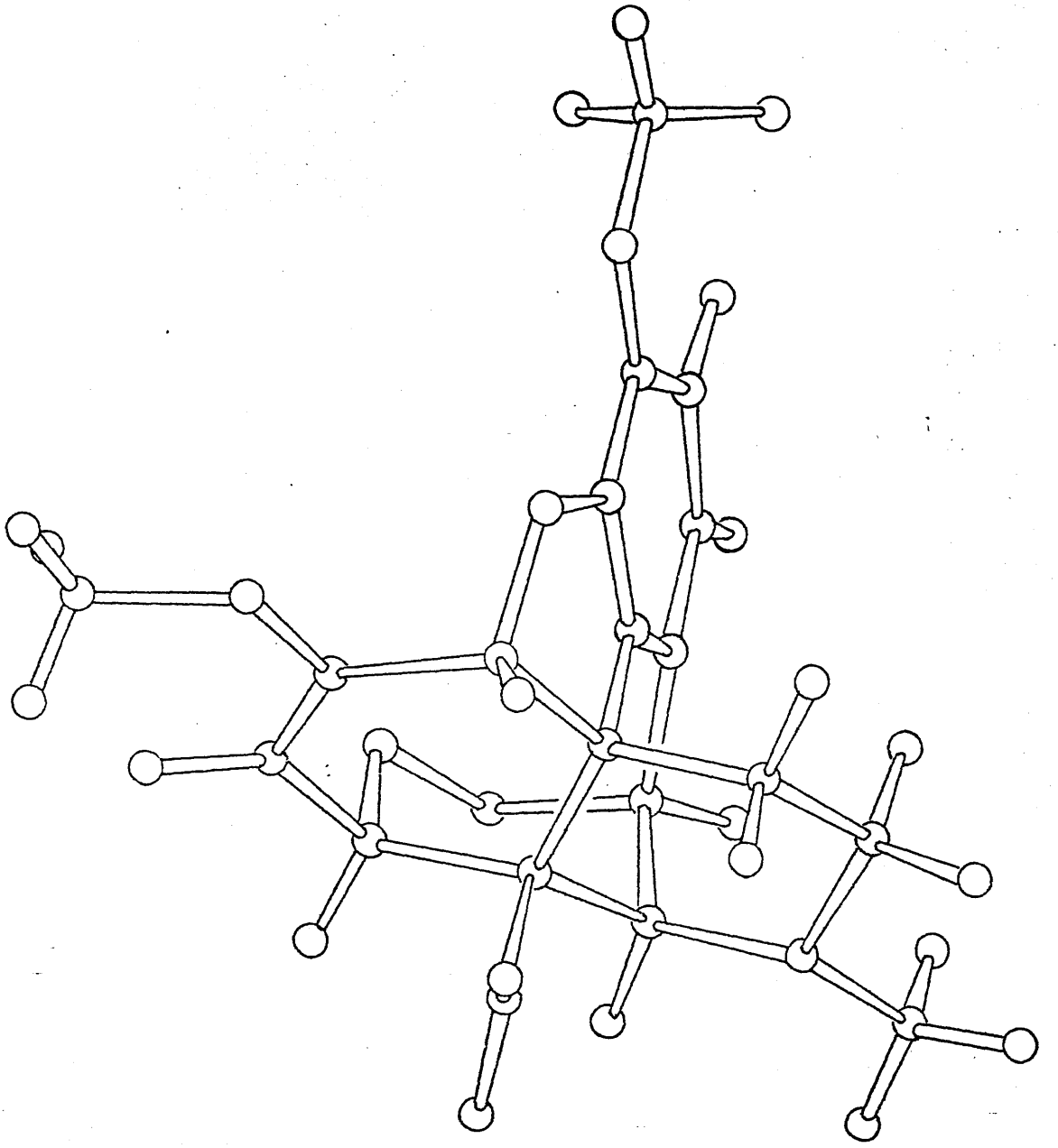
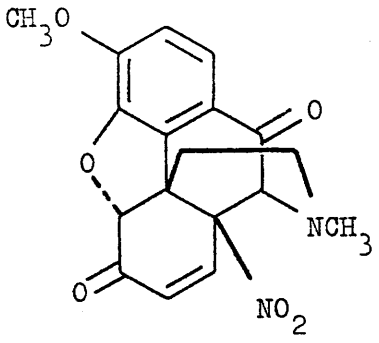
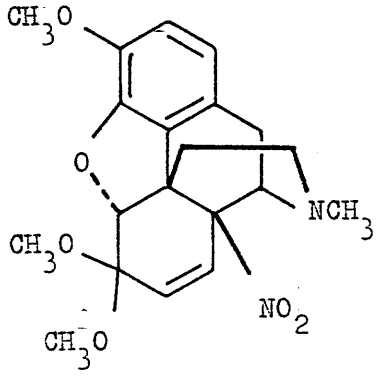


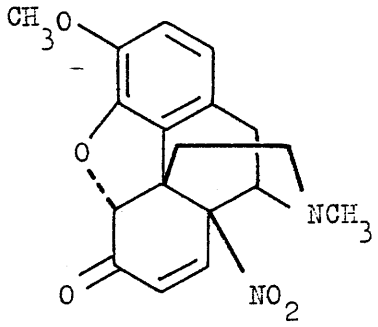
Figure 5



(128)



(72)

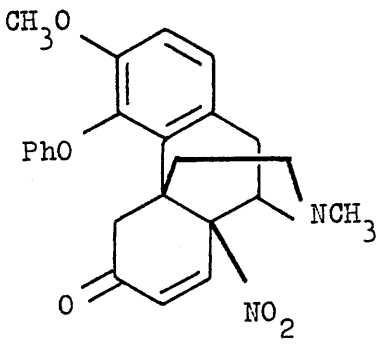


(73)

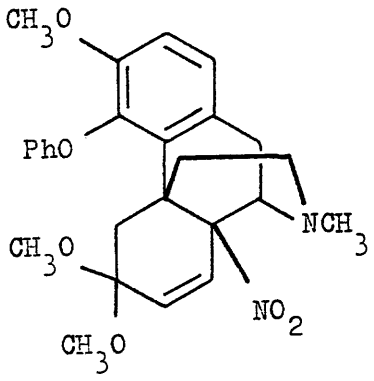
analysing correctly for $C_{19}H_{20}N_2O_7$, the maximum deviation from theory being + 0.09% for hydrogen. As further proof that this compound did indeed possess the novel peroxide bridged system (74), the X-ray structure was obtained[64] and is shown in figure 5.

An alternative preparation of the compound (128), a degradation product of (74)[37], was sought, so that samples of this compound, prepared by two different routes could be compared. Thus, thebaine was treated with tetranitromethane by the literature method[42] in methanolic ammonia to yield the dimethyl acetal (72) which was hydrolysed to the codeinone (73) with dilute acid. Attempts to oxidise the codeinone (73) to the 10-oxo compound (128) with selenium dioxide in refluxing dioaxane were unsuccessful. N.m.r. spectroscopy showed the loss of the N-methyl signal and the addition of a signal at δ 8.1, tentatively assigned to an N-formyl proton. Therefore, as the N-methyl group had been apparently oxidised in preference to the benzylic methylene group, this attempt to confirm the structure of (74) was abandoned.

After an initial attempt to react β-dihydrothebaine with tetranitromethane had yielded an intractable black tar, the reaction of the 4-phenyl ether (127) with tetranitromethane was studied. Two different sets of reaction conditions were employed, namely, using benzene as solvent in an attempt to make the compound analogous to the peroxide (74), and using



(129)



(130)

methanol and ammonia, to prepare the compound analogous to the dimethyl acetal (72).

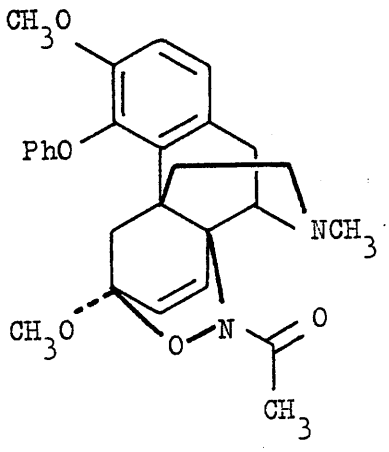
The reaction of tetranitromethane with the 4-phenyl ether (127) in benzene with passage of oxygen yielded at least eight different compounds, separable by t.l.c. on alumina. No compound containing an 8α,10α-dioxide bridge was obtained, although several of the components did not contain sufficient material for the n.m.r. spectrum to be recorded. The major product of this reaction was the 5,6-dihydro-14β-nitrocodeinone (129).

The i.r. spectrum contained bands at 1 679 and 1 539 cm^{-1}, showing the presence of an αβ-unsaturated ketone and a nitro-group respectively, while the n.m.r. spectrum was similar to that of the known compound (73), the major changes being the introduction of the aromatic multiplet (δ 6.2 to 7.4) and the loss of the signal attributed to H-5, formerly at δ 5.14. In addition, the C-4 phenyl ether now shielded the C-3 methyl ether and so caused an upfield shift of 0.2 ppm. The mass spectrum showed a molecular ion peak at m/e 420, with the base peak (374, M-46) presumably being caused by loss of the nitro-group.

Among the other products isolated in very low yield by preparative t.l.c. of the total reaction mixture was the dimethyl acetal (130). The n.m.r. spectrum of this material was identical

to that prepared by a different method (see below), and it was interesting to note that the additional methoxy group now attached at C-6 must have come from another molecule of starting material that had been transformed into the ketone. The other component isolated by t.l.c. consisted of a mixture of unreacted starting material and strangely, a compound which appeared to be the 4-phenyl ether derived from dihydrothebaine-Ø. As stated earlier, the β-dihydrothebaine obtained from the sodium/liquid ammonia reduction of thebaine was contaminated with a small amount of dihydrothebaine-Ø, so presumably, this material had also been converted by the Ullmann reaction into the corresponding 4-phenyl ether. This compound, being unable to react with tetranitromethane due to the non-conjugated nature of the diene system, increased in relative concentration to become visible in the n.m.r. spectrum of the unreacted starting material.

When the 4-phenyl ether (127) was subjected to the reaction conditions that had previously transformed thebaine into the dimethyl acetal (72), a crystalline product was obtained in low yield which was assigned the structure (130). As expected, the spectroscopic data for this compound were similar to those of the dimethyl acetal (72). The i.r. spectrum contained a band at 1 537 cm^{-1}, showing the presence of the nitro-group, and the n.m.r. spectrum, when compared to that of compound (72), had gained the aromatic multiplet in the region δ 6.7 to 7.4 and



(131)

lost the H-5 signal, formerly at δ 5.04. Shielding of the 3-methoxy group by the 4-phenyl ether group had caused an upfield shift of 0.2 ppm for the appropriate singlet and the signal for H-9, which was not observed previously, was now visible as a doublet centred at δ 3.71. The mass spectrum showed only a very weak molecular ion peak at m/e 466 but the prominent peak at 420 due to the loss of the nitro group was observed and the base peak appeared at m/e 306 (M-160).

As a final experiment it was decided to attempt the formation of a cyclo-adduct from the 4-phenyl ether (127) and nitrosocarbonylmethane, formed by the oxidation of acetohydroxamic acid. Using the reaction conditions that had proved to be successful in earlier studies, the cyclo-adduct (131) was prepared. At the time this reaction was attempted the 4-phenyl ether used as starting material was not available in pure form, so several impurities were carried through into the product. Separation was accomplished by preparative t.l.c., but the cyclo-adduct (131) still failed to crystallise. The n.m.r. spectrum was consistent with this structure and was, as expected, similar to the spectrum of the thebaine adduct (46; R = CH_3), with the addition of the aromatic signals in the region δ 6.6 to 7.4 and the loss of the H-5 singlet, formerly at δ 4.60. Shielding of the 3-methoxy group by the 4-phenyl ether group again caused an upfield shift of 0.2 ppm for the methoxy singlet.

It was therefore shown that the 4-phenyl ether (127) was capable of performing nitration reactions with tetranitromethane, and forming cyclo-adducts with nitrosocarbonyl intermediates.

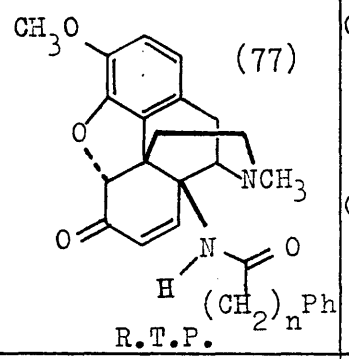
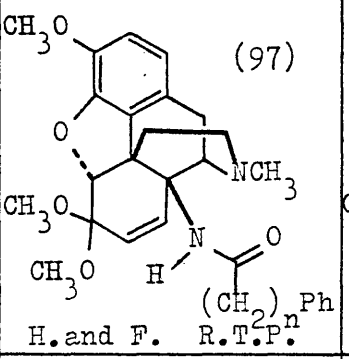
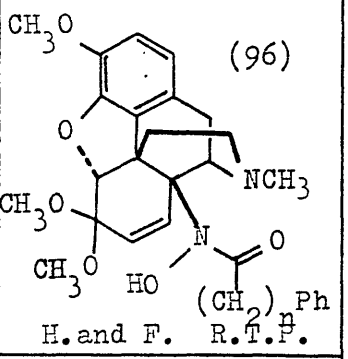
2.8 Results of Pharmacological Testing

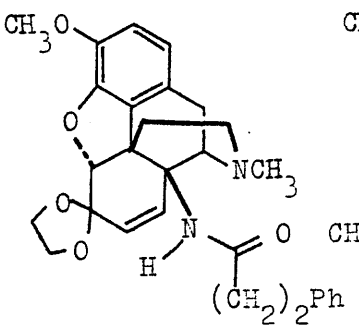
The analgesic potency of several of the compounds prepared by the nitrosocarbonyl route was determined by animal testing experiments.[65] Several different methods are available for determining whether or not a compound is an analgesic, and the techniques used in this study were the Rat Tail Pressure (R.T.P)[66] and Hendershot and Forsaith (H. and F.) methods.

The R.T.P. method involves injecting the animal with the test substance, then applying pressure to the rat's tail until the animal struggles and squeaks. Analgesia is assumed when the threshold is at least twice that of the mean control experiment. The H. and F. method involves injecting the animal with the compound under test, followed, after a short delay, by an aqueous solution of 2-phenyl-1,4-benzoquinone, which causes the animal to writhe. The number of writhes in a given time is noted and compared to that of the control experiment.

The results of these experiments are shown in table 1, and the graphs on the facing page. These are quoted as the dose, in mg per kg of body weight, of the test compound, injected

Table 1. Results of Animal Tests

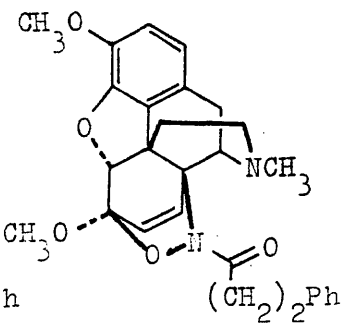
	 (77)	 (97)		 (96)	
	R.T.P.	H.and F.	R.T.P.	H.and F.	R.T.P.
n = 0	0.1	1.15	0.205	8	>10
n = 1	0.4	2.85	11.4	0.27	0.26
n = 2	0.018	0.03	0.027	0.34	0.70
n = 3	0.02	0.20	0.52	2.5	8.8



(112; R=CH_2CH_2Ph)

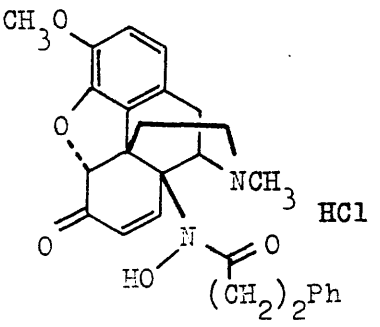
H.and F. = 0.12

R.T.P. = 0.76



(46; R=CH_2CH_2Ph)

R.T.P. = 22.0



HCl

(102; R=CH_2CH_2Ph)

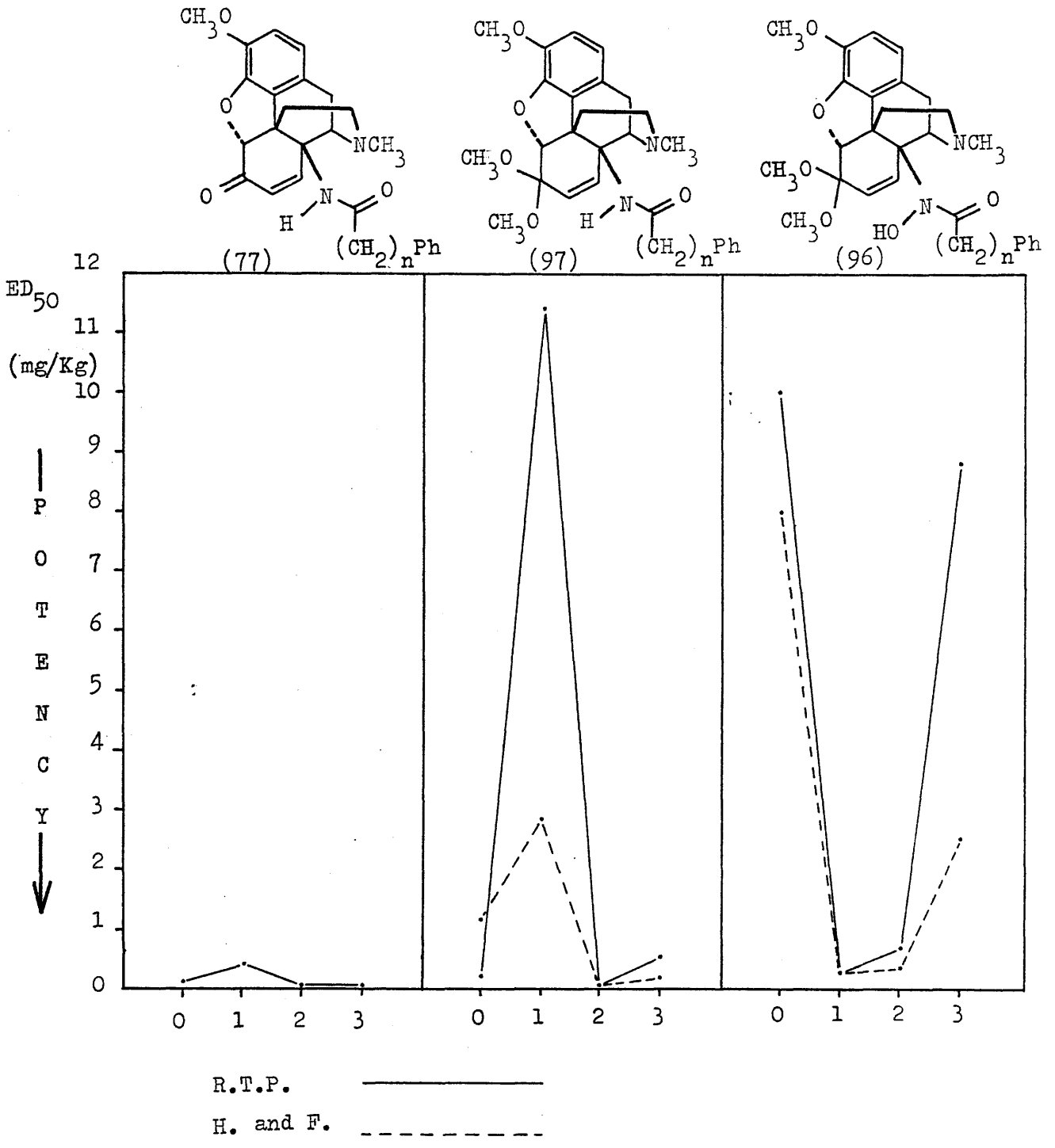
R.T.P. = <u>ca.</u> 10

For comparison :- Morphine sulphate : R.T.P. = 2.6

Codeine phosphate : R.T.P. = 13.5

All results are LD_{50} mg/Kg (subcutaneous)

Results of Animal Tests (contd.)



subcutaneously, that produced analgesia in 50% of the animals under test (ED_{50}). Thus, the lower the numerical value for the ED_{50}, the more potent is the analgesic.

The most potent compounds in the codeinone series (77) were those with n = 2 and n = 3, with the least active being that with n = 1. This behaviour was followed by the corresponding dimethyl acetals (97), but a much larger spread of results was obtained. Thus, although the most potent compound (97; n = 2) was of approximately the same activity as the codeinone (77, n = 2), the dimethyl acetal (97, n = 1) was ca. 30 times less potent that the codeinone (77, n = 1). There was little difference in potency between the codeinones (77; n = 2 and n = 3), but the dimethyl acetal (97, n = 3) was several times less potent than the dimethyl acetal (97, n = 2).

A different structure-activity relationship was observed with the N-hydroxy compounds (96). These compounds were generally weaker analgesics than the corresponding codeinones (77) or dimethyl acetals (97) except where n = 1, where the maximum potency was achieved. The compound with n = 2 was also active, but the compounds with n = 0 and n = 3, in contrast to the compounds in the series (77 and 97), were now relatively poor analgesics.

The ethylene ketal (112; R = CH_2CH_2Ph) was also shown to be a potent analgesic, though not nearly as active as the dimethyl

acetal (97; n = 2), while the cyclo-adduct (46; R = CH_2CH_2Ph) and the N-hydroxycodeinone hydrochloride (102; R = CH_2CH_2Ph) were only slightly active,

CHAPTER 3 EXPERIMENTAL

Instrumentation

m.p.s (corrected)	-	Reichert hot-stage apparatus.
i.r. spectra	-	Perkin-Elmer 257 and 197.
u.v. spectra	-	Unicam SP 800B.
^{1}H n.m.r. spectra	-	Varian T-60 (60 MHz)
		Perkin-Elmer R32 (90 MHz).
mass spectra	-	A.E.I. MS 12 at an ionising voltage of 70 eV.

Notes

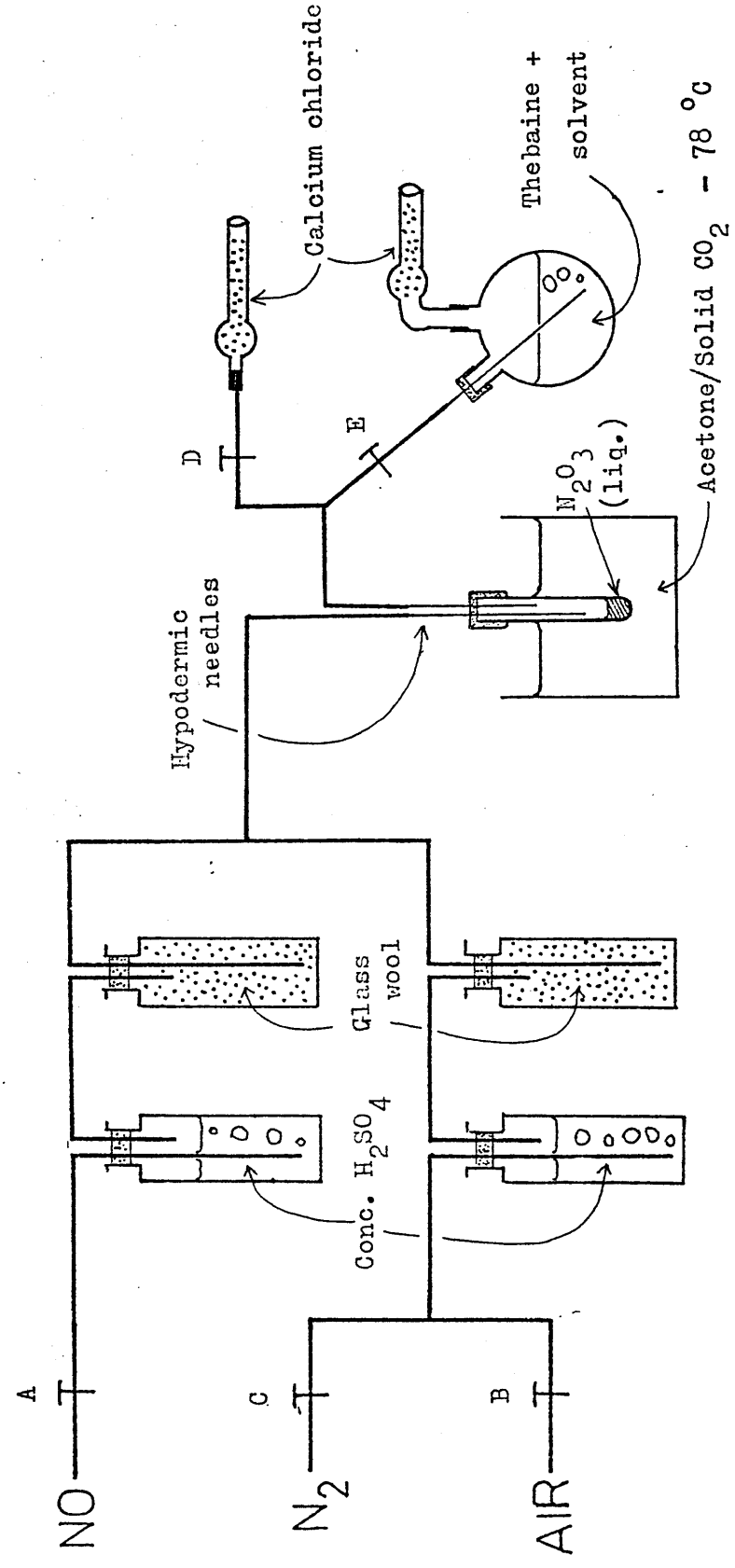
(a) N.m.r. refers to ^{1}H n.m.r. spectra with tetramethylsilane as internal standard.

(b) 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.

(c) THF refers to tetrahydrofuran and ether refers to diethyl ether.

(d) T.l.c. was carried out on Merck GF_{254} silica and alumina with detection of components by u.v. Column chromatography utilised Woelm neutral alumina.

(e) Elemental analyses were carried out by the microanalytical service, Chemistry Department, Glasgow University.



Apparatus for the Preparation of Dinitrogen Trioxide

Figure 6

The Preparation of Dinitrogen Trioxide

Dintrogen trioxide was prepared in the apparatus shown in figure 6 . The apparatus was first flushed with nitrogen, then, with valve D open and valves C and E closed, valves A and B were carefully contolled such that approximately equal volumes of nitric oxide and air were allowed to mix together. The rate of mixing was measured by the passage of the bubbles of gas through the Drechsel bottles of sulphuric acid. Dinitrogen trioxide condensed as a bright blue liquid and was either weighed (by removal of the collection trap), or measured by volume (using a previously calibrated trap). Once the required amount had been collected, valves A, D, and B were closed, and valves C and E opened. Thus, as the trap was allowed to warm to room temperature, the dinitrogen trioxide was carried into the thebaine solution by the nitrogen carrier gas.

Reaction of Thebaine with Dinitrogen Trioxide

Dinitrogen trioxide (0.25 ml, 4.76 mmol) was collected at - 78 °C under dry nitrogen as a bright blue liquid. This was allowed to warm to room temperature and was carried by a stream of dry nitrogen into a solution of thebaine (1 g, 3.21 mmol) in ethyl acetate (30 ml), precipitating a thebaine salt as a yellow solid. This was removed by filtration and the constituents of the filtrate sparated by preparative t.l.c. on silica, (chloroform - methanol, 9:1). The major component (R_F 0.68) was removed and crystallised from benzene - ethyl acetate to yield the oxime (78) (108 mg, 9%), m.p. 231 °C (with colour

change at 203 °C). (Found: C, 58.71; H, 5.52; N, 11.08. $C_{19}H_{21}N_3O_6$ requires C, 58.91; H, 5.43; N, 10.85%); $\lambda_{max.}$ (CH_3OH) 209 (ε 3.93 x 10^4) and 230 (ε 1.42 x 10^4) nm; $\nu_{max.}$ (KBr) 3 280, 1 634, and 1 550 cm^{-1}; δ (D_6DMSO) 2.32 (3H, s, N-CH_3), 3.63 (3H, s, O-CH_3 at C-6), 3.78 (3H, s, O-CH_3 at C-3), 4.28 (1H, d, $J_{H-10\alpha}$ 7 Hz, H-9), 5.31 (1H, s, H-5), 5.76 (1H, s, H-7), 6.70 (1H, d, J_{H-2} 8 Hz, H-1), 6.85 (1H, d, J_{H-1} 8 Hz, H-2), and 11.70 (1H, s, D_2O exchangeable, N-OH); m/e 387.

Preparation of Northebaine

Northebaine was prepared by a modification of the method of E. Lilly and Co.[68] Thus, thebaine (6.24 g, 20 mmol) and diethyl azodicarboxylate (prepared by the method of J. Kauer[69]) (3.48 g, 22 mmol) in benzene were heated under reflux for 3 h. The solvent was then evaporated to yield the intermediate N-(1,2-diethoxycarbonylhydrazino-methyl) northebaine (30) as an oil. This material was dissolved in ethanol (40 ml), water (30 ml) and ammonium hydroxide (0.88 sp. g., 20 ml), and heated under reflux for a further 6.5 h, then left at room temperature for 17 h. The solution was extracted with methylene chloride, dried and evaporated to yield a brown oil. This oil was dissolved in refluxing ethyl acetate and, on cooling, the by-product urethane precipitated and was removed by filtration. The filtrate was evaporated and the residue dissolved in methanol and treated with methanolic hydrogen chloride (24 N; ca. 21 ml) till the solution was just acidic. Northebaine hydrochloride precipitated from the solution and was recrystallised from water (2.54 g, 43%), m.p. 269 °C (decomp.) (Lit.,[68] 270-272 °C(decomp.)).

Preparation of N-Benzyloxycarbonylnorthebaine[48]

A solution of northebaine (1.4 g, 4.7 mmol) in chloroform (28 ml) was treated with water (14 ml) and sodium hydrogen carbonate (1.68 g). The mixture was then cooled to 0 °C, treated with benzyl chloroformate (0.73 ml, 5.1 mmol), and stirred for 2 h. The chloroform was then separated and the aqueous layer extracted twice with chloroform. The combined extracts were washed with water, dried and evaporated to give a pale yellow oil. Trituration of this oil with ether - light petroleum (b.p. 40-60 °C) and a small quantity of ethanol led to crystallisation after 24 h at - 78 °C. The solid was removed by filtration, washed with a small portion of cold ether and dried to give N-benzyloxycarbonylnorthebaine (1.02 g, 50%), m.p. 113-115 °C (lit.,[48] 116-117 °C); δ ($CDCl_3$) 3.59 (3H, s, O-CH_3 at C-6), 3.83 (3H, s, O-CH_3 at C-3), 5.02 (1H, d, J_{H-8} 7 Hz, H-7), 5.18 (2H, s, O-CH_2Ph), 5.28 (1H, s, H-5), 5.61 (1H, br d, J_{H-7} 7 Hz, H-8), 6.56 (1H, d, J_{H-2} 9 Hz, H-1), 6.69 (1H, d, J_{H-1} 9 Hz, H-2), and 7.35 (5H, s, Ph).

Reaction of N-Benzyloxycarbonylnorthebaine with Dinitrogen Trioxide

Dinitrogen trioxide (26 mg, 0.34 mmol) was collected at - 78 °C under dry nitrgen as a bright blue liquid. This was allowed to warm to room temperature and was carried by a stream of dry nitrgen into a solution of N-benzyloxycarbonylnorthebaine (147 mg, 0.34 mmol) in deuteriochloroform (2 ml). The constituents of the total reaction mixture were separated by

preparative t.l.c. on silica (chloroform - methanol, 20:1), and the component with R_F 0.69 was removed and crystallised from toluene at - 5 °C to yield the impure oxime (83) (12 mg, 7 %), m.p. 199-201 °C; $\nu_{max.}$(KBr) 3 280, 1 632, and 1 549 cm^{-1}; $\lambda_{max.}$ (CH_3OH) 212 (ε 2.10 x 10^4) and 231 (ε 7.69 x 10^3) nm; δ ($CDCl_3$) 3.68 (3H, s, O-CH_3 at C-6), 3.86 (3H, s, O-CH_3 at C-3), 5.19 (2H, s, O-CH_2Ph), 5.34 (1H, s, H-5), 5.87 (1H, s, H-7), 6.63 (1H, d, J_{H-2} 9 Hz, H-1), 6.81 (1H, d, J_{H-1} 9 Hz, H-2), 7.29 (5H, s, Ph), and 7.38 (1H, br s, N-OH); m/e 507 with impurities at m/e 494 and m/e 534.

Alternative Procedure for the Reaction of N-Benzyloxycarbonylnorthebaine with Dinitrogen Trioxide

N-Benzyloxycarbonylnorthebaine (267 mg, 0.62 mmol) in deuteriochloroform (2 ml) was injected directly into liquid dinitrogen trioxide (40 mg, 1 mol. equiv.) at ca. 0 °C, in a sealed container under a nitrogen atmosphere. The constituents of the total reaction mixture were separated by preparative t.l.c. on silica (chloroform - methanol, 20:1). The component with R_F 0.70 consisted of the oxime (83) (30 mg, 10%) which was identified by n.m.r. spectroscopy. Mass spectrometry indicated that this material was impure.

Preparation of Mesitylenesulphonylhydroxylamine (86)

The preparation of mesitylenesulphonylhydroxylamine is covered in the review by Y. Tamura et al,[49] and is represented in scheme 5.

Mesitylenesulphonyl Chloride (87)

The procedure of Wang and Cohen[70] was carried out with mesitylene (100 ml) and chlorosulphonic acid (131 ml). Mesitylenesulphonyl chloride was crystallised from ethyl acetate - light petroleum (b.p. 40-60 °C), m.p. 52-55 °C (lit., 57 °C).

Ethyl Imidoacetate Hydrochloride (88)

The procedure of Reitter and Hess,[71] using dry acetonitrile (25 ml) and dry ethanol (25 ml) gave ethyl imidoacetate hydrochloride, which crystallised from acetone (52.8 g, 85%).

Ethyl Acetohydroxamate (89)

The procedure of Houben and Schmidt[72] yielded, from ethyl imidoacetate hydrochloride (10 g), ethyl acetohydroxamate (5.1 g, 61%), b.p. 60 °C / 13 mm Hg.

Ethyl O-(Mestylenesulphonyl) acetohydroxamate (90)

The procedure of Tamura[73] was followed, and afforded, from mesitylenesulphonyl chloride (72 g) and ethyl acetohyroxamate (34 g), ethyl O-(mesitylenesulphonyl) acetohydroxamate which crystallised from light petroleum (b.p. 40-60 °C) (44 g, 46%), m.p. 52-54 °C.

Mesitylenesulphonylhydroxylamine (86)

The procedure of Tamura[49] was carried out immediately before the mesitylenesulphonylhydroxylamine was required for use, using

the quantities required for a specific reaction. The product was used either as a dried methylene chloride solution, or was recrystallised from ether - light petroleum (b.p. 60-80 °C).

Attempted 14β-Amination of N-Benzyloxycarbonylnorthebaine with Mesitylenesulphonylhydroxylamine (86)

N-Benzyloxycarbonylnorthebaine (51 mg, 0.12 mmol) was dissolved in deuteriochloroform and treated with freshly prepared mesitylenesulphonylhydroxylamine (28 mg, 0.14 mmol), which had been crystallised from ether - light petroleum (b.p. 60-80 °C). The mixture was kept at 30 °C and the reaction followed by n.m.r. spectroscopy. No significant reaction appeared to take place till after ca. 10 h, after which the spectra became progressively more complex. The reaction appeared to stop at ca. 100 h by which time, the n.m.r. spectrum was unrecognisable and the contents of the n.m.r. tube had been transformed into a dark brown solution. No product was obtained from this process.

Attempted 14β-Amination of N-Benzyloxycarbonylnorthebaine with Hydroxylamine-O-sulphonic Acid (85)[74]

Several attempts were made to aminate N-benzyloxycarbonylnorthebaine directly in the 14β-position using hydroxylamine-O-sulphonic acid, with no success. The following procedure was typical.

N-Benzyloxycarbonylnorthebaine (100 mg, 0.23 mmol) in deuteriochloroform (1 ml) and deuteriomethanol (1 ml) was treated

with hydroxylamine-O-sulphonic acid (89%; 30 mg, 0.23 mmol). The temperature was maintained at 30 °C and the reaction progress moniored by n.m.r. spectroscopy and t.l.c. After 3 h, no starting material remained, and after 19 h, the two main constituents were separated by preparative t.l.c. on silica (chloroform - methanol, 9:1). The i.r. spectra indicated that neither compound contained an -NH group, but both contained an -OH group, and the n.m.r. spectra did not correspond to that of the desired product. No aminated material was recovered from this process.

Attempted N-Amination of Northebaine with Mesitylenesulphonylhydroxylamine (86)

Northebaine hydrochloride (100 mg, 0.30 mmol) was treated with sodium hydrogen carbonate solution (ca. 20 ml), extracted with chloroform and evaporated to give northebaine (83 mg, 0.28 mmol) as a pale yellow oil. This oil was dissolved in deuteriochloroform (2 ml) and treated with freshly prepared, crystalline mesitylenesulphonylhydroxylamine (57 mg, 0.28 mmol). Within 5 min, the starting material had mostly disappeared and had been replaced by a new northebaine-like compound. The reaction was left overnight, then washed with 5M-hydrochloric acid (3 x 1 ml) followed by water. The aqueous phase was basified by the addition of aqueous sodium hydrogen carbonate, extracted with chloroform and dried to yield, after evaporation, starting material (9 mg). The n.m.r. spectrum of the acid insoluble material indicated that the new northebaine-like product was

present, along with a mesitylene derivative. These compounds were not separated, but n.m.r. data for the postulated N-aminonorthebaine was as follows δ ($CDCl_3$) 3.65 (3H, s, O-CH_3 at C-6), 3.87 (3H, s, O-CH_3 at C-3), 4.54 (1H, d, $J_{H-10\alpha}$ 7 Hz, H-9), 5.05 (1H, d, J_{H-8} 6 Hz, H-7), 5.27 (1H, s, H-5), 5.75 (1H, d, J_{H-7} 6 Hz, H-8), 6.72 (2H, s, H-1 and H-2), and ca, 7.0 (2H, br s, NH_2).

Attempted N-Amination of Northebaine with Hydroxylamine-O-sulphonic Acid (85)

Northebaine (176 mg, 0.59 mmol) was dissolved in methanol (10 ml) and treated with a solution of hydroxylamine-O-sulphonic acid (89%; 113 mg, 0.89 mmol) and potassium hydroxide (55 mg, 0.98 mmol) in water (3 ml). The mixture was heated under reflux for 30 min, then the solvent was removed under reduced pressure and the inorganic residue extracted with ethanol. To this ethanol solution was added hydriodic acid (45%; 169 µl, 0.89 mmol), then the reaction mixture was cooled for 17 h at - 78 °C. Northebainehydriodide precipitated from this solution. No N-aminated product was observed.

Preparation of Hydroxamic Acids

The preparation of the hydroxamic acids was an adaptation of the procedure of Sandler and Karo.[75] Thus, the relevant carboxylic acid was first converted into its ethyl ester, which was in turn treated with hydroxylamine hydrochloride in the

presence of sodium hydroxide to form the hydroxamic acid. The yields varied from 30% to 56%, and the products generally were low m.p. solids, which crystallised from ethyl acetate or benzene.

Preparation of the Thebaine/2-phenylnitrosocarbonylethane Adduct (46; R = CH_2CH_2Ph)

Thebaine (2 g, 6.4 mmol) in ethyl acetate (150 ml) and sodium periodate (2.05 g, 9.6 mmol) in aqueous sodium acetate (0.2 M, adjusted to pH 6 with concentrated hydrochloric acid)(50 ml) were stirred rapidly at 0 °C. N-(3-Phenylpropanoyl)hydroxylamine (1.58 g, 9.6 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 and the combined ethyl acetate layers were washed with dilute aqueous sodium thiosulphate and then water, The dried ethyl acetate solution was evaporated to yield a crystalline solid (3.49 g). Crystallisation from ethyl acetate or ethanol gave the thebaine adduct as needles, m.p. 156-157 °C (80-90% yield)(Found: C, 70.6; H, 6.6; N, 5.63. $C_{28}H_{30}N_2O_5$ requires C, 70.89; H, 6.33; N, 5.91%); $\nu_{max.}$(KBr) 1 675 cm^{-1}; δ ($CDCl_3$) 2.50 (3H, s, N-CH_3), 3.55 (3H, s, O-CH_3 at C-6), 3.83 (3H, s, O-CH_3 at C-3), 4.65 (1H, s, H-5), 4.90 (1H, d, $J_{H-10\alpha}$ 7 Hz, H-9), 6.00 (1H, d, J_{H-8} 9 Hz, H-7), 6.15 (1H, d, J_{H-7} 9 Hz, H-8), 6.60 (1H, d, J_{H-2} 7 Hz, H-1), 6.68 (1H, d, J_{H-1} 7 Hz, H-2), and 7.22 (5H, br s, Ph); m/e 474.

Preparation of the Dimethyl Acetal (96 ; R = CH_2CH_2Ph)

The thebaine adduct (46 ; R = CH_2CH_2Ph) (1 g, 2.1 mmol) in 0.175 M anhydrous methanolic hydrogen chloride (40 ml) was kept at 0 °C for 10 min. A white solid separated. The mixture was neutralised by the addition of solid sodium hydrogen carbonate and water was added to the resulting paste to dissolve salts. The mixture was extracted with chloroform and the extract was then dried and evaporated to yield the dimethyl acetal which crystallised from ethyl acetate as needles (703 mg, 66%), m.p. 172-173 °C (Found: C, 68.62; H, 6.84; N, 5.05. $C_{29}H_{34}N_2O_6$ requires C, 68.77; H, 6.72; N, 5.53%); $\nu_{max.}$(KBr) 3 245 and 1 640 cm^{-1}; δ ($CDCl_3$) 2.40 (3H, s, N-CH_3), 3.12 (3H, s, O-CH_3 at C-6β), 3.50 (3H, s, O-CH_3 at C-6α), 3.90 (3H, s, O-CH_3 at C-3), 4.32 (1H, d, $J_{H-10\alpha}$ 6 Hz, H-9), 4.86 (1H, s, H-5), 5.56 (1H, d, J_{H-8} 10 Hz, H-7), 6.40 (1H, d, J_{H-7} 10 Hz, H-8), 6.56 (1H, d, J_{H-2} 8 Hz, H-1), 6.74 (1H, d, J_{H-1} 8 Hz, H-2), and 7.30 (5H, br s, Ph); m/e 506.

Unsuccessful Reductions of the Acetal (96 ; R = CH_2CH_2Ph) to the Acetal (97 ; R = CH_2CH_2Ph)

Many attempts were made to carry out this reduction and the unsuccessful attempts are given below. The experimental details given are representative of the general procedure used, but several attempts, using differing amounts of reagents, reaction times and temperatures were also carried out, all with equally negative results.

1) Zinc/Acetic Acid

The dimethyl acetal (50 mg, 0.1 mmol) in glacial acetic acid (2 ml) was treated with zinc dust (10 mg, 1.5 mol. equiv.) and the reaction temperature maintained at 80 °C for 30 min. The mixture was then basified by the addition of aqueous sodium hydrogen carbonate solution, extracted with chloroform, the extract dried and evaporated to yield the cyclic adduct (46 ; R = CH_2CH_2Ph) (identified by n.m.r. spectroscopy), which crystallised from ethyl acetate, m.p. 157-158 °C (lit. p 121 156-157 °C).

2) Lithium Aluminium Hydride/THF

The dimethyl acetal (101 mg, 0.2 mmol) in dry THF (3 ml) was slowly added to lithium aluminium hydride (15 mg, 0.4 mmol) in dry THF (3 ml) under argon. After 1 h at room temperature followed by 1 h at reflux temperature, the reaction mixture was cooled and quenched by the cautious dropwise addition of saturated ammonium chloride solution (ca. 0.5 ml). Excess water was removed with anhydrous sodium sulphate, then the mixture was filtered and the inorganic salts washed with THF. Evaporation then yielded an oil (98 mg). T.l.c. on alumina (ethyl acetate) indicated that multiple products had been formed, but the n.m.r. spectrum indicated that predominantly one compound was present, δ ($CDCl_3$) 2.37 (3H, s, N-CH_3), 3.17 (3H, s, O-CH_3 at C-6β), 3.43 (3H, s, O-CH_3 at C-6α), 3.84 (3H, s, O-CH_3 at C-3), 4.83 (1H, s, H-5). 5.57 (1H, d, J_{H-8} 10 Hz, H-7), 5.86 (1H, d, J_{H-7} 10 Hz, H-8), 6.47 (1H, d,

J_{H-2} 8 Hz, H-1), 6.57 (1H, br s), 6.62 (1H, d, J_{H-1} 8 Hz, H-2), and 7.19 (5H, br s, Ph). All attempts to crystallise this material, and to remove the impurities by chromatography failed. This material was never identified and attempts to hydrolyse it to the codeinone with dilute acid also failed.

3) Sodium Amalgam

The dimethyl acetal (100 mg, 0.2 mmol) in THF (5 ml) and water (1 ml) was treated with sodium amalgam (300 mg; 3%). After 18 h at room temperature, t.l.c. indicated that no reaction had taken place, so a further portion of the amalgam was added and the mixture heated under reflux for 4 h, then left at room temperature for a further 17 h. T.l.c. and n.m.r. spectroscopy again showed that no reaction had taken place. Filtration and evaporation yielded crystalline starting material m.p. 168-169 °C (lit. p122 172-173 °C).

4) Bouveault-Blanc Reduction (Ethanol/Sodium)

The dimethyl acetal (100 mg, 0.2 mmol) in ethanol (4 ml) and THF (4 ml) was heated under reflux and treated with sodium (18 mg, 0.8 mmol). After 10 min, water (10 ml) was added, the mixture extracted with chloroform, the extract dried and evaporated to yield a crystalline solid (77 mg). N.m.r. spectroscopy indicated that this consisted mostly of starting material and t.l.c. on silica (methanol - chloroforom, 2:8) indicated that ca. 10 by-products had also been formed. No product was isolated from this reaction.

5) Chromous Acetate

The dimethyl acetal (100 mg, 0.2 mmol) in THF (3 ml) was treated with chromous acetate (85 mg, 0.5 mmol) in dimethyl sulphoxide (2 ml) under an atmosphere of carbon dioxide. After 3 h at room temperature, water was added, the mixture extracted with chloroform and the extract washed (8 x) with water. The extract was dried and evaporated to yield unreacted starting material, identified by n.m.r. spectroscopy.

The above reaction was repeated at 85 °C. The n.m.r. spectrum indicated that all the starting material had been consumed, but a plethora of products had now been formed. No reduced material was obtained from this process.

6) Chromous Chloride[76]

The dimethyl acetal (100 mg, 0.2 mmol) in acetone (15 ml) was treated with an aqueous solution of chromous chloride (5 ml) at 0 °C with passage of carbon dioxide, then allowed to warm to room temperature. After 72 h, the mixture was diluted with water, extracted with chloroform and the extract dried. Evaporation then yielded impure thebaine hydrochloride as an oil. Further attempts using this reducing system led to multiple product formation with no evidence of formation of the reduced dimethyl acetal.

7) Zinc/Ammonium Acetate

The dimethyl acetal (100 mg, 0.2 mmol) in THF (3 ml) was treated with zinc (65 mg, 1 mmol) and ammonium acetate (77 mg, 1 mmol) in methanol (3 ml). After heating under reflux for

6 h, the mixture was filtered and evaporated to yield starting material, which was identified by n.m.r. spectroscopy. No reaction took place.

8) Zinc/Ammonium Chloride

The dimethyl acetal (100 mg, 0.2 mmol) in THF (5 ml) was treated with zinc (65 mg, 1 mmol) and ammonium chloride (54 mg, 1 mmol) in water (3 ml). The mixture was heated under reflux for 48 h, then kept at room temperature for 5 days. Water (20 ml) was added, the mixture extracted with chloroform, then the extract dried and evaporated. T.l.c. on silica (methanol - chloroform, 2:8) indicated that some starting material remained along with 4 other products. These were not identified.

9) Copper Chromite/Hydrogen

The dimethyl acetal (200 mg, 0.4 mmol) in dry THF (10 ml) and dry ethanol (5 ml) was hydrogenated for 3 h at atmospheric pressure in the presence of copper chromite catalyst[77] (100 mg). Hydrogen was not taken up by the reaction, and, after filtration, starting material was recovered which was identified by its n.m.r. spectrum.

10) Sodium/Liquid Ammonia

The dimethyl acetal (147 mg, 0.3 mmol) in dry liquid ammonia (ca. 25 ml) was treated with sodium (40 mg, 6 mol. equiv.). After the blue colour had disappeared, water (ca. 20 ml) was added and the products precipitated by the addition of solid carbon dioxide. The solid material was filtered, washed with

water and dried under vacuum. T.l.c. on silica (methanol - chloroform 2:8) indicated that there was still starting material present, and n.m.r. spectroscopy proved that the major product was dihydrothebaine-ø (101).

11) Lithium/Liquid Ammonia

The dimethyl acetal (100 mg, 0.2 mmol) in dry liquid ammonia (ca. 25 ml) was treated with lithium (5 mg, 3 mol. equiv.). After 30 min, water (ca. 25 ml) was added and the products precipitated by the addition of solid carbon dioxide. Extraction with chloroform, drying and evaporation then yielded a crystalline solid which was shown by n.m.r. spectroscopy to consist of dihydrothebaine-ø (101) (ca. 30%) and starting material (ca. 70%).

12) Palladium/Hydrogen

The dimethyl acetal (100 mg, 0.2 mmol) in THF (3 ml) and ethanol (3 ml) was hydrogenated for 5 h with palladium/charcoal catalyst (10%; 10 mg). Filtration and evaporation yielded only starting material which was identified by its n.m.r. spectrum.

13) Titanium Trichloride

The cyclic adduct (50 mg, 0.1 mmol) in 0.2 N anhydrous methanolic hydrogen chloride (2 ml) was treated at 0 °C with anhydrous titanium trichloride (40 mg, 2.5 mol. equiv.) under an atmosphere of nitrogen. A further 2 ml of the methanolic hydrogen chloride was added, then the reaction mixture was

left at 0 °C for 1.5 h. The mixture was basified by the addition of solid sodium hydrogen carbonate, extracted with chloroform, the extract dried and evaporated to yield a crystalline solid (40 mg). The n.m.r. spectrum indicated that this consisted mostly of the non-reduced dimethyl acetal.

14) Sodium Dithionite

The dimethyl acetal (50 mg, 0.1 mmol) in THF (3 ml) was treated with sodium dithionite (174 mg, 10 mol. eqiv.) in water (3 ml) under nitrogen, and heated under reflux for 30 h. The mixture was basified with aqueous sodium hydrogen carbonate, extracted with chloroform, the extract dried and evaporated. N.m.r. examination of the residue indicated that predominantly 2 compounds were present, neither of which was starting material or the reduced dimethyl acetal. These compounds were never identified.

15) Sodium Sulphite/Sodium Hydrogen Sulphite

The dimethyl acetal (50 mg, 0.1 mmol) in THF (2 ml), was treated with sodium sulphite (190 mg, 1.5 mmol) and sodium metabisulphite (140 mg, 0.75 mmol) in water (2 ml) and heated under reflux. After 19 h, the reaction mixture was cooled, basified with aqueous sodium hydrogen carbonate and extracted with chloroform. The extract was dried and evaporated to yield a crystalline mass of starting material. No reaction took place.

Reduction of the Acetal (96 ; R = CH_2CH_2Ph) to the Acetal (97 ; R = CH_2CH_2Ph)

The dimethyl acetal (96 ; R = CH_2CH_2Ph) (100 mg, 0.20 mmol) in dry pyridine was treated with phosphorus trichloride (20 µl, 1.1 mol. equiv.) at room temperature for 10 min. The mixture was diluted with 5 N sodium hydroxide (5 ml) and water (20 ml), then extracted with chloroform. The extract was dried and evaporated. Pyridine was removed by azeotroping with toluene (4 x) to give a crystalline residue of the reduced dimethyl acetal, which crystallised from ethyl acetate as prisms (78 mg, 80%), m.p. 170–172 °C (Found: C, 70.9; H, 6.96; N, 5.66. $C_{29}H_{34}N_2O_5$ requires C, 71.02; H, 6.94; N, 5.71%); $\nu_{max.}$($CHCl_3$) 3 460 and 1 665 cm^{-1}; δ ($CDCl_3$) 2.33 (3H, s, N-CH_3), 3.03 (3H, s, O-CH_3 at C-6β), 3.43 (3H, s, O-CH_3 at C-6α), 3.90 (3H, s, O-CH_3 at C-3), 4.10 (1H, d, $J_{H-10\alpha}$ 5 Hz, H-9), 4.62 (1H, d, J_{H-7} *ca.* 1 Hz, H-5), 5.60 (1H, dd, J_{H-8} 10 Hz and J_{H-5} *ca.* 1 Hz, H-7), 6.22 (1H, br s, exchangeable with D_2O, NH), 6.28 (1H, d, J_{H-7} 10 Hz, H-8), 6.58 (1H, d, J_{H-2} 8 Hz, H-1), 6.64 (1H, d, J_{H-1} 8 Hz, H-2), and 7.32 (5H, br s, Ph); m/e 490.

Hydrolysis of the Acetal (97 ; R = CH_2CH_2Ph) to give 14β-(3-phenylpropanoylamino)codeinone (77 ; R = CH_2CH_2Ph)

The dimethyl acetal (97 ; R = CH_2CH_2Ph) (45 mg, 0.09 mmol) in methanol (3 ml) containing 6N hydrochloric acid (0.2 ml) and water (1 ml) was heated at *ca.* 80 °C for 30 min. The mixture was basified with aqueous sodium hydrogen carbonate and extracted with chloroform. The extract was dried and

evapoarted to yield the codeinone which crystallised from ethyl acetate (24 mg, 59%), m.p. 187-188 °C (Found: C, 72.96; H, 6.30; N, 6.28. $C_{27}H_{28}N_2O_4$ requires C, 72.97; H, 6.31; N, 6.31%); $\nu_{max.}$(KBr) 3 360 and 1 680 cm^{-1}; δ ($CDCl_3$) 2.39 (3H, s, N-CH_3), 3.88 (3H, s, O-CH_3 at C-3), 4.89 (1H, s, H-5), 6.08 (1H, d, J_{H-8} 10 Hz, H-7), 6.20 (1H, d, J_{H-7} 10 Hz, H-8), 6.59 (1H, d, J_{H-2} 9 Hz, H-1), 6.68 (1H, d, J_{H-1} 9 Hz, H-2), 6.74 (1H, br s, exchangeable with D_2O, NH), and 7.27 (5H, br s, Ph); m/e 444.

Preparation of the Thebaine/Nitrosocarbonylmethane Adduct (46 ; R = CH_3)

Thebaine (5 g, 16.1 mmol) in ethyl acetate (400 ml) and sodium periodate (5 g, 23.4 mmol) in aqueous sodium acetate (0.2 M, adjusted to pH 6 with concentrated hydrochloric acid) (125 ml) were stirred rapidly at 0 °C. Acetohydroxamic acid (1.80 g, 24.0 mmol) was added slowly over 10 min, then rapid stirring was continued for 1 h. The mixture was basified by the addition of aqueous sodium hydrogen carbonate and the layers separated. The aqueous layer was extracted with ethyl acetate and the combined ethyl acetate layers washed with aqueous sodium thiosulphate and then water. The dried ethyl acetate solution was evaporated to yield the thebaine adduct, which crystallised from ethyl acetate as cuboids (5.63 g, 91%), m.p. 189-190 °C (lit.,[37] 194-196 °C) (Found: C, 65.8; H, 6.09; N, 7.16. $C_{21}H_{24}N_2O_5$ requires C, 65.61; H, 6.29; N, 7.29%); $\nu_{max.}$(KBr) 1 680 cm^{-1}; δ ($CDCl_3$) 2.01 (3H, s, $COCH_3$), 2.49 (3H, s, N-CH_3),

3.60 (3H, s, O-CH_3 at C-6), 3.82 (3H, s, O-CH_3 at C-3), 4.60 (1H, s, H-5), 4.82 (1H, d, $J_{H-10\alpha}$ 7 Hz, H-9), 6.13 (1H, d, J_{H-8} 8 Hz, H-7), 6.22 (1H, d, J_{H-7} 8 Hz, H-8), 6.66 (1H, d, J_{H-2} 8 Hz, H-1), and 6.80 (1H, d, J_{H-1} 8 Hz, H-2); m/e 384.

Preparation of the Dimethyl Acetal (96 ; R = CH_3)

The thebaine adduct (46 ; R = CH_3) (2 g, 5.2 mmol) in 0.20 M anhydrous methanolic hydrogen chloride (80 ml) was kept at 0 °C for 10 min. The mixture was neutralised by the addition of solid sodium hydrogen carbonate and water was added to the resulting paste to dissolve the salts. The mixture was extracted with chloroform and the extract dried and evaporated to yield an equilibrium mixture of cyclic adduct (ca. 15%) and dimethyl acetal (ca. 85%). Crystallisation from chloroform - ethyl acetate yielded the dimethyl acetal (1.67 g, 77%), m.p. 181 °C (Found: C, 63.05; H, 6.45; N, 6.47. $C_{22}H_{28}N_2O_6$ requires C, 63.45; H, 6.78; N, 6.73%); $\nu_{max.}$(KBr) 3 290 and 1 640 cm^{-1}; δ ($CDCl_3$) 2.17 (3H, s, $COCH_3$), 2.45 (3H, s, N-CH_3), 3.23 (3H, s, O-CH_3 at C-6β), 3.50 (3H, s, O-CH_3 at C-6α), 3.85 (3H, s, O-CH_3 at C-3), 4.31 (1H, d, $J_{H-10\alpha}$ 7 Hz, H-9), 4.83 (1H, s, H-5), 5.54 (1H, d, J_{H-8} 10 Hz, H-7), 6.34 (1H, d, J_{H-7} 10 Hz, H-8), 6.60 (1H, d, J_{H-2} 6 Hz, H-1), and 6.66 (1H, d, J_{H-1} 6 Hz, H-2); m/e 416.

Reduction of the Acetal (96 ; R = CH_3) to the Acetal (97 ; R = CH_3).

The dimethyl acetal (96 ; R = CH_3) (1 g, 2.4 mmol) in dry pyridine (10 ml) was cooled to 10 °C, and treated with phosphorus trichloride (0.21 ml, 1.1 mol. equiv.) then left at room temperature for 10 min. The mixture was diluted with 5 **N** sodium hydroxide (50 ml) and water (120 ml), then extracted with chloroform. The extract was dried and evaporated. Pyridine was removed by azeotroping (4 x) with toluene to give a crystalline residue of the acetal. Crystallisation from methanol yielded the reduced acetal (703 mg, 73%), m.p. 177-178 °C (Found: C, 65.6; H, 6.78; N, 7.45. $C_{22}H_{28}N_2O_5$ requires C, 66.00; H, 7.00; N, 7.00%); $\nu_{max.}$(KBr) 3 330 and 1 638 cm^{-1}; δ ($CDCl_3$) 2.00 (3H, s, $COCH_3$), 2.38 (3H, s, N-CH_3), 3.13 (3H, s, O-CH_3 at C-6β), 3.46 (3H, s, O-CH_3 at C-6α), 3.89 (3H, s, O-CH_3 at C-3), 4.14 (1H, d, $J_{H-10\alpha}$ 6 Hz, H-9), 4.69 (1H, d, J_{H-7} ca. 1 Hz, H-5), 5.57 (1H, dd, J_{H-8} 10 Hz and J_{H-5} ca. 1 Hz, H-7), 6.29 (1H, br s, NH), 6.32 (1H, d, J_{H-7} 10 Hz, H-8), 6.56 (1H, d, J_{H-2} 9 Hz, H-1), and 6.70 (1H, d, J_{H-1} 9 Hz, H-2); m/e 400.

Hydrolysis of the Acetal (97 ; R = CH_3) to give 14β-Acetylaminocodeinone (77 ; R = CH_3)

The dimethyl acetal (97 ; R = CH_3) (200 mg, 0.5 mmol) in methanol (15 ml) containing 6N hydrochloric acid (1 ml) and water (5 ml) was heated under reflux for 30 min. The mixture was basified with aqueous sodium hydrogen carbonate

extracted with chloroform and the extract dried. Evaporation then yielded the codeinone which crystallised from methanol (148 mg, 84%), m.p. 253-254 °C (Found: C, 67.5; H, 5.95; N, 8.35. $C_{20}H_{22}N_2O_4$ requires C, 67.80; H, 6.21; N, 7.91%); $\nu_{max.}$(KBr) 3 360 and 1 676 to 1 665 cm^{-1}; δ ($CDCl_3$) 1.99 (3H, s, $COCH_3$), 2.39 (3H, s, N-CH_3), 3.80 (3H, s, O-CH_3 at C-3), 4.87 (1H, s, H-5), 6.12 (2H, s, H-7 and H-8), 6.43 (1H, d, J_{H-2} 9 Hz, H-1), 6.64 (1H, d, J_{H-1} 9 Hz, H-2), and 6.82 (1H, br s, NH); m/e 354.

Preparation of the Thebaine/Nitrosocarbonylbenzene Adduct[36,37] (46 ; R = Ph)

Thebaine (2 g, 6.4 mmol) in ethyl acetate (150 ml) and sodium periodate (2.05 g, 9.6 mmol) in aqueous sodium acetate (0.2 M, adjusted to pH 6 with concentrated hydrochloric acid) (50 ml) were stirred rapidly at 0 °C. N-Benxoylhydroxylamine (1.32 g, 9.6 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 and the combined ethyl acetate layers were washed with aqueous sodium thiosulphate and then water. The dried ethyl acetate solution was evaporated to yield a crystalline mass. Crystallisation from ethyl acetate then afforded the adduct (2.23 g, 78 %), m.p. 162-163 °C (lit.[37], 170-172 °C (from benzene - petrol)) (Found: C, 69.9; H, 5.83; N, 6.27. $C_{26}H_{26}N_2O_5$ requires C,

69.95; H, 5.83; N, 6.28%); $\nu_{max.}$(KBr) 1 665 cm^{-1}; δ ($CDCl_3$) 2.48 (3H, s, N-CH_3), 2.96 (3H, s, O-CH_3 at C-6), 3.84 (3H, s, O-CH_3 at C-3), 4.62 (1H, s, H-5), 4.97 (1H, d, $J_{H-10\alpha}$ 7 Hz, H-9), 5.98 (1H, d, J_{H-8} 9 Hz, H-7), 6.33 (1H, d, J_{H-7} 9 Hz, H-8), 6.65 (1H, d, J_{H-2} 8 Hz, H-1), 6.70 (1H, d, J_{H-1} 8 Hz, H-2), and 7.28 to 7.88 (5H, m, Ph); m/e 446.

Preparation of the Dimethyl Acetal (96 ; R = Ph)

The thebaine adduct (46 ; R = Ph) (2.86 g, 6.4 mmol) in 0.20 N anhydrous methanolic hydrogen chloride (100 ml) was kept at 0 °C for 15 min. The mixture was basified by the addition of solid sodium hydrogen carbonate, then water was added to the resultant paste to dissolve salts. The mixture was extracted with chloroform, dried and evaporated to yield an equilibrium mixture of ca. 37% cyclic adduct and ca. 63% dimethyl acatal. Crystallisation from ethyl acetate yielded only a small amount of cyclic adduct. The dimethyl acetal was obtained by preparative t.l.c. of this mixture on Merck GF_{254} alumina (chloroform - benzene, 1:1), but the recovery was low, eg 1 g of mixture yielding only ca. 200 mg of pure acetal. The dimethyl acetal crystallised from methanol as needles, m.p. 161 °C (Found: C, 67.90; H, 6.35; N, 6.07. $C_{27}H_{30}N_2O_6$ requires C, 67.78; H, 6.28; N, 5.86%); $\nu_{max.}$(KBr) 3 220 and 1 633 cm^{-1}; δ ($CDCl_3$) 2.36 (3H, s, N-CH_3), 3.06 (3H, s, O-CH_3 at C-6β), 3.42 (3H, s, O-CH_3 at C-6α), 3.83 (3H, s, O-CH_3 at C-3), 4.28 (1H, d, $J_{10\alpha}$ 5 Hz, H-9), 4.78 (1H, d, J_{H-7} 1 Hz,

H-5), 5.56 (1H, dd, J_{H-8} 10 Hz and J_{H-5} 1 Hz, H-7), 6.35 (1H, d, J_{H-7} 10 Hz, H-8) 6.50 (1H, d, J_{H-2} 9 Hz, H-1), 6.63 (1H, d, J_{H-1} 9 Hz, H-2), and 7.25 to 7.81 (5H, m, Ph); m/e 478.

Reduction of the Acetal (96; R = Ph) to the Acetal (97; R = Ph)

A mixture of the dimethyl acetal (96; R = Ph) (ca. 80%) and unreacted cyclic adduct (46; R = Ph) (ca. 20%) (300 mg) was dissolved in dry pyridine (4 ml) and treated with phosphorus trichloride (48 µl, ca. 1.1 mol. equiv.) at room temperature for 10 min. The mixture was diluted with 5 N sodium hydroxide (10 ml) and water (40 ml), then extracted with chloroform. The extract was dried and evaporated. Pyridine was removed by azeotroping with toluene (4 x) to give a crystalline residue. N.m.r. spectroscopy showed this to be a mixture of cyclic adduct and reduced dimethyl acetal, (ca. 20:80). Crystallisation from ethyl acetate yielded the reduced dimethyl acetal (90 mg, 39%), m.p. 230-232 °C (Found: C, 70.23: H, 6.74: N, 5.7. $C_{27}H_{30}N_2O_5$ required C, 70.13: H, 6.49: N, 6.06%) $\nu_{max.}$ (KBr) 3 460 and 1 660 cm^{-1}; δ ($CDCl_3$) 2.38 (3H, s, N-CH_3), 2.90 (3H, s, O-CH_3 at C-6β), 3.44 (3H, s, O-CH_3 at C-6α), 3.89 (3H, s, O-CH_3 at C-3), 4.28 (1H, d, $J_{H-10\alpha}$ 5 Hz, H-9), 4.80 (1H, d, J_{H-7} ca. 1 Hz, H-5), 5.62 (1H, dd, J_{H-8} 10 Hz and J_{H-5} ca. 1 Hz, H-7), 6.47 (1H, d, J_{H-7} 10 Hz, H-8), 6.62 (1H, d, J_{H-2} 8 Hz, H-1), 6.74 (1H, d, J_{H-1} 8 Hz, H-2), and 7.3 to 8.0 (5H, m, Ph); m/e 462.

Hydrolysis of the Acetal (97 ; R = Ph) to give 14β-Benzoylaminocodeinone (77 , R = Ph)

The dimethyl acetal (97 ; R = Ph) (60 mg, o.14 mmol) in methanol (3 ml) containing 5 N hydrochloric acid (1 ml) and water (1 ml) was heated under reflux for 30 min. The mixture was basified with aqueous sodium hydrogen carbonate, extracted with chloroform and the extract dried. Evaporation then yielded the codeinone which crystallised from ethyl acetate as cuboids, (47 mg, 87%), m.p. 256-259 °C (Found: C, 71.75; H, 5.68; N, 6.74. $C_{25}H_{24}N_2O_4$ requires C, 72.11; H, 5.77; N, 6.73%); $\nu_{max.}$(KBr) 3 335, 1 682 and 1 657 cm^{-1}; δ ($CDCl_3$) 2.50 (3H, s, N-CH_3), 3.86 (3H, s, O-CH_3 at C-3), 5.07 (1H, s, H-5), 6.28 (2H, s, H-7 and H-8), 6.65 (1H, d, J_{H-2} 9 Hz, H-1), 6.71 (1H, d, J_{H-1} 9 Hz, H-2), and 7.2 to 7.9 (5H, m, Ph); m/e 416.

Preparation of the Thebaine/Benzylnitrosocarbonyl Adduct (46 ; R = CH_2Ph)

Thebaine (2 g, 6.4 mmol) in ethyl acetate (150 ml) and sodium periodate (2.05 g, 7.6 mmol) in aqueous sodium acetate (0.2 M, adjusted to pH 6 with concentrated hydrochloric acid) (50 ml) were stirred rapidly at 0 °C. N-(2-Phenylethanoyl)-hydroxylamine (1.46g, 9.6 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 and the combined ethyl acetate layers were washed with aqueous

sodium thiosulphate and then water. The dried ethyl acetate solution was evaporated to give a quantitative yield of thebaine adduct as an oil. A small specimen crystallised from ethyl acetate/di-isopropyl ether after cooling at 0 °C for 14 months, m.p. 146–146.5 (Found: C, 70.26; H, 6.3; N, 5.96. $C_{27}H_{28}N_2O_5$ requires C, 70.43; H, 6.08; N, 6.08%); $\nu_{max.}$(KBr) 1 676 cm^{-1}; δ ($CDCl_3$) 2.41 (3H, s, N-CH_3), 3.46 (3H, s, O-CH_3 at C-6), 3.79 (3H, s, O-CH_3 at C-3), 4.61 (1H, s, H-5), 4.82 (1H, d, $J_{H-10\alpha}$ 7 Hz, H-9), 5.93 (1H, d, J_{H-8} 10 Hz, H-7), 6.10 (1H, d, J_{H-7} 10 Hz, H-8), 6.52 (1H, d, J_{H-2} 8 Hz, H-1), 6.66 (1H, d, J_{H-1} 8 Hz, H-2), and 7.18 (5H, m, Ph); m/e 460.

Preparation of the Dimethyl Acetal (96 ; R = CH_2Ph)

The thebaine adduct (46 ; R = CH_2Ph) (3 g, 6.1 mmol) in 0.20 M anhydrous methanolic hydrogen chloride (100 ml) was kept at 0 °C for 10 min. The mixture was basified by the addition of solid sodium hydrogen carbonate and water was added to the resultant paste to dissolve salts. The mixture was extracted with chloroform and the extract dried and evaporated to yield an equilibrium mixture of the cyclic adduct (ca. 10%) and dimethyl acetal (ca. 90%). Crystallisation from ethyl acetate - light petroleum (b.p. 60–80 °C) gave the dimethyl acetal (1.68 g, 52%), m.p. 151–152 °C (Found: C, 68.41; H, 6.41; N, 5.64. $C_{28}H_{32}N_2O_6$ requires C, 68.23: H, 6.50; N, 5.69%); $\nu_{max.}$(KBr) 3 250 and 1 648 cm^{-1}; δ ($CDCl_3$)

2.42 (3H, s, N-CH_3), 2.68 (3H, s, O-CH_3 at C-6β), 3.44 (3H, s, O-CH_3 at C-6α), 3.86 (3H, s, O-CH_3 at C-3), 4.37 (1H, d, $J_{H-10\alpha}$ 6 Hz, H-9), 4.80 (1H, d, J_{H-7} *ca.* 1 Hz, H-5), 5.51 (1H, dd, J_{H-8} 10 Hz and J_{H-5} *ca.* 1 Hz, H-7), 6.28 (1H, d, J_{H-7} 10 Hz, H-8), 6.54 (1H, d, J_{H-2} 8 Hz, H-1), 6.66 (1H, d, J_{H-1} 8 Hz, H-2), and 7.1 to 7.4 (5H, br s, Ph); M^+ (492) was very weak, but M-OH (475) was observed.

Reduction of the Acetal (96 ; R = CH_2Ph) to the Acetal (97 ; R = CH_2Ph)

The dimethyl acetal (96 ; R = CH_2Ph) (500 mg, 1.02 mmol) in dry pyridine (5 ml) was treated with phosphorus trichloride (100 µl, 1.1 mol. eqiv.) at room temperature for 10 min. The mixture was diluted with 5 N sodium hydroxide (25 ml) and water (*ca.* 60 ml), them extracted with chloroform. The extract was dried and evaporated. Pyridine was removed by azeotroping with toluene (4 x), then the residue was dissolved in chloroform and passed through a grade I neutral alumina column (20 mm x 200 mm). The dimethyl acetal crystallised from ethyl acetate - di-isopropyl ether (130 mg, 27%), apparantly as the half hydrate, m.p. 164-165 °C with darkening at 92-93 °C (Found: C, 69.68; H, 6.69; N, 5.44. $C_{28}H_{32}N_2O_5 \cdot \frac{1}{2} H_2O$ requires C, 69.27; H, 6.80; N, 5.77%); $\nu_{max.}$(KBr) 3 260 and 1 630 cm^{-1}; δ ($CDCl_3$) 2.34 (3H, s, N-CH_3), 3.00 (3H, s, O-CH_3 at C-6β), 3.39 (3H, s, O-CH_3 at C-6α), 3.58 (2H, s, COCH_2Ph), 3.85 (3H, s, O-CH_3 at C-3), 4.00 (1H, d, $J_{H-10\alpha}$ 6 Hz, H-9),

4.54 (1H, d, J_{H-7} ca. 1 Hz, H-5), 5.60 (1H, dd, J_{H-8} 9 Hz, and J_{H-5} ca. 1 Hz, H-7), 6.26 (1H, d, J_{H-7} 9 Hz, H-8), 6.26 (1H, br s, N-H), 6.58 (1H, d, J_{H-2} 8 Hz, H-1), 6.70 (1H, d, J_{H-1} 8 Hz, H-2) and 7.37 (5H, m, Ph); m/e 476.

Hydrolysis of the Acetal (97 ; R = CH_2Ph) to give 14β-(2-Phenylethanoylamino)codeinone (77 ; R = CH_2Ph)

The dimethyl acetal (; R = CH_2Ph) (222 mg, 0.47 mmol) in methanol (15 ml) containing 6 N hydrochloric acid (1 ml) and water (5 ml), was heated under reflux for 30 min. The mixture was basified with aqueous sodium hydrogen carbonate extracted with chloroform and the extract dried. Evaporation then yielded the codeinone which crystallised from chloroform - ethyl acetate (70 mg, 35%), m.p. 237-240 °C, with crystal growth above 207 °C (Found C, 72.30; H, 6.17; N, 6.44. $C_{26}H_{26}N_2O_4$ requires C, 72.56; H, 6.46; N, 6.51%); $\nu_{max.}$(KBr) 3 300, 1 676, and 1 662 cm^{-1}; δ ($CDCl_3$) 2.23 (3H, s, N-CH_3), 3.60 (2H, s, $COCH_2Ph$), 3.82 (3H, s, O-CH_3 at C-3), 4.91 (1H, s, H-5), 6.17 (2H, s, H-7 and H-8), 6.61 (1H, d, J_{H-2} 9 Hz, H-1), 6.74 (1H, d, J_{H-1} 9 Hz, H-2), 7.00 (1H, br s, NH), and 7.35 (5H, s, Ph); m/e 430.

Preparation of the Thebaine/3-phenylnitrosocarbonylpropane Adduct (46 ; R = $CH_2CH_2CH_2Ph$)

Thebaine (2g, 6.4 mmol) in ethyl acetate (150 ml) and sodium periodate (2.05 g, 9.6 mmol) in aqueous sodium acetate

(0.2 M, adjusted to Ph 6 with concentrated hydrochloric acid) (50 ml) were stirred rapidly at 0 °C. N-(4-Phenylbutanoyl)hydroxylamine (1.73 g, 9.6 mmol) was added slowly over 10 min, the 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 and the combined ethyl acetate layers were washed with aqueous sodium thiosulphate and then water. The dried ethyl acetate solution was evaporated to yield the thebaine adduct as an oil (2.99 g, 96%). An analytical specimen was prepared by passing some of the crude material through a grade III alumina column (20 mm x 200 mm) in chloroform. The thebaine adduct then crystallised from ethyl acetate, m.p. 109-111 °C (Found: C, 71.03; H, 6.12; N, 5.71. $C_{29}H_{32}N_2O_5$ requires C, 71.31; H, 6.56; N, 5.74%); $\nu_{max.}$(KBr) 1 667 cm^{-1}; δ ($CDCl_3$) 2.48 (3H, s, N-CH_3), 3.46 (3H, s, O-CH_3 at C-6), 3.83 (3H, s, O-CH_3 at C-3), 4.59 (1H, s, H-5), 4.88 (1H, d, $J_{H-10\alpha}$ 7 Hz, H-9), 6.01 (1H, d, J_{H-8} 10 Hz, H-7), 6.11 (1H, d, J_{H-7} 10 Hz, H-8), 6.62 (1H, d, J_{H-2} 8 Hz, H-1), 6.70 (1H, d, J_{H-1} 8 Hz, H-2), and 7.24 (5H, br s, Ph); m/e 488.

Preparation of the Dimethyl Acetal (96 ; R = $CH_2CH_2CH_2Ph$)

The thebaine adduct (46 ; R = $CH_2CH_2CH_2Ph$) (1.17 g, 2.4 mmol) in 0.20 M anhydrous methanolic hydrogen chloride (50 ml) was kept at 0 °C for 10 min. The mixture was

neutralised by the addition of solid sodium hydrogen carbonate and water was added to the resultant paste to dissolve salts. The mixture was extracted with chloroform and the extract dried and evaporated to yield an equilibrium mixture of cyclic adduct (ca. 40%) and dimethyl acetal (ca. 60%). Crystallisation from ethyl acetate yielded the dimethyl acetal (423 mg, 34%), m.p. 125–127 °C (Found: C, 68.41; H, 6.41; N, 5.64. $C_{28}H_{32}N_2O_6$ requires C, 68.23; H, 6.50; N, 5.69%); $\nu_{max.}$(KBr) 3 220 and 1 640 cm^{-1}; δ ($CDCl_3$) 2.40 (3H, s, N-CH_3), 3.12 (3H, s, O-CH_3 at C-6β), 3.48 (3H, s, O-CH_3 at C-6α), 3.86 (3H, s, O-CH_3 at C-3), 4.31 (1H, d, $J_{H-10\alpha}$ 7 Hz, H-9), 4.82 (1H, d, J_{H-7} ca. 1 Hz, H-5), 5.54 (1H, dd, J_{H-8} 10 Hz and J_{H-5} ca. 1 Hz, H-7), 6.34 (1H, d, J_{H-7} 10 Hz, H-8), 6.57 (1H, d, J_{H-2} 8 Hz, H-1), 6.63 (1H, d, J_{H-1} 8 Hz, H-2), and 7.23 (5H, br s, Ph); M^+ (520) was very weak, but M–OH (503) was observed.

Reduction of the Acetal (96 ; R = $CH_2CH_2CH_2Ph$) to the Acetal (97 ; R = $CH_2CH_2CH_2Ph$)

The dimethyl acetal (96 ; R = $CH_2CH_2CH_2Ph$) (200 mg, 0.38 mmol) in dry pyridine (4 ml) was treated with phosphorus trichloride (41 µl, 1.1 mol. equiv.) at room temperature for 10 min. The mixture was diluted with 5 N sodium hydroxide (10 ml) and water (40 ml), then extracted with chloroform. The extract was dried and evaporated. Pyridine was removed by azeotroping with toluene (4 x), and the resulting solid crystallised from ethyl acetate to yield the reduced dimethyl

acetal (130 mg, 67%), m.p. 80 °C. T.l.c. on silica (methanol - chloroform, 2:8) indicated that even after three recrystallisations the main product (R_F 0.60) was contaminated with a small amount of impurity (R_F 0.74). $\nu_{max.}$(KBr) 3 530 and 1 635 cm^{-1}; δ ($CDCl_3$) 2.38 (3H, s, N-CH_3), 3.04 (3H, s, O-CH_3 at C-6β), 3.44 (3H, s, O-CH_3 at C-6α), 3.87 (3H, s, O-CH_3 at C-3), 4.44 (1H, d, $J_{H-10\alpha}$ 5 Hz, H-9), 4.66 (1H, d, J_{H-7} ca. 1 Hz, H-5), 5.57 (1H, dd, J_{H-8} 10 Hz and J_{H-5} ca. 1 Hz, H-7), 6.24 (1H, br s, NH), 6.30 (1H, d, J_{H-7} 10 Hz, H-8), 6.58 (1H, d, J_{H-2} 8 Hz, H-1), 6.67 (1H, d, J_{H-1} 8 Hz, H-2), and 7.2 to 7.4 (5H, br s, Ph); m/e 504.

Hydrolysis of the Acetal (97 ; R = $CH_2CH_2CH_2Ph$) to give 14β-(4-phenylbutanoylamino)codeinone (77 ; R = $CH_2CH_2CH_2Ph$)

The dimethyl acetal (97 ; R = $CH_2CH_2CH_2Ph$) (60 mg, 0.12 mmol) in methanol (4 ml) containing 6 N hydrochloric acid (1 ml) and water (2 ml) was heated under reflux for 30 min. The mixture was basified with aqueous sodium hydrogen carbonate, extracted with chloroform and the extract dried. Evaporation then yielded the codeinone which crystallised from ethyl acetate (48 mg, 88%), m.p. 195 °C (Found: C, 73.36; H, 6.29; N, 5.72. $C_{28}H_{30}N_2O_4$ requires C, 73.36; H, 6.55; N, 6.11%); $\nu_{max.}$(KBr) 3 380 and 1 682 cm^{-1}; δ ($CDCl_3$) 2.40 (3H, s, N-CH_3), 3.80 (3H, s, O-CH_3 at C-3), 4.92 (1H, s, H-5), 6.15 (2H, s, H-7 and H-8), 6.60 (1H, d, J_{H-2} 8 Hz, H-1) 6.69 (1H, d, J_{H-1} 8 Hz, H-2), 6.81 (1H, br s, NH), and 7.1 to 7.4 (5H, br s, Ph); m/e 458.

Preparation of the Thebaine/Nitrosocarbonylpentane Adduct (46 ; R = $(CH_2)_4CH_3$)

Thebaine (1 g, 3.2 mmol) in ethyl acetate (75 ml) and sodium periodate (1.02 g, 4.8 mmol) in aqueous sodium acetate (0.2 M, adusted to pH 6 with concentrated hydrochloric acid) (25 ml) were stirred rapidly at 0 °C. N-Hexanoylhydroxylamine (0.63 g, 4.8 mmol) in ethyl acetate (20 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 and the combined ethyl acetate layers washed with aqueous sodium thiosulphate, then water. The dried ethyl acetate solution was evaporated to yield the thebaine adduct as a foam (1.40 g, 99%); δ ($CDCl_3$) 0.7 to 1.7 (ca. 11H, m, $(CH_2)_4CH_3$), 2.48 (3H, s, N-CH_3), 3.64 (3H, s, O-CH_3 at C-6), 3.84 (3H, s, O-CH_3 at C-3), 4.63 (1H, s, H-5), 4.91 (1H, d, $J_{H-10\alpha}$ 7 Hz, H-9), 6.10 (1H, d, J_{H-8} 10 Hz, H-7), 6.17 (1H, d, J_{H-7} 10 Hz, H-8), 6.67 (1H, d, J_{H-2} 10 Hz, H-1), and 6.74 (1H, d, J_{H-1} 10 Hz, H-2).

Preparation of the Dimethyl Acetal (96 ; R = $(CH_2)_4CH_3$)

The thebaine adduct (46 ; R = $(CH_2)_4CH_3$) (7 g, 15.9 mmol) in 0.20 M anhydrous methanolic hydrogen chloride (200 ml) was kept at 0 °C for 10 min. The mixture was neutralised by the addition of solid sodium hydrogen carbonate and water was added to the resultant paste to dissolve salts.

The mixture was extracted with chloroform and the extract dried and evaporated to yield an equilibrium mixture of cyclic adduct (ca. 30%) and dimethyl acetal (ca. 70%). Crystallisation from ethyl acetate - light petroleum (b.p. 40-60 °C) yielded the dimethyl acetal (3.32 g, 44%), m.p. 116-117 °C (Found: C, 66.0; H, 7.33; N, 6.09. $C_{26}H_{36}N_2O_6$ requires C, 66.10; H, 7.63; N, 5.93%); $\nu_{max.}$(KBr) 3 250 and 1 642 cm^{-1}; δ ($CDCl_3$) 0.7 to 1.9 (ca. 11H, m, $(CH_2)_4CH_3$), 2.41 (3H, s, N-CH_3), 3.19 (3H, s, O-CH_3 at C-6β), 3.49 (3H, s, O-CH_3 at C-6α), 3.85 (3H, s, O-CH_3 at C-3), 4.29 (1H, d, $J_{H-10\alpha}$ 6 Hz, H-9), 4.83 (1H, d, J_{H-7} ca. 1 Hz, H-5), 5.53 (1H, dd, J_{H-8} 10 Hz and J_{H-5} ca. 1 Hz, H-7), 6.38 (1H, d, J_{H-7} 10 Hz, H-8), 6.56 (1H, d, J_{H-2} 9 Hz, H-1), and 6.66 (1H, d, J_{H-1} 9 Hz, H-2); M^+ (472) was very weak, but M-OH (455) was observed.

Reduction of the Acetal (96; R = $(CH_2)_4CH_3$) to the Acetal (97; R = $(CH_2)_4CH_3$)

The dimethyl acetal (96; R = $(CH_2)_4CH_3$) (400 mg, 0.85 mmol) in dry pyridine (10 ml) was treated with phosphorus trichloride (82 μl, 1.1 mol. equiv.) at room temperature for 10 min. The mixture was diluted with 5 N sodium hydroxide (20 ml) and water (80 ml), then extracted with chloroform. The extract was dried and evaporated. Pyridine was removed by azeotroping with toluene (4 x), then the residue was dissolved in chloroform and passed through a grade III neutral alumina column (10 mm x 200 mm). Crystallisation

from di-isopropyl ether gave the reduced dimethyl acetal (230 mg, 60%), m.p. 97-102 °C. T.l.c. on silica (methanol - chloroform, 2:8) indicated that even after 3 recrystallisations the main product (R_F 0.57) was contaminated with a small amount of impurity (R_F 0.71). $\nu_{max.}$(KBr) 3 333 and 1 638 cm^{-1}; δ ($CDCl_3$) 0.7 to 2.0 (ca. 11H, m, $(CH_2)_4CH_3$), 2.40 (3H, s, N-CH_3), 3.09 (3H, s, O-CH_3 at C-6β), 3.44 (3H, s, O-CH_3 at C-6α), 3.87 (3H, s, O-CH_3 at C-3), 4.15 (1H, d, $J_{H-10\alpha}$ 5 Hz, H-9), 4.68 (1H, d, J_{H-7} ca. 1 Hz, H-5), 5.59 (1H, dd, J_{H-8} 10 Hz and J_{H-5} ca. 1 Hz, H-7), 6.24 (1H, br s, NH), 6.34 (1H, d, J_{H-7} 10 Hz, H-8), 6.56 (1H, d, J_{H-2} 8 Hz, H-1), and 6.69 (1H, d, J_{H-1} 8 Hz, H-2); m/e 456.

Hydrolysis of the Acetal (97 ; R = $(CH_2)_4CH_3$) to give 14β-Hexanoylaminocodeinone (77 ; R = $(CH_2)_4CH_3$)

The dimethyl acetal (97 ; R = $(CH_2)_4CH_3$) (43 mg, 0.09 mmol) in methanol (3 ml) containing 6 N hydrochloric acid (0.5 ml) and water (1 ml) was heated under reflux for 30 min. The mixture was basified with aqueous sodium hydrogen carbonate, extracted with chloroform and the extract dried. Evaporation then yielded the codeinone which crystallised from ethyl acetate (25 mg, 65%), m.p. 207-209 °C (Found: C, 69.99; H, 7.6; N, 7.12. $C_{24}H_{30}N_2O_4$ requires C, 70.24; H, 7.32; N, 6.83%); $\nu_{max.}$(KBr) 3 360 and 1 679 cm^{-1}; δ ($CDCl_3$) 0.7 to 1.8 (ca. 11H, m, $(CH_2)_4CH_3$), 2.47

(3H, s, N-CH_3), 3.88 (3H, s, O-CH_3 at C-3), 4.98 (1H, s, H-5), 6.20 (2H, s, H-7 and H-8), 6.64 (1H, d, J_{H-2} 6 Hz, H-1), 6.75 (1H, d, J_{H-1} 6 Hz, H-2), and 6.85 (1H, br s, NH); m/e 410.

Hydrolysis of the Thebaine Adduct (46 ; R = CH_2CH_2Ph)

The thebaine adduct (46 ; R = CH_2CH_2Ph) (200 mg, 0.42 mmol) in methanol (4 ml) and 5 N hydrochloric acid (20 ml) was kept at 0 °C for 17 h, then the resulting solid was filtered off, washed with cold water and dried at 70 °C, ca. 1 mm Hg to yield a crystalline solid (49 mg, 23%). A specimen was crystallised from acetone to yield the N-hydroxycodeinone hydrochloride (102; R = CH_2CH_2Ph), m.p. 164-167 °C (Found: C, 65.05; H, 5.90; N, 5.25. $C_{27}H_{28}N_2O_5$. HCl requires C, 65.26; H, 5.84; N, 5.63%); $\nu_{max.}$ (KBr) 3 575, 1 688, and 1 679 cm^{-1}; δ (D_6 acetone at 50 °C) 2.89 (3H, s, N-CH_3), 3.79 (3H, s, O-CH_3 at C-3), 5.08 (1H, s, H-5), 5.31 (1H, br s, N-OH), 6.10 (1H, d, J_{H-8} 10 Hz, H-7), 6.72 (1H, d, J_{H-2} 9 Hz, H-1), 6.78 (1H, d, J_{H-7} 10 Hz, H-8), 6.84 (1H, d, J_{H-1} 9 Hz, H-2), and 7.19 (5H, br s, Ph); m/e 460.

Preparation of the 5,14-Bridged Phenol (103; R = CH_2CH_2Ph)

The N-hydroxycodeinone hydrochloride (102; R = CH_2CH_2Ph) (156 mg, 0.3 mmol) was treated with a solution of sodium ethoxide prepared from sodium (18 mg, 0.78 mmol) in ethanol (5 ml) and THF (5 ml) at room temperature for 3.5 h. Water (30 ml)

was then added and the mixture extracted with chloroform. The extract was dried and evaporated to yield the 5,14-bridged phenol (103; R = CH_2CH_2Ph) which crystallised from ethyl acetate (91 mg, 65%), m.p. 185-186 °C (Found: C, 70.39; H, 6.07; N, 5.92. $C_{27}H_{28}N_2O_5$ requires C, 70.43; H, 6.09; N, 6.09%); $\nu_{max.}$(KBr) 3 390 and 1 660 - 1 680 cm^{-1}; δ ($CDCl_3$) 2.46 (3H, s, N-CH_3), 3.80 (3H, s, O-CH_3 at C-3), 4.28 (1H, d, $J_{H-10\alpha}$ 6 Hz, H-9), 5.20 (1H, d, J_{H-7} *ca.* 1 Hz, H-5), 5.95 (1H, dd, J_{H-8} 9 Hz and J_{H-5} *ca.* 1 Hz, H-7), 6.70 (2H, s, H-1 and H-2), 7.14 (1H, d, J_{H-7} 9 Hz, H-8), and 7.25 (5H, s, Ph); m/e 460.

Attempted Preparation of the 5,14-Bridged Phenol Dimethyl Acetal (98; R = CH_2CH_2Ph)

The dimethyl acetal (96; R = CH_2CH_2Ph) (103 mg, 0.20 mmol) in dry THF (2 ml) and dry ethanol (2 ml) was treated with sodium ethoxide (1.5 mol. equiv.) at room temperature for 17 h. After dilution with water (20 ml), the mixture was extracted with chloroform and the extract dried and evaporated to yield a yellow oil (54 mg). N.m.r. spectroscopy indicated that the side chain had been lost. No cyclised product was isolated.

The above reaction was repeated with sodium t-butoxide and yielded multiple products, none of which was identified. Attempted cyclisation with triethylamine in THF at reflux also failed.

Preparation of the N-Hydroxy Oxazolidine (106; R = CH_2CH_2Ph)

Preparation of the N-Hydroxy Oxazolidine (106; R = CH_2CH_2Ph)

The thebaine adduct (46; R = CH_2CH_2Ph) (95 mg, 0.2 mmol) was dissolved in dry THF (10 ml). A trace of methyl orange indicator was added, followed by sodium cyanoborohydride (19 mg, 0.3 mmol). Dry hydrogen chloride was slowly passed into the mixture until the indicator gave a red colouration. Hydrogen chloride was added carefully over 15 min to just maintain the red colouration, then the mixture was left at room temperature for 22 h. The mixture was then basified by the addition of solid sodium hydrogen carbonate, then water was added to the resultant paste to dissolve salts. The mixture was extracted with chloroform, the extract dried and evaporated to yield the N-hydroxy oxazolidine which crystallised from ethanol - di-isopropyl ether as needles (50 mg, 52%), m.p. 170-172 °C (Found: C, 70.34; H, 6.72; N, 5.77. $C_{28}H_{32}N_2O_5$ requires C, 70.58; H, 6.72; N, 5.88%); $\nu_{max.}$(KBr) 3 288 and 1 659 cm^{-1}; δ ($CDCl_3$) 2.39 (3H, s, N-CH_3), 3.52 (3H, s, O-CH_3 at C-6), 3.83 (3H, s, O-CH_3 at C-3), 4.26 (1H, dd, J_{H-8} 2 Hz and J_{H-5} *ca.* 1 Hz, H-7), 4.58 (1H, d, J_{H-7} 2 Hz, H-8), 4.74 (1H, q, J_{H-18} 7 and 4 Hz, H-17), 4.95 (1H, d, J_{H-7} *ca.* 1 Hz, H-5), 6.47 (1H, br s, N-OH), 6.59 (1H, d, J_{H-2} 9 Hz, H-1), 6.71 (1H, d, J_{H-1} 9 Hz, H-2), and 7.20 (5H, br s, Ph); m/e 476.

Preparation of the N-Benzyloxycarbonylnorthebaine Adduct (108a; R = CH_2CH_2Ph)

N-Benzyloxycarbonylnorthebaine (276 mg, 0.64 mmol) in ethyl acetate (15 ml) and sodium periodate (205 mg, 0.96 mmol) in aqueous sodium acetate (0.20 M, adjusted to pH 6 with concentrated hydrochloric acid) (5 ml) were stirred rapidly at 0 °C. N-(3-phenylpropanoyl)hydroxylamine (158 mg, 0.96 mmol) in ethyl acetate (4 ml) was added 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 and the combined ethyl acetate layers were washed with aqueous sodium thiosulphate then water. The dried ethyl acetate solution was evaporated to yield the N-benzyloxycarbonylnorthebaine adduct as an oil (360 mg, 95%); δ ($CDCl_3$) 3.50 (3H, s, O-CH_3 at C-6), 3.81 (3H, s, O-CH_3 at C-3), 4.62 (1H, d, J_{H-7} ca. 1 Hz, H-5), 5.18 (2H, s, CH_2Ph), 6.00 (1H, dd, J_{H-8} 9 Hz and J_{H-5} ca. 1 Hz, H-7), 6.22 (1H, d, J_{H-7} 9 Hz, H-8), 6.58 (1H, d, J_{H-2} 9 Hz, H-1), 6.74 (1H, d, J_{H-1} 9 Hz, H-2), 7.22 (5H, br s, $COCH_2CH_2Ph$), and 7.38 (5H, br s, O-CH_2Ph).

Attempted Preparation of the N-Benzyloxycarbonylnorthebaine Adduct (108a; R = CH_3)

N-Benzyloxycarbonylnorthebaine (100 mg; 0.23 mmol) in ethyl acetate (4 ml) and sodium periodate (98 mg, 0.46 mmol) in aqueous sodium acetate (0.2 M, adjusted to pH 6

with concentrated hydrochloric acid) (4 ml) were stirred rapidly at 0 °C. Acetohydroxamic acid (35 mg, 0.46 mmol) was added over 10 min, then rapid stirring was continued for 2 h. T.l.c. of the organic phase indicated that little reaction had taken place, so a further 2 mol. equiv. of acetohydroxamic acid and sodium periodate were added and stirring continued at 0 °C. After a further 1.5 h, t.l.c. indicated that the majority of the starting material had still not reacted so a further 6 mol. equiv. of acetohydroxamic acid and sodium periodate were added and stirring continued at room temperature. After 1 h, the layers were separated, the organic phase was washed twice with aqueous sodium thiosulphate solution, dried and evaporated to yield a yellow oil (110 mg). The n.m.r. spectrum of this material indicated that it contained unreacted starting material, plus a small amount of unidentified compound.

Preparation of the Ethylene Ketal (109; R = Ph)

The thebaine adduct (46 ; R = Ph) (90 mg, 0.2 mmol) in dry methylene chloride (1 ml) was treated with anhydrous glycolic hydrogen chloride (3 ml, 0.3 M). The reaction mixture was stirred at 20 °C for 90 min, then basified with solid sodium hydrogen carbonate, followed by water to dissolve the salts, The mixture was extracted with chloroform and the extract washed with brine then dried and evaporated

to yield the crude ketal (93 mg, 97%). Crystallisation from chloroform - ethyl acetate gave needles (55 mg, 57%), m.p. 172-172.5 °C (Found: C, 68.2; H, 5.69; N, 5.60. $C_{27}H_{28}N_2O_6$ requires C, 68.07; H, 5.87; N, 5.87%); $\nu_{max.}$ (KBr) 3 275 and 1 621 cm^{-1}; δ ($CDCl_3$) 2.38 (3H, s, N-CH_3), 3.87 (3H, s O-CH_3), 3.9 to 4.3 (4H, m, O-CH_2CH_2-O), 4.33 (1H, dd, $J_{H-10\alpha}$ 5 Hz and $J_{H-10\beta}$ ca. 1 Hz, H-9), 4.84 (1H, d, J_{H-7} ca. 1 Hz, H-5), 5.72 (1H, dd, J_{H-8} 10 Hz and J_{H-5} ca. 1 Hz, H-7), 6.26 (1H, d, J_{H-7} 10 Hz, H-8), 6.56 (1H, d, J_{H-2} 8 Hz, H-1), 6.69 (1H, d, J_{H-1} 8 Hz, H-2), and 7.2 to 7.8 (5H, m, Ph); m/e 476.

Reduction of the Ketal (109; R = Ph) to the Ketal (112; R = Ph)

The ethylene ketal (109; R = Ph) (48 mg, 0.1 mmol) was dissolved in dry pyridine (3 ml). Dry sulphur dioxide was was slowly bubbled through the solution for 5 min, then the solution was heated under reflux for 30 min. The mixture was then cooled and diluted with aqueous sodium hydrogen. carbonate (ca. 10 ml), extracted with chloroform and dried. The solution was evaporated and the residual pyridine removed by azeotroping four times with toluene. The resulting solid (45 mg, 97%) consisted of the reduced ethylene ketal, which crystallised from methanol as needles, (29 mg, 63%), m.p. 251-253 °C (Found: C, 70.70; H, 6.08; N, 6.50. $C_{27}H_{28}N_2O_5$ requires C, 70.43; H, 6.09; N, 6.09%); $\nu_{max.}$ (KBr) 3 445

and 1 675 cm^{-1}; δ ($CDCl_3$) 2.37 (3H, s, N-CH_3), 3.69 (1H, dd, $J_{H-10\alpha}$ 5 Hz and $J_{H-10\beta}$ ca. 1 Hz, H-9), 3.85 (3H, s, O-CH_3), 3.8 to 4.2 (4H, m, O-CH_2CH_2-O), 4.84 (1H, s, H-5), 5.74 (1H, d, J_{H-8} 10 Hz, H-7), 6.03 (1H, d, J_{H-7} 10 Hz, H-8), 6.54 (1H, d, J_{H-2} 9 Hz, H-1), 6.68 (1H, d, J_{H-1} 9 Hz, H-2), and 7.1 - 7.9 (5H, m, Ph); m/e 460.

Alternative Reduction of the Ketal (109; R = Ph) to the Ketal (112; R = Ph)

The ethylene ketal (109; R = Ph) (48 mg, 0.10 mmol) in dry pyridine was treated with phosphorus trichloride (9.6 µl, 0.11 mmol) at room temperature for 10 min. The reaction mixture was diluted with 5 N sodium hydroxide (3 ml) and water (10 ml), then extracted with chloroform. The extract was dried and evaporated. Pyridine was removed by azeotroping (4 x) with toluene to give a crystalline solid (34 mg). Crystallisation from ethyl acetate then yielded the reduced ethylene ketal (18 mg, 39%), m.p. 249-252 °C. The m.p. of this compound prepared by a different route was 251-253 °C, and the n.m.r. and mass spectra were identical (see above).

Hydrolysis of the Ketal (112; R = Ph) to give 14β-Benzoylaminocodeinone (77; R = Ph)

The ethylene ketal (112; R = Ph) (90 mg, 0.2 mmol) in methanol (3 ml) containing 6 N hydrochloric acid (1 ml)

and water (1 ml) was heated under reflux for 30 min. The mixture was basified with aqueous sodium hydrogen carbonate extracted with chloroform and the extract dried. Evaporation then yielded the impure codeinone in effectively quantitative yield. Crystallisation from ethyl acetate gave the pure compound (63 mg, 77%), m.p. 257-260 °C. The m.p. of this compound prepared by an alternative route was 256-259 °C, and the n.m.r. spectra were identical (see p 136).

Preparation of the Ethylene Ketal (109; R = CH_2CH_2Ph)

The thebaine adduct (46 ; R = CH_2CH_2Ph) (95 mg, 0.2 mmol) in dry methylene chloride (1 ml) was treated with anhydrous glycolic hydrogen chloride (3 ml, 0.3 M). The reaction mixture was stirred at 20 °C for 90 min, then basified with solid sodium hydrogen carbonate, followed by water to dissolve the salts. The mixture was extracted with chloroform and the extract was washed with brine then dried and evaporated to yield the crude ketal in quantitative yield. Crystallisation from ethyl aceate gave plates (80 mg, 80%), m.p. 181-183 °C (Found: C, 68.65; H, 6.16; N, 4.98. $C_{29}H_{32}N_2O_6$ requires C, 69.05; H, 6.34; N, 5.55%); $\nu_{max.}$ (KBr) 3 270 and 1 639 cm^{-1}; δ ($CDCl_3$) 2.46 (3H, s, N-CH_3), 3.86 (3H, s, O-CH_3), 3.9 to 4.3 (4H, m, O-CH_2CH_2-O), 4.32 (1H, dd, $J_{H-10\alpha}$ 5 Hz and $J_{H-10\beta}$ ca. 1 Hz, H-9), 4.87 (1H, s, H-5), 5.65 (1H, d, J_{H-8} 10 Hz, H-7), 6.13 (1H, d, J_{H-7} 10 Hz, H-8), 6.54 (1H, d, J_{H-2} 8 Hz, H-1), 6.70 (1H, d, J_{H-1} 8 Hz, H-2), 7.22 (5H, br s, Ph), and ca. 8.0 (1H, br s, NH); m/e 504.

Reduction of the Ketal (109; R = CH_2CH_2Ph) to the Ketal (112; R = CH_2CH_2Ph)

The ethylene ketal (109; R = CH_2CH_2Ph) (50.4 mg, 0.1 mmol) was dissolved in dry pyridine (3 ml). Dry sulphur dioxide was slowly bubbled through the solution for 5 min, then the solution was heated under reflux for 30 min. The mixture was cooled and diluted with aqueous sodium hydrogen carbonate (ca. 10 ml), extracted with chloroform and dried. The solution was evaporated and the residual pyridine removed by azeotroping 4 times with toluene. The resulting solid (46 mg, 94%) consisted of the reduced ethylene ketal which crystallised from methanol as needles (38 mg, 78%), m.p. 202.5-203 °C (Found: C, 70.92; H, 6.51; N, 5.82. $C_{29}H_{32}N_2O_5$ requires C, 71.31; H, 6.56; N, 5.74%); $\nu_{max.}$(KBr) 3 440 and 1 663 cm^{-1}; δ ($CDCl_3$) 2.30 (3H, s, N-CH_3), 3.41 (1H, dd, $J_{H-10\alpha}$ 5 Hz and $J_{H-10\beta}$ ca. 1 Hz, H-9), 3.84 (3H, s, O-CH_3), 3.8 to 4.2 (4H, m, O-CH_2CH_2-O), 4.71 (1H, s, H-5), 5.67 (1H, d, J_{H-8} 10 Hz, H-7), 5.87 (1H, d, J_{H-7} 10 Hz, H-8), 6.39 (1H, br s, NH), 6.51 (1H, d, J_{H-2} 8 Hz, H-1), 6.66 (1H, d, J_{H-1} 8 Hz, H-2), and 7.22 (5H, br s, Ph); m/e 488.

Alternative Reduction of the Ketal (109; R = CH_2CH_2Ph) to the Ketal (112; R = CH_2CH_2Ph)

The ethylene ketal (109; R = CH_2CH_2Ph) (50.4 mg, 0.1 mmol) in dry pyridine (1 ml) was treated with phosphorus trichloride (9.6 µl, 0.11 mmol) at room temperature for

15 min. The reaction mixture was then diluted with 5 N sodium hydroxide (3 ml) and water (10 ml), then extracted with chloroform. The extract was dried and evaporated. Pyridine was removed by azeotroping with toluene (4 x) to give a crystalline solid (54 mg). Crystallisation from ethyl acetate gave the reduced ethylene ketal (30 mg, 61%). N.m.r. spectroscopy and t.l.c. showed that this material, though similar to a samples prepared previosly by a different route (see above) was contaminated with unreacted starting material (ca. 10%) which was not removable by fractional crystallisation.

Hydrolysis of the Ketal (112; R = CH_2CH_2Ph) to give 14β-(3-Phenylpropanoylamino)codeinone (77 ; R = CH_2CH_2Ph)

The ethylene ketal (112; R = CH_2CH_2Ph) (45 mg, 0.92 mmol) in methanol (3 ml) containing 6 N hydrochloric acid (1 ml) and water (1 ml) was heated under reflux for 30 min. The mixture was basified with aqueous sodium hydrogen carbonate, extracted with chloroform and the extract dried. Evaporation the yielded then impure codeinone in effectively quantitative yield. Crystallisation from ethyl acetate gave pure material (28 mg, 69%), m.p. 188-190 °C. The m.p. of this compound prepared by an alternative route was 187-188 °C and the n.m.r. spectra were identical (see p.130).

Preparation of the Oxazoline (115 ; R = Ph)

The dimethyl acetal (96 ; R = Ph) (47.8 mg, 0.1 mmol) was dissolved in dry pyridine (3 ml). Dry sulphur dioxide was slowly bubbled through the solution for 5 min, then the solution was heated at reflux for 35 min. The mixture was cooled and diluted with aqueous sodium hydrogen carbonate (ca. 20 ml), extracted with chloroform and the extract dried. The solution was evaporated and the residual pyridine removed by azeotroping 4 times with ca. 10 ml portions of toluene. Crystallisation from ethanol yielded the oxazoline as prisms (27 mg, 63%), m.p. 226–228 °C; m/e 430. The m.p. of this compound prepared by D. McDougal was 227–231 °C, and the n.m.r. and i.r. spectra were identical.

Preparation of the Oxazoline (115; R = Ph) followed by hydrolysis to 14β-Benzoylaminocodeinone (77 ; R = Ph)

The oxazoline (115; R = Ph) was prepared as previosly detailed above from the dimethyl acetal (96 ; R = Ph) (47.8 mg, 0.1 mmol), but was not crystallised. After examination of the crude oxazoline by n.m.r., it was hydrolysed to the codeinone by dissolving it in methanol (3 ml) containing 5 N hydrochloric acid (1 ml) and water (1 ml). This mixture was heated under reflux for 30 min, then cooled, basified with sodium hydrogen carbonate, extracted with chloroform and the extract dried. Evaporation then yielded the crude

codeinone, which crystallised from methanol (29 mg, 70%), m.p. 258–261 °C. This m.p. agrees with the previosly recorded value of 256–259 °C, and the n.m.r. spectra of the compounds were identical (see p.136).

Preparation of the Oxazoline (115; R = CH_2CH_2Ph)

The dimethyl acetal (96 ; R = CH_2CH_2Ph) (506 mg, 1.0 mmol) was dissolved in dry pyridine (15 ml). Dry sulphur dioxide was slowly bubbled through the solution for 5 min, then the solution was heated under reflux for 30 min. The mixture was then cooled and diluted with aqueous sodium hydrogen carbonate (ca. 100 ml), extracted with chloroform and the extract dried. The solution was evaporated and the residual pyridine was removed by azeotroping 4 times with ca. 10 ml portions of toluene. The resultant oil was purified by heating under reflux in chloroform with charcoal for 1 h, followed by passage through a grade 0 neutral alumina column in chloroform, to remove any polar material. Crystallisation from ethyl acetate - di-isopropyl ether gave the oxazoline as needles (262 mg, 57%), m.p. 169–170 °C (Found: C, 73.56; H, 6.48; N, 6.44. $C_{28}H_{30}N_2O_4$ requires C, 73.36; H, 6.55; N, 6.11%); $\nu_{max.}$(KBr) 1 662 and 1 649 cm^{-1}; δ ($CDCl_3$) 2.32 (3H, s, N-CH_3), 3.41 (3H, s, O-CH_3 at C-6), 3.82 (3H, s, O-CH_3 at C-3), 4.45 (1H, d, J_{H-7} 3 Hz, H-8), 4.57 (1H, d, J_{H-8} 3 Hz, H-7), 4.82 (1H, s, H-5), 6.58 (1H, d, J_{H-2} 9 Hz, H-1), 6.68 (1H, d, J_{H-1} 9 Hz, H-2), and 7.08 to 7.41 (5H, br s, Ph); m/e 458.

Preparation of the Oxazoline (115; R = CH_2CH_2Ph) followed by Hydrolysis to 14β-(3-Phenylpropanoylamino)codeinone (77 ; R = CH_2CH_2Ph)

The oxazoline (115; R = CH_2CH_2Ph) was prepared as previously detailed (p.157) from the dimethyl acetal (96 ; R = CH_2CH_2Ph) (50.6 mg, 0.1 mmol), but was not crystallised. After examination of the crude oxazoline by n.m.r., it was hydrolysed to the codeinone by dissolving it in methanol (3 ml) containing water (1 ml) and 5 N hydrochloric acid (1 ml). This mixture was heated under reflux for 30 min, then cooled, basified with aqueous sodium hydrogen carbonate, extracted with chloroform and the extract dried. Evaporation then yielded the crude codeinone (39 mg, 88%) which was crystallised from ethyl acetate (29 mg, 65%), m.p. 189-190 °C. This m.p. agrees with the previosly recorded value of 187-188 °C, and the n.m.r. spectra of the compounds were identical (see p.130).

Preparation of N-Benzylhydroxylamine

The method of Feuer et al[78] was carried out using benzaldoxime (24.2 g) and borane/THF solution (320 ml, 1 M). N-Benzylhydroxylamine crystallised from pentane (7.4 g, 30%), m.p. 55 °C (Lit., 57 °C)

Preparation of N-Phenylhydroxylamine

The method of Vogel[79] was followed using nitrobenzene (50 g), ammonium chloride (25 g), water (800 ml), and zinc powder (59 g). N-Phenylhydroxylamine crystallised from benzene (14.03 g, 32%), m.p. 77-82 °C (Lit., 81 °C).

Preparation of N-Acetyl-N-phenyldioxylamine (118)

N-Phenylhydroxylamine (45 g, 0.41 mol) in THF (100 ml) and pyridine (100 ml) was treated at room temperature with acetyl chloride (27.8 ml, 0.49mol.) for 1 h, then the reaction mixture was poured into crushed ice and water (ca. 500 ml) and extracted with chloroform. The extract was dried and evaporated. After excess pyridine had been removed by azeotroping with toluene (4 x), the residue was extracted with ammonium hydroxide solution (ca. 30 ml, 0.88 sp. g.) and filtered. The filtrate was then acidified with cold 5M sulphuric acid. This was then extracted with chloroform, the extract was dried ($MgSO_4$) and evaporated. Crystallisation of the residue from ethyl acetate - light petroleum (b.p. 60-80 °C) gave N-acetyl-N-phenylhydroxylamine (118) as cuboids (17.2 g, 28%), m.p. 66-67 °C (lit., 67 °C).

Preparation of N-Acetyl-N-benzylhydroxylamine (120)[80]

N-Benzylhydroxylamine (3.20 g, 26 mmol) in THF (64 ml) and pyridine (32 ml) was treated at room temperature with acetyl chloride (2.24 ml, 31.2 mmol) for 17 h, then the reaction mixture was poured into crushed ice and water (ca. 500 ml), and extracted with chloroform. The extract was dried and evaporated, then the residue was extracted with ammonium hydroxide solution (ca. 30 ml, 0.88 sp. g.) and the insoluble material removed by filtration. The filtrate was acidified with cold 5 M sulphuric acid, and extracted with chloroform. After the extract had been dried it was evaporated to give an orange crystalline mass of N-acetyl-N-benzylhydroxylamine (120) which crystallised from ethanol at 0 °C (2.10 g, 49%), m.p. 125-126 °C (lit., 127 °C).

Preparation of N-Benzoyl-N-phenylhydroxylamine (119)

The method of Shome[81] was followed using N-phenylhydroxylamine (6 g) and benzoyl chloride (7.44 ml, 1.2 mol. equiv.). N-Benzoyl-N-phenylhydroxylamine (119) crystallised from ethanol (3.95 g, 34%), m.p. 122 °C (lit., 121-122 °C).

Preparation of N-Benzoyl-N-benzylhydroxylamine (121)

The method of Shome[81] was followed using N-benzylhydroxylamine (3.38 g) and benzoyl chloride (3.72 ml, 1.2 mol. equiv.). N-Benzoyl-N-benzylhydroxylamine (121) crystallised from ethanol (2.78 g, 45%), m.p. 107-108 °C (lit.,[82] 108 °C).

Reduction of N-Acetyl-N-phenylhydroxylamine with Sulphur Dioxide in Pyridine

N-Acetyl-N-phenylhydroxylamine (100 mg, 0.66 mmol) was dissolved in dry pyridine saturated with sulphur dioxide (5 ml) then heated under reflux for 1 h. After cooling, water (5 ml) followed by 6 M hydrochloric acid (10 ml) was added. The mixture was then extracted with chloroform (5 x 15 ml) and the extract was washed with water, dried and evaporated to yield a crystalline solid (84 mg). Crystallisation from water yielded acetanilide (53 mg, 60%), m.p. 112-113 °C (lit., 114 °C).

Reduction of N-Benzoyl-N-phenylhydroxylamine with Sulphur Dioxide in Pyridine

N-Benzoyl-N-phenylhydroxylamine (100 mg, 0.47 mmol) was dissolved in dry pyridine saturated with sulphur dioxide (5 ml) then heated under reflux for 1 h. After cooling, water (5 ml) followed by 6 M hydrochloric acid (10 ml) was added. The mixture was then extracted with chloroform and the extract was washed with water, dried and evaporated to give a crystalline solid (86 mg). Crystallisation from chloroform yielded benzanilide (59 mg, 64%), m.p. 162 °C (lit., 163 °C).

Reduction of N-Acetyl-N-benzylhydroxylamine with Sulphur Dioxide in Pyridine

N-Acetyl-N-benzylhydroxylamine (100 mg, 0.61 mmol) was dissolved in dry pyridine saturated with sulphur dioxide (5 ml)

and heated under reflux. Dry sulphur dioxide was occasionally bubbled through the solution over the first 5 h, then the reaction mixture was left under reflux for a further 15 h. Water (5 ml) followed by 6 M hydrochloric acid (10 ml) was added to the cooled solution. The mixture was then extrcated with chloroform, and the extract washed with water, dried and evaporated to give an oil (70 mg). Crystallisation with difficulty from diethyl ether yielded benzylacetamide (16 mg, 18%) m.p. 59-60 °C (lit., 61 °C).

Reduction of N-Benzoyl-N-benzylhydroxylamine with Sulphur Dioxide in Pyridine

N-Benzoyl-N-benzylhydroxylamine (100 mg, 0.44 mmol) was dissolved in dry pyridine saturated with sulphur dioxide (5 ml), then heated under reflux for 45 min. After cooling, water (5 ml) followed by 6 M hydrochloric acid (10 ml) was added. The mixture was then extracted with chloroform and the extract was washed with water, dried and evaporated to give an oil (87 mg). Crystallisation from di-isopropyl ether yielded N-benzylbenzamide (57 mg, 61%), m.p. 101-103 °C (lit., 105-106 °C).

Attempted Reduction of N-Acetyl-N-phenylhydroxylamine with Phosphorus Trichloride in Pyridine

N-Acetyl-N-phenylhydroxylamine (100 mg, 0.66 mmol) in dry pyridine (1 ml) was treated with phosphorus trichloride (57.8 µl, 1.0 mol. equiv.) for 10 min. Water (3 ml) was added

and the reaction mixture kept at 0 °C for a further 5 min. The mixture was then extracted with chloroform and the extract dried and evaporated. Pyridine was removed by azeotroping with toluene (4 x). The residue (43 mg) was shown by n.m.r. spectroscopy to contain impure acetanilide. Attempts to crystallise this product from water failed.

Reduction of N-Benzoyl-N-phenylhydroxylamine with Phosphorus Trichloride in Pyridine

N-Benzoyl-N-phenylhydroxylamine (100 mg, 0.47 mmol) in dry pyridine (1 ml) was treated at 0 °C with phosporus trichloride (45.1 µl, 1.1 mol. equiv.) for 30 min. Water (2 ml) was added and the reaction kept at 0 °C for 5 min. The mixture was then extracted with chloroform, dried and evaporated. Pyridine was removed by azeotroping with toluene (4 x), then the residue was dissolved in ethanol and heated under reflux with activated charcoal for 1 h. Filtration followed by evaporation then gave impure benzanilide which crystallised from chloroform (30 mg, 32%), m.p. 156-161 °C (lit., 163 °C). Further attempts at purification were unsuccessful.

Attempted Reduction of N-Acetyl-N-benzylhydroxylamine with Phosporus Trichloride in Pyridine

N-Acetyl-N-benzylhydroxylamine (100 mg, 0.61 mmol) in dry pyridine (1 ml) was treated with phosphorus trichloride (58 µl, 1.1 mol. equiv.) at 0 °C and the reaction mixture left at room temperature for 20 min. Water (5 ml) followed by

5 M sodium hydroxide (5 ml) was added and the mixture was extracted with ethyl acetate. The extract was washed with 5M Hydrochloric acid, then water, dried and evaporated to yield a brown oil (8 mg). This material was not identified.

Attempted Reduction of N-Benzoyl-N-benzylhydroxylamine with Phosphorus Trichloride in Pyridine

N-Benzoyl-N-benzylhydroxylamine (100 mg, 0.44 mmol) in dry pyridine (1 ml) was treated at 0 °C with phosphorus trichloride (43 µl, 1.1 mol. equiv.) and the reaction mixture kept at room temperature for 35 min. Water (5 ml) followed by 5 M sodium hydroxide (5 ml) was added and the mixture was extracted with ethyl acetate. The extract was washed with 5 N hydrochloric acid, then water, dried and evaporated to give a yellow oil (33 mg). The n.m.r. spectrum indicated that this oil contained N-benzylbenzamide, but crystallisation from di-isopropyl ether was unsuccessful.

Reduction of N-Acetyl-N-phenylhydroxylamine with Borane

N-Acetyl-N-phenylhydroxylamine (755 mg, 5 mmol) in dry THF (5 ml) under a nitrogen atmosphere at 0 °C was treated with a solution of borane in THF (10 ml; 1 M, 2 mol. equiv.). The mixture was heated under reflux for 1 h, then cooled. 5 M Hydrochloric acid (10 ml) was then cautiously added and heating under reflux continued for 20 min. The reaction mixture was then basified by the addition of 5 M sodium hydroxide

(15 ml) and extracted with ethyl acetate. The extract was dried and evaporated to yield a brown oil. Distillation under reduced pressure then afforded N-ethylaniline as a pale yellow oil (518 mg, 86%), b.p. 199-201 °C/760 mm Hg (lit., 205 °C/760 mm Hg). When compared to a genuine sample of N-ethylaniline, n.m.r spectroscopy and t.l.c. both indicated that an impurity was present (ca. 10%), which was not identified.

Reduction of N-Benzoyl-N-phenylhydroxylamine with Borane

N-Benzoyl-N-phenylhydroxylamine (213 mg, 1 mmol) in dry THF (5 ml) under nitrogen was treated with a solution of borane in THF (10 ml; 1 M, 10 mol. equiv.). The mixture was heated under reflux for 2 h, then a further portion of borane in THF (5 ml; 1 M, 5 mol. equiv.) was added and heating under reflux continued for 10 h. After cooling, the reaction was terminated by cautiously adding a solution of THF - water (6:4) till all frothing ceased, then 5 M hydrochloric acid (2 ml) was added and the mixture heated under reflux for 40 min. The reaction mixture was basified with 5 M sodium hydroxide (3 ml) and extracted with ethyl acetate. The extract was dried and evaporated to yield an oil (182 mg). This oil was extracted with boiling light petroleum (b.p. 60-80 °C) to yield after evaporation, an oil (159 mg) which was distilled (ca. 200 °C/10 mm Hg), then crystallised from light petroleum (b.p. 60-80 °C) to yield N-benzylaniline as needles (15 mg, 8%) m.p. 35-36 °C (lit., 36 °C). The product was homogeneous by t.l.c. and the n.m.r spectrum agreed with that of a genuine specimen of N-benzylaniline.

Reduction of N-Acetyl-N-benzylhydroxylamine with Borane

N-Acetyl-N-benzylhydroxylamine (165 mg, 1 mmol) in dry THF (3 ml) under nitrogen at 0 °C was treated with a solution of borane in THF (2 ml; 1 M, 2 mol. equiv.). The mixture was heated under reflux for 20 min then cooled. 5 M Hydrochloric acid (2 ml) was then cautiously added and heating under reflux continued for 20 min. The reaction mixture was then basified by the addition of 5 M sodium hydroxide (3 ml) and extracted with ethyl acetate. The extract was dried and evaporated to yield a pale yellow oil (160 mg). Distillation under reduced pressure gave N-ethylbenzylamine (60 mg, 48%) as a colourless oil, b.p. 190-195 °C/760 mm Hg (lit., 191-194 °C/760 mm Hg). This material was homogeneous by t.l.c. and the n.m.r. spectrum agreed with that of a genuine specimen of N-ethylbenzylamine.

Reduction of N-Benzoyl-N-benzylhydroxylamine with Borane

N-Benzoyl-N-benzylhydroxylamine (227 mg, 1.0 mmol) in dry THF (5 ml) under nitrogen at 0 °C was treated with a solution of borane in THF (2 ml; 1 M, 2 mol. equiv.). The mixture was heated under reflux for 20 min then cooled. 5 M Hydrochloric acid (2 ml) was then cautiously added and heating under reflux continued for 20 min. The reaction mixture was then basified by the addition of 5 M sodium hydroxide (3 ml) and extracted with ethyl acetate. The extract was washed with water, dried and evaporated to yield a pale yellow oil (197 mg). Crystallisation from methanol gave NN-dibenzylhydroxylamine as needles (51 mg,

24%), m.p. 117-119 °C (lit., 123 °C); m/e 213. This material was homogeneous by t.l.c. and the structure confirmed by n.m.r. spectroscopy.

Reduction of N-Hydroxysuccinimide with Phosphorus Trichloride in Pyridine

N-Hydroxysuccinimde (1.15 g, 10 mmol) in pyridine (10 ml) was treated with phosphorus trichloride (0.96 ml, 1.1 mol. equiv.) at room temperature for 10 min. The mixture was diluted with 5 N sodium hydroxide (20 ml) and water (130 ml), then extracted for 18 h with ethyl acetate. The extract was dried and evaporated to give a crystalline solid (107 mg). Crystallisation from ethanol yielded succinimide monohydrate (65 mg, 6%), m.p. 123-126 °C (lit., 126-127 °C). The i.r. and n.m.r. spectra were identical to a genuine sample of succinimide.

Attempted Reduction of N-Hydroxysuccinimide with Sulphur Dioxide in Pyridine

N-Hydroxysuccinimide (230 mg, 2.0 mmol) in dry pyridine (5 ml) was treated with dry sulphur dioxide for 5 min, then heated under reflux for 24 h, with occasional passage of sulphur dioxide. The mixture was then evaporated, and the pyridine removed by azeotroping with toluene to yield a yellow oil (290 mg). T.l.c. (silica; ethyl acetate) indicated that no reaction had taken place and the resultant yellow oil consisted of starting material.

Reduction of N-Acetyl-N-phenylhydroxylamine with Zinc in Acetic Acid

N-Acetyl-N-phenylhydroxylamine (151 mg, 1 mmol) in glacial acetic acid (1.5 ml) was treated with powdered zinc (98 mg, 1.5 mmol) and the mixture warmed at 70-80 °C for 30 min. The mixture was filtered, and the filtrate diluted with water (ca. 20 ml) then basified to pH 11 with 5 M sodium hydroxide solution. This solution was extracted with chloroform, the extract dried and evaporated to yield acetanilide (37 mg) as a crystalline solid. Crystallisation from water gave 26 mg (19%), m.p. 113-114 °C (lit., 114 °C).

Attempted Reductions of N-Acetyl-N-phenylhydroxylamine with Silicon containing Reagents

(a) Trichlorosilane[58]

N-Acetyl-N-phenylhydroxylamine (151 mg, 1.0 mmol) in dry benzene (8 ml) and triethylamine (0.14 ml, 1.0 mmol) was treated with trichlorosilane (0.20 ml, 2 mmol). The mixture was heated under reflux for 3 days, then left at room temperature for 4 days. Water (10 ml) followed by benzene (20 ml) was then added and the organic layer was separated, washed with water, dried and evaporated to yield an oil (36 mg). N.m.r. spectroscopy showed this to consist mostly of unreacted starting material.

(b) Polymethylhydrosiloxane[59]

N-Acetyl-N-phenylhydroxylamine (200 mg, 1.3 mmol) was dissolved in methylene chloride (ca. 5 ml) and treated with

excess polymethylhydrosiloxane (1 ml). The mixture was heated under reflux for 15 min after which a positive ferric chloride test indicated that starting material was still present. Triethylamine (1 drop) was added and the reaction left at room temperature for 10 days. A positive ferric chloride test again indicated that starting material was present.

(c) Hexachlorodisilane[60]

N-Acetyl-N-phenylhydroxylamine (45 mg, 296 μmol) was dissolved in deuteriochloroform (1 ml) in an n.m.r. tube. The tube was flushed with dry nitrogen, then to this solution was added hexachlorodisilane (50 μl, 296 μmol). Bubbles of gas were immediately evolved and the n.m.r. spectrum showed that all the starting material had been converted to an unknown product. Hydrolysis of this material with 5 M sodium hydroxide yielded a compound whose spectrum was even more complicated. T.l.c. showed that 3 compounds were present, none of which was acetanilide.

Reduction of Thebaine with Sodium/Liquid Ammonia

(A) Sodium (460 mg, 20 mmol) and hydrated iron III nitrate (404 mg, 1 mmol) were dissolved in dry liquid ammonia (ca. 80 ml) with passage of oxygen over 20 min at - 78 °C to form sodamide. Thebaine (3.11 g, 10 mmol) was then added, followed by sodium (460 mg, 20 mmol) and the reaction mixture allowed to warm to - 33 °C with stirring. After the ammonia had mostly evaporated (ca. 3 h), ethanol (15 ml) and water (50 ml) was added and the mixture filtered, to remove unreacted thebaine. The products were precipitated from the filtrate by the addition of solid carbon dioxide, and were extracted into chloroform. The extract was dried and evaporated to yield a pink foam (2.59 g). N.m.r. spectroscopy showed this to consist of β-dihydrothebaine (123) (50%) and dihydrothebaine-ϕ (101) (50%).

(B) The above procedure was repeated with sodamide (30 mmol) and sodium (30 mmol), and the ammonia was allowed to evaporate for 17 h at room temperature. After workup, analysis of the total reaction mixture by n.m.r. spectroscopy showed that it contained β-dihydrothebaine (55%) and dihydrothebaine-ϕ (45%).

(C) The procedure of experiment (B) was repeated, but after the ammonia had evaporated (ca. 3 h), a further 80 ml of liquid ammonia was added and evaporation left to continue overnight.

This procedure yielded β-dihydrothebaine (65%), and dihydrothebaine-ϕ (35%), as identified by n.m.r. spectroscopy.

The products from experiments (A), (B), and (C) were separted by fractional crystallisation as follows. The mixture of β-dihydrothebaine and dihydrothebaine-ϕ was heated in refluxing light petroleum (b.p. 60-80 °C), then ethyl acetate was added dropwise until the residue just dissolved. Upon cooling, β-dihydrothebaine crystallised (904 mg, 29% from (A)). Dihydrothebaine-ϕ crystallised from the mother liquors after treatment with ether and benzene (682 mg, 22% from (A)). The n.m.r. spectra for both compounds agreed with those of the literature, but both compounds were still coloured.

Preparation of 5,6-Dihydrothebaine Phenyl Ether (127).

This procedure is based on that of Sawa *et al.*[63], for the preparation of the 4-phenylether of dihydrothebaine-ϕ. β-Dihydrothebaine (3.13 g, 10 mmol), pyridine (30 ml), finely ground anhydrous potassium carbonate (2.16 g), precipitated copper metal (0.31 g), and redistilled bromobenzene (2.57 ml, 24 mmol) were heated together under reflux for 10 h. The solution was filtered while still hot and the residue washed with hot pyridine. Evaporation of the pyridine solution afforded a brown oil which was dissolved in benzene and washed

with water, the resulting emulsion being separated by centrifugation. The benzene solution was dried (K_2CO_3) and evaporated to yield a black tar (4.51 g). Preparative t.l.c. on silica (methanol - chlroform, 1:9) yielded 4-phenyl ether (127) (R_F 0.31) (3.24 g, 83%) as an oil, δ ($CDCl_3$) 2.37 (3H, s, NCH_3), 3.51 (3H, s, O-CH_3 at C-6), 3.63 (3H, s, O-CH_3 at C-3), 4.83 (1H, br d, J_{H-8} 6 Hz, H-7), 5.80 (1H, d, J_{H-7} 6 Hz, H-8), and 6.7 to 7.4 (7H, m, aromatics); m/e 389.

Preparation of 8,14-Dihydro-8α,10α-epidioxy-14β-nitrothebaine (74)

Thebaine (1.56 g, 5 mmol) was dissolved in benzene (70 ml). Dry oxygen was slowly bubbled through the solution, then tetranitromethane (0.60 ml, 5 mmol) in benzene (12 ml) was added over 12 min. The reaction mixture was left at room temperature for 3 h with passage of oxygen, then the yellow precipitated nitroform salt was filtered off, and the filtrate concentrated under vacuum at 30 °C. The components of the filtrate were separated by preparative t.l.c. on alumina (chloroform - benzene, 1:1) to yield thebaine (18 mg), 14β-nitrocodeinone (154 mg), both identified by n.m.r. spectroscopy, and 8,14-dihydro-8α,10α-epidioxy-14β-nitrothebaine (600 mg, 31%), which crystallised from ethyl acetate to yield prisms, m.p. 160-161 °C (after drying at 65 °C/*ca.* 1 mm Hg for 3 days) (Lit.[37] 159-159.5 °C). (Found: C, 58.68; H, 5.28; N, 7.24. $C_{19}H_{20}N_2O_7$ requires C, 58.76; H, 5.28; N, 7.21%). The n.m.r. and i.r. spectra agreed with those of the literature.

Preparation of 14β-Nitrocodeinone Dimethyl Acetal (72)

Thebaine (1.56 g, 5 mmol) in methanol (100 ml) and anhydrous methanolic ammonia (2.28 M; 6.6 ml, 15 mmol) were stirred at 0 °C. To this solution was added over 15 min, tetranitromethane (1.56 ml, 13 mmol) and the mixture left without stirring at room temperature for 17 h, to allow the product to crystallise. The slurry of crystals was concentrated under vacuum at 30 °C, then the solid material was removed by filtration and washed with cold methanol, then light petroleum (b.p. 40-60 °C), and finally ether, to yield 14β-nitrocodeinone dimethyl acetal (584 mg, 30%). A specimen was recrystallised from ethanol, m.p. 225-227 °C (lit.,[37] 227-227.5 °C), and the n.m.r. spectrum was identical to that in the literature.

Preparation of 14β-Nitrocodeinone (73) by Hydrolysis of the Dimethyl Acetal (72)

14β-Nitrocodeinone dimethyl acetal (300 mg, 0.77 mmol) was dissolved in methanol (6 ml) containing 5 N hydrochloric acid (2 ml) and water (2 ml) and heated under refux for 30 min. The mixture was then basified with aqueous sodium hydrogen carbonate, extracted with chloroform, dried and evaporated to yield 14β-nitrocodeinone (241 mg, 91%). A small sample crystallised from ethanol had m.p. 170-171.5 °C (lit.,[37] 172.5-173 °C), and the n.m.r. spectrum was identical to that in the literature.

Attempted Oxidation of 14β-Nitrocodeinone (73) to 10-Oxo-14β-nitrocodeinone (128)

14β-Nitrocodeinone (114 mg, 0.33 mmol) in refluxing dioxane (5 ml) was treated with resublimed selenium dioxide (44 mg, 0.40 mmol). After 3 days reflux, t.l.c. on silica (ethyl acetate) indicated that ca. half of the starting material was still present, so selenium dioxide (44 mg, 0.40 mmol) was again added and the reflux continued. After a further 4 days, the reaction mixture was cooled, chloroform was added and the solution evaporated in vacuo to give a dark brown solid. This solid was dissolved in methanol, heated under reflux for 30 min with charcoal, then filtered and evaporated to yield a crystalline solid (62 mg). N.m.r. spectroscopy indicated that the N-methyl group had been oxidised to N-formyl, but the product was never isolated or characterised.

Attempted Nitration of β-Dihydrothebaine with Tetranitromethane

β-Dihydrothebaine (313 mg, 1.0 mmol) in methanol (20 ml) was stirred at 0 °C and treated with tetranitromethane (0.36 ml, 3.0 mmol) over 15 min, then the reaction mixture was left at room temperature for 17 h. Removal of the precipitated salts by filtration, followed by cautious evaporation of the solvent under vacuum at 20 °C, yielded a chloroform insoluable black tar. The n.m.r. spectrum recorded in D_6-acetone, showed that along with several by-products, a compound that appeared to

contain 3 methoxy singlets was present. This material was tentatively assumed to be the 14β-nitro dimethyl acetal compound but it was not isolated or positively identified.

Preparation of 5,O-Dihydro-14β-nitrocodeinone Phenyl Ether (129)

4 -Phenyl ether (127) (770 mg, 1.98 mmol) was dissolved in dry benzene (30 ml). Oxygen was slowly bubbled through the solution then tetranitromethane (0.30 ml, 2.50 mmol) in benzene (5 ml) was slowly added over 8 min with stirring. Passage of oxygen was maintained for 2 h, then the reaction mixture was left at room temperature for 10 h. Filtration of the oily residue, followed by cautious evaporation of the filtrate, yielded a yellow foam (630 mg). Preparative t.l.c. on alumina (benzene - chlroform, 1:1) yielded at least 8 different compounds, of which the two major components consisted of the 14β-nitro dimethyl acetal (130) (R_F 0.50) (20 mg, 2%), identified by n.m.r. spectroscopy, and the 5,O-dihydro-14β-nitrocodeinone (129) (R_F 0.33) (96 mg, 12%) which crystallised from ethyl acetate as needles (48 mg, 6%), m.p. 166 °C (decomp., with evolution of gas) (Found: C, 68.63; H, 5.93; N, 6.68. $C_{24}H_{24}N_2O_5$ requires C, 68.57;, H, 5.71; N, 6.67%); $\nu_{max.}$(KBr) 1 679 and 1 539 cm^{-1}; δ ($CDCl_3$) 2.42 (3H, s, N-CH_3), 3.61 (3H, s, O-CH_3), 3.84 (1H, dd, $J_{H-10\alpha}$ 6 Hz, and $J_{H-10\beta}$ *ca.* 1 Hz, H-9), 6.24 (1H, d, J_{H-8} 10 Hz, H-7), and 6.2 to 7.4 (8H, m, H-1, H-2, H-8, and Ph); m/e 420.

Preparation of 5,6-Dihydro-14β-nitrocodeinone Phenyl Ether Dimethyl Acetal (130)

The 4-phenyl ether (127) (773 mg, 1.99 mmol) in methanol (17 ml) and anhydrous methanolic ammonia (2.28 M; 2.64 ml, 6.0 mmol) was stirred at 0 °C. To this solution was added tetranitromethane (0.62 ml, 5.2 mmol) over 15 min, then the mixture was left at room temperature without stirring for 12 h to allow the product to crystallise. The crystals of the product were collected by filtration and washed with cold methanol, then light petroleum (b.p. 40-60 °C), and finally ether to yield the dimethyl acetal (130) (205 mg, 22%) as needles. A specimen was recrystallised from methanol, m.p. 140-142 °C (decomp. with evolution of gas) (Found: C, 66.91; H, 6.43; N, 5.74. $C_{26}H_{30}N_2O_6$ requires C, 66.95; H, 6.44; N, 6.01%); $\nu_{max.}$ (KBr) 1 537 cm^{-1}; δ ($CDCl_3$) 2.40 (3H, s, N-CH_3), 2.77 (3H, s, O-CH_3 at C-6β), 3.14 (3H, s, O-CH_3 at C-6α), 3.62 (3H, s, O-CH_3 at C-3), 3.71 (1H, d, $J_{H-10\alpha}$ 6 Hz, H-9), 6.10 (2H, s, H-7 and H-8), and 6.7 to 7.4 (7H, m, H-1, H-2, and Ph); m/e 466.

Preparation of 5-O-Dihydrothebaine Phenyl Ether/Nitrsocarbonyl-methane Adduct (131)

The crude 4-phenyl ether (127) (102 mg, 262 μmol) in ethyl acetate (10 ml) and sodium periodate (84 mg, 393 μmol) in aqueous sodium acetate (0.2 M, adjusted to pH 6 with

concentrated hydrochloric acid) (3 ml) were stirred rapidly at 0 °C. Acetohydroxamic acid (29 mg, 393 μmol) was added slowly over 10 min, then rapid stirring was continued for 1 h. The mixture was basified by the addition of aqueous sodium hydrogen carbonate and the layers separated. The aqueous layer was extracted with ethyl acetate and the combined ethyl acetate layers washed with aqueous sodium thiosulphate and then water. The ethyl acetate solution was dried and evporated to yield an oil (79 mg, 62%) which was purified by preparative t.l.c. on silica (methanol - chloroform, 2:8) to yield the cyclo-adduct (131) (R_F 0.78) (56 mg, 44%) as an oil, δ ($CDCl_3$) 1.86 (3H, s, $COCH_3$), 2.38 (3H, s, N-CH_3), 3.34 (3H, s, O-CH_3 at C-6), 3.62 (3H, s, O-CH_3 at C-3), 4.50 (1H, dd, $J_{H-10\alpha}$ 6 Hz and $J_{H-10\beta}$ ca. 1 Hz, H-9), 6.22 (1H, d, J_{H-8} 9 Hz, H-7), and 6.6 to 7.4 (8H, m, H-1, H-2, H-8, and Ph); m/e 462.

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