THE SYNTHESIS OF 14-NITRO- AND 14-AMINO-CODEINONE DERIVATIVES

A Thesis Presented to the University of Glasgow

for the Degree of

Doctor of Philosophy

by

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September, 1975

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ACKNOWLEDGEMENTS

I would like to acknowledge my debt and gratitude to my supervisor, Professor G.W. Kirby, for his tolerant guidance throughout the course of this work and in the presentation of this thesis. I also wish to thank my laboratory colleagues for their help, both direct and indirect, and advice.

The work described in this thesis was carried out during the tenure of an award from the Science Research Council and Reckitt and Colman (Hull) Ltd., and to these bodies I express my gratitude.

My thanks are also due to the technical staff of the Chemistry Department for elemental analyses and recording mass spectra, n.m.r. spectra and high resolution i.r. spectra.

DAVID McDOUGALL

TO MY PARENTS

SUMMARY

The reaction of tetranitromethane with thebaine (4) has beed studied and alternative routes to 14β-amino-derivatives of codeine (2) investigated.

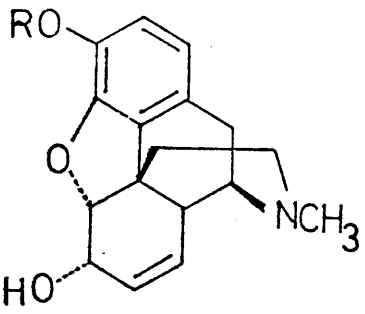
The nitration of thebaine with tetranitromethane gave 14β-nitrocodeinone (53) or its ketal, and a second nitration product whose structure has been identified as 8,14-dihydro-8α,10α-epidioxy-14β-nitrothebaine (59). Reaction conditions which preclude or optimise the formation of either product have been found. The structure of the latter product was determined by reduction to either 8,14-dihydro-8α,10α-dihydroxy-14β-nitrothebaine (61) or 8,14-dihydro-8α,10α-epoxy-14β-nitrothebaine (65) and by base catalysed hydrolysis to 8,14-dihydro-8β-hydroxy-10-oxo-14β-nitrothebaine(55:R=H). The interconversion of these degradation products has been achieved and their chemistry studied. The cleavage of 8,14-dihydro-8,10-dioxo-14β-nitrothebaine (64) with alkoxides gave products with unusual spectrometric properties, which have been tentatively identified as the esters (70).

Nitryl chloride, dinitrogen tetroxide and nitric acid have been investigated as nitrating agents for thebaine but were found to be unsuitable for the preparation of 14β-amino-derivatives.

The chemistry of the Diels-Alder adducts of C-nitrosocarbonyl-compounds with thebaine, with respect to the preparation of 14β-amino-derivatives, has been investigated. Acid hydrolysis of these adducts was found to be very dependent upon conditions, yielding a series of N-substituted 14β-hydroxyamino-derivatives. A preliminary study of the chemistry of these compounds has been undertaken.

CONTENTS

INTRODUCTION



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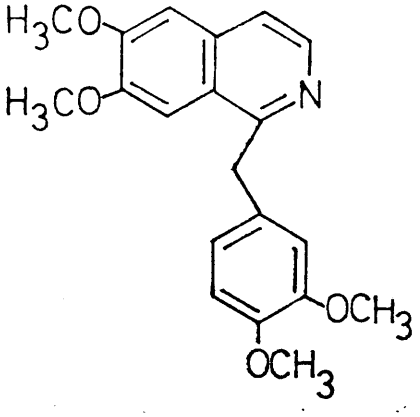
(2) R CH_3



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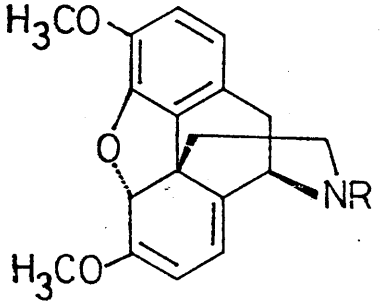
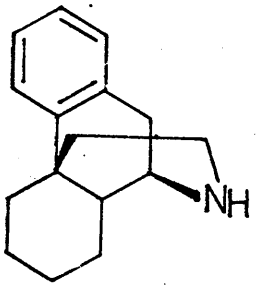


(4) R = CH_3
(8) R = H



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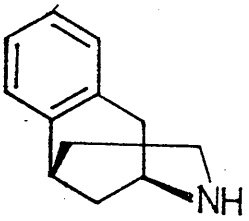

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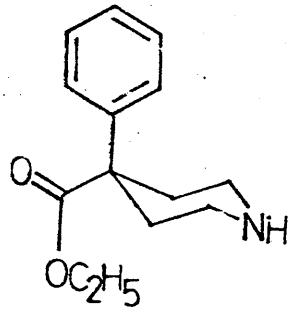

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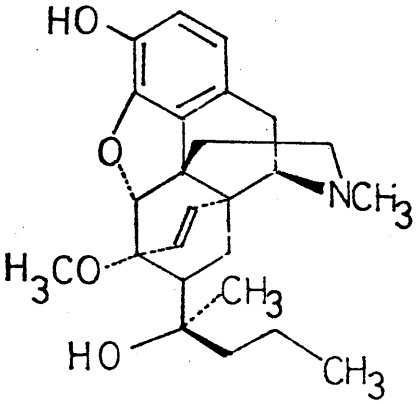

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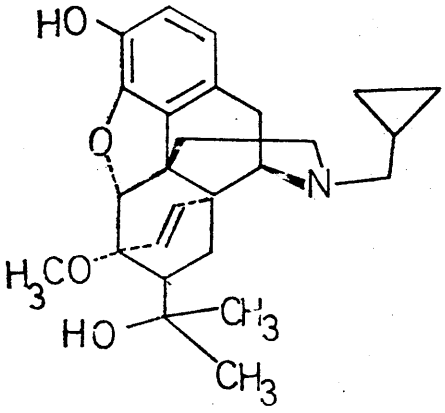

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A. 14-NITROGEN SUBSTITUTED DERIVATIVES OF THE MORPHINE ALKALOIDS

Although opium, the dried sap from the seed capsule of the poppy Papaver somniferum, has been used since time immemorial as a painkiller and producer of euphoria, it was not until 1805 that morphine (1), its most active constituent (10 - 20% by weight), was isolated in a pure form[1]. It took many years and much effort by many chemists before its true chemical structure was deduced in 1925 by Gilland and Robinson[2], and a further thirty years before the synthesis of morphine was successfully carried out by Gates and Tschudi[3].

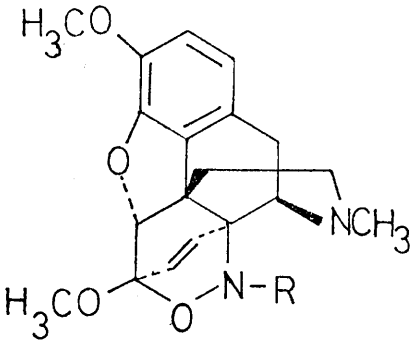
Other pharmacologically active compounds in opium are codeine (2)(0.2 - 0.8%), a milder more specialised analgesic than morphine and widely used for control of the cough reflex, papaverine (3)(0.5 - 1%), used as a muscle relaxant, and thebaine (4)(0.2 - 1%), which is too toxic to be pharmacologically useful. The mode of action of these alkaloids is not fully understood. Excepting papaverine all contain an aromatic nucleus linked to a quaternary carbon which is further linked by two carbons to a tertiary nitrogen. These structural features appear to be essential for physiological activity. The substitution on nitrogen is important in determining whether a compound has agonist (morphine like) or antagonist (morphine blocking) activity, and the functionality at C-7 is important in determining analgesic activity.

Although morphine is still widely used it is not an ideal analgesic. Drawbacks to use include psychological and physical

addiction, respiratory depression and tolerance. The search for alternative compounds with a better pharmacological profile or those with a blocking effect on the euphoriant action of heroin, thus providing effective treatment for addiction, has been intense.

A large proportion of earlier work consisted in the preparation of simpler fragments of the morphine molecule. The morphinans (5) have the morphine structure without the oxygen bridge. They show weak analgesic properties with optimum activity in 3-hydroxy derivatives. Variation in substitution on nitrogen produces[4] changes in activity similar to those in the morphine series. The benzomorphans[5] (6), which lack ring C, have activity, but residues of ring C at the 5 and 6 positions are essential for high analgesic potency. The 4-phenyl piperidines[6], e.g. pethidine[7] (7) have proved useful analgesics. Few, if any, of these compounds show any significant separation in the desirable and undesirable effects of morphine.

Beckett[8] has described the shape and approximate dimensions of a hypothetical opiate receptor in the central nervous system and has shown how common analgesics can be accommodated on it. He suggested the three dimensional fit of a drug to this system was an important requirement for physiological activity. Bentley[9] suggested that the above less complex molecules should fit as well or better than morphine to the receptor and thus initiate the same effects. He suggested that derivatives more complex and rigid than morphine itself should produce a greater separation of the various activities. The widely explored series of ring C bridged derivatives of thebaine and oripavine (8),



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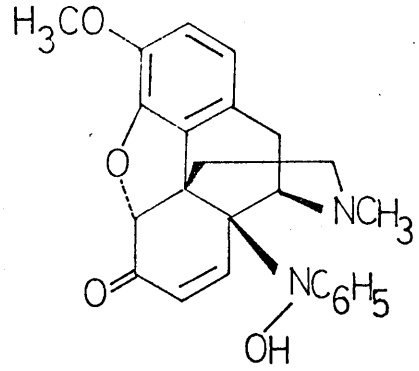

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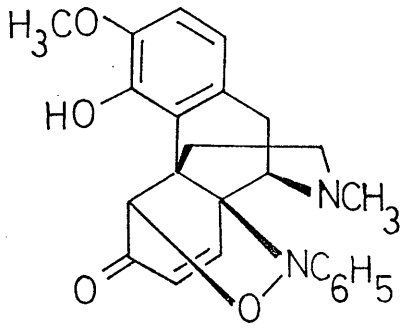

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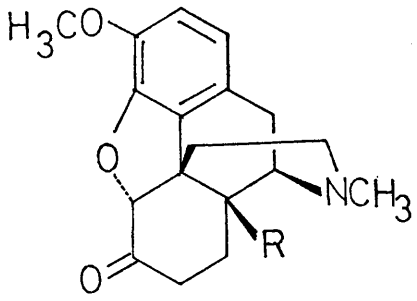

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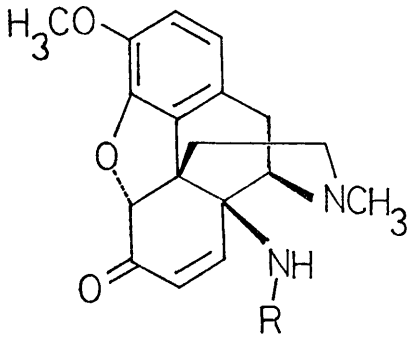

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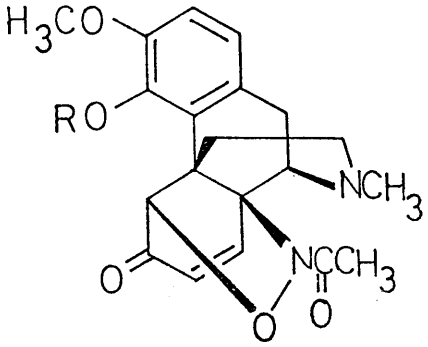

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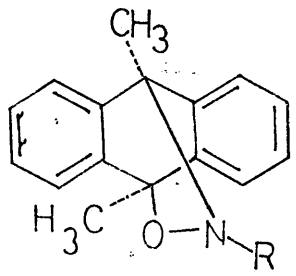

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derived from Diels-Alder reactions on thebaine[9,10], a pharmacologically useless by-product, vide supra, has led to compounds of greatly differing pharmacological profiles and potencies e.g. etorphine (9) and diprenorphine (10), which are currently marketed in the veterinary field in the United Kingdom. Etorphine is an analgesic with an activity on animal tests varying between 1,000 and 10,000 times that of morphine[11]. Diprenorphine, a powerful antagonist, is used as its antidote. However this series of compounds has failed to yield drugs with appreciable dissociation of analgesic and dysphoric properties[11].

A postulated receptor in the central nervous system of humans and monkeys has been isolated[12]. It is a proteolipid complex of around 60,000 a.m.u. per opiate molecule and results indicate that the more potent the drug, the stronger the binding to the receptor.

Other researches centred on simpler derivatives of the opiates, such as 14-hydroxy-compounds[13]. 14-hydroxydihydrocodeinone (14; R = OH) was discovered to be a more potent analgesic[14] administered orally than morphine by injection. Evidence was also presented[14b] that it had a lower addictive liability than morphine. This stimulated further research into the preparation of other simple derivatives and led to investigations into the synthesis of 14-nitrogen substituted opiates, in the hope that they might show similar properties to the 14-hydroxy-compounds.

C-nitroso-compounds react with conjugated dienes[15] to form 1,4 adducts and the first route to 14-aminocodeinone derivatives was through the Diels-Alder addition of nitroso-arenes to the

methoxy-diene system of thebaine[16,17]. The adducts (11; R = C_6H_5, $pCl.C_6H_4$, $pCH_3C_6H_4$) were obtained in high yield. In solution the adducts partially dissociated. The 14-amino-compounds were formed by trituration of the adduct (11; R = C_6H_5) with 1M-hydrochloric acid to give 14-(N-hydroxyphenylamino) codeinone (12). This compound rapidly cyclised with base at room temperature to give the phenol (13). Catalytic hydrogenation (Pd/H_2) of the hydroxylamine (12) gave 14-phenylamino-7,8-dihydro-codeinone (14; R = C_6H_5NH). Several of these 14-aminocodeinone-derivatives lived up to expectation and were found to possess analgesic properties, thus stimulating further work.

The trapping of C-nitroso-compounds by thebaine was later used in providing evidence for the formation of nitrosyl cyanide (ONCN) from silver cyanide and nitrosyl chloride[18]. Silver cyanide suspended in chloroform with thebaine and nitrosyl cyanide gave in variable yield (52 - 11%) the adduct (11; R = CN). This adduct could be hydrogenated in methanol (Pt) to give the cyanamide (14; R = NCN) corresponding to the hydroxylamines obtained from the adducts with nitroso-arenes. Unlike these compounds the adduct from nitrosyl cyanide did not detectably dissociate in solution.

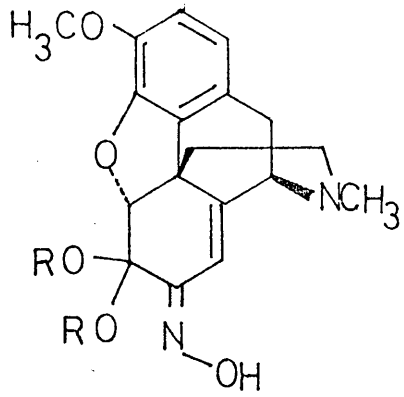
The extremely powerful dienophilic character of nitrosyl cyanide suggested that nitroso-carbonyl-compounds (RCO NO) should be dienophilic, and be readily trapped by thebaine, thus giving a variation on the route to 14-aminocodeinones.

Nitrosocarbonyl-compounds were first described by Reckwith and Evans[19] who postulated them as intermediates in the pyrolysis of alkyl nitrites in the presence of aldehydes to give acids,

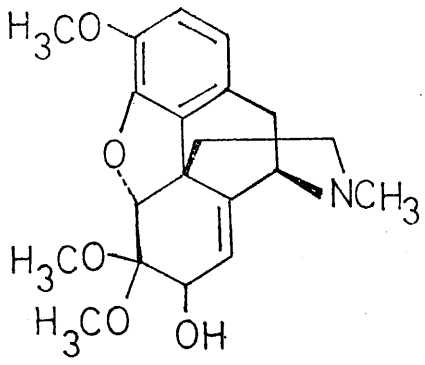
acid anhydrides and esters. The discovery that many oxidants e.g. periodic acid[20], bromine[21,23], codine[22], mercuric oxide[22], t-butylhypochlorite[21], N-bromosuccinimide[20] and potassium ferricyanide[20,24] would convert hydroxamic acids into active acylating agents aroused interest as it was suggested that this type of acylation was significant in connection with the carcinogenity of aromatic amines[22]. The reaction was also useful as a route to amides used as intermediates in peptide synthesis. The first step in the reaction was considered[20,21] to be the oxidation of the hydroxamic acid (RCO.NHOH) into a reactive intermediate (RCO.NO), that later was claimed[24], for ferricyanide oxidations, to be a radical anion ($RCO-\dot{N}-\bar{O}$), the acylating agent here being the NO-diacylhydroxylamine $\left(RCO\ ON(OH)OCR\right)$

It was found[25] that benzohydroxamic acid and acetohydroxamic acid, when oxidised by tetraethyl ammonium periodate in the presence of thebaine gave the Diels-Alder adducts (11; R = CH_3CO, C_6H_5CO) corresponding to those obtained from nitroso-arenes, and with a similar chemistry. The adduct (11; R = CH_3CO) hydrolysed with acid to give (15; R = CH_3CO) which cyclised with base to (16; R = H) which could be acetylated to give (16; R = CH_3CO). The adduct (11; R = C_6H_5CO), nominally derived from nitroso-carbonylbenzene, hydrolysed completely with acid to (15; R = H). Acetylation (Ac_2O, pyridine) of this compound gave (16; R = CH_3CO). An attempt to obtain 14-(acetylamino) codeinone by reductive (PtO_2/H_2) cleavage of the N - O bond in (11; R = CH_3CO) failed and the corresponding 7,8-dihydro-compound formed.

Further evidence for the existence of nitrosocarbonylmethane and nitrosocarbonylbenzene was obtained by trapping them with



(18) R = CH_3
or
R = C_2H_5



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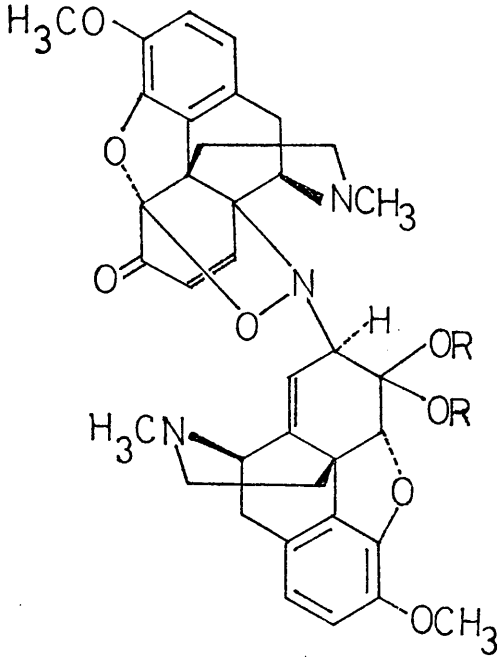
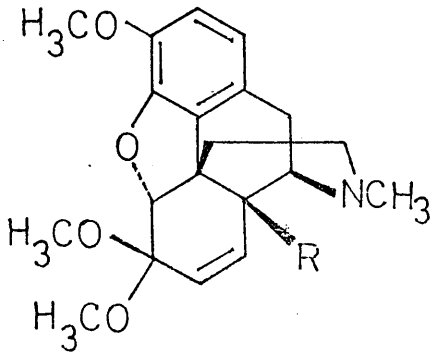


(19) R = CH_3 or C_2H_5



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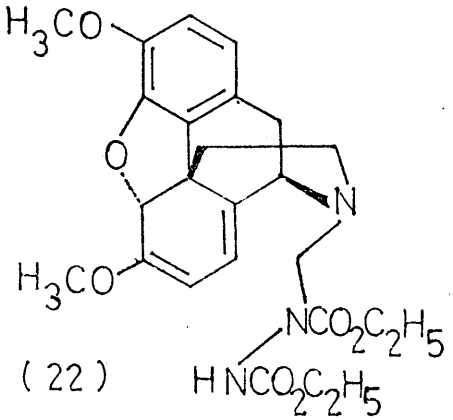

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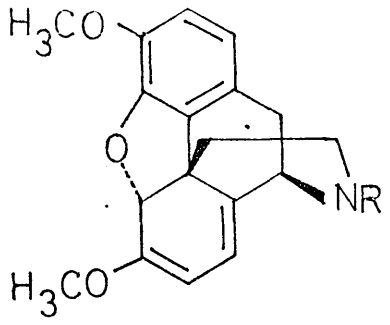
9,10-dimethylanthracene to give the adducts (17; R = CH_3CO, R = C_6H_5CO). Both these adducts were stable at room temperature but in refluxing benzene rapidly transferred the nitrosocarbonyl moiety to thebaine, giving the corresponding thebaine adducts (11; R = CH_3CO, R = C_6H_5CO).

Bromination and chlorination of thebaine occurs at C-14 to give the 14-halogenocodeinones or their corresponding acetals[26], and nitrosation of thebaine appeared to present an attractive route to 14-aminocodeinones. Nitrosation of thebaine in methanol or ethanol was earlier reported to give compounds of composition $C_{20}H_{24}N_2O_5$ and $C_{22}H_{28}N_2O_5$ respectively, but no structural assignments had been made[27]. Unfortunately nitrosation with nitrosylchloride[28] (and later[29] with nitrosyl sulphuric acid and pentylnitrite) gave mainly C-7 substitution yielding oximes of the type (18). A minor product[29] in the reaction (19) arose from the Diels-Alder addition of an intermediate 7-nitroso-compound to thebaine.

Iodination of thebaine was observed[30] to occur at C-7, as was bromination of metho-salts of thebaine[31], but nitration with methanolic tetranitromethane[30], vide infra, gave 14-nitrocodeinone dimethyl ketal (21; R = NO_2). An additional substituent on nitrogen might hinder approach of the electrophile but why iodination and nitrosation should occur at C-7 is not clear. Possibly nitrosation could occur reversibly at C-14 but as the resultant product could not tautomerise to an oxime it might be unstable with respect to the 7-oximino derivative. Similarly iodination of thebaine may occur at C-14, the product then undergoing an S_N2 reaction involving iodide attack at C-7 cf. the



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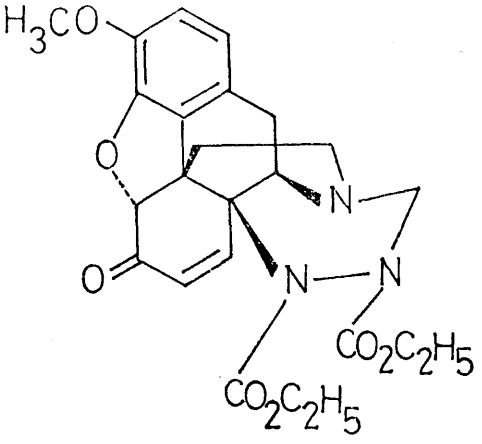

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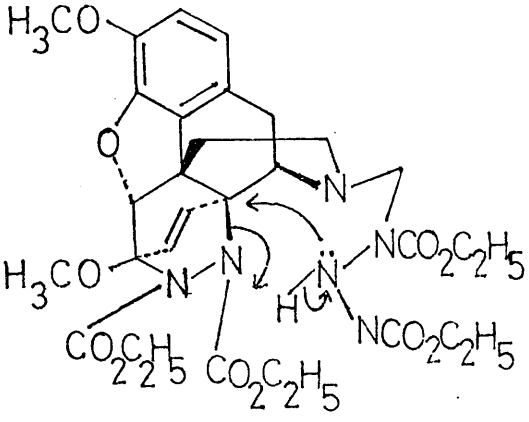

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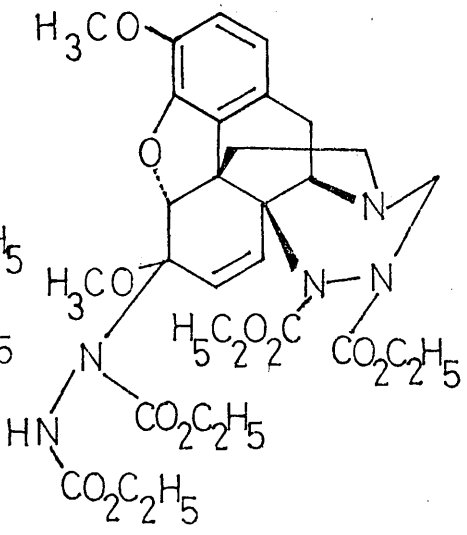

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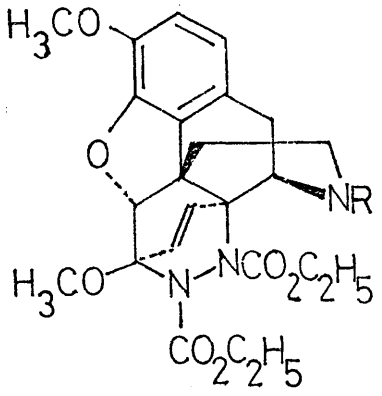

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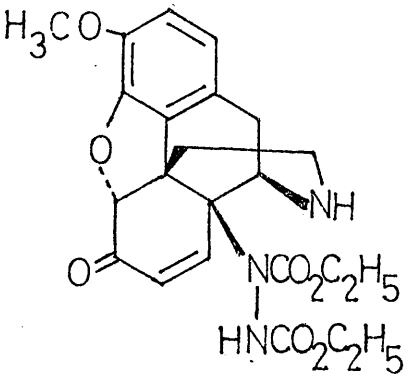


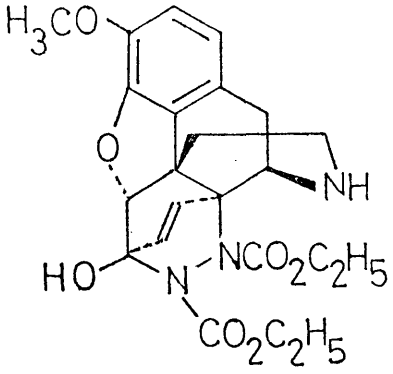
(28)

synthesis of 7-hydroxyneopinone dimethyl ketal (20) from 14-bromocodeinone dimethyl ketal (21; R = Br)

The aim of these nitrosation experiments was eventually achieved with the reaction of thebaine hydrochloride with 1-chloro-1-nitrosocyclohexane in aqueous ethanol to give 14-hydroxyaminocodeinone (15; R = OH). Support of the idea of reversible nitrosation at C-14 came from the observation[32] that 14-hydroxyaminocodeinone (15; R = OH), when oxidised with periodic acid, led to 7-oximinoneopinone, the ketonic parent of the ketals (18), and not 14-nitrocodeinone.

Another attempted route to 14-aminocodeinone derivatives was through Diels-Alder adducts of thebaine with azo-compounds. The first such dienophiles used were the dialkyl azodicarboxylates ($RO_2CN{:}NCO_2R$; R = C_2H_5, CH_3 or $CH_2C_6H_5$). Surprisingly, when equimolar quantities of thebaine and diethyl azodicarboxylate were used[33] the product was 17-(NN -diethoxycarbonylhydrazinomethyl) northebaine (22) which readily hydrolysed to northebaine (23; R = H), providing an important route to synthetically useful nor-derivatives of the morphine alkaloids. When two molar equivalents of diethyl azodicarboxylate were used[33] the product was found to be 14,17-(NN -diethoxycarbonylhydrazomethyl)-norcodeinone (24).

The mechanism proposed for this reaction was the initial formation of (22) which then formed a Diels-Alder adduct with another molecule of diethyl azodicarboxylate to give the intermediate (25) which decomposed as indicated to give (26) and then (24). N-Trifluoracetylnorthebaine (23; R = CF_3CO) did react with one mole of diethyl azodicarboxylate and gave the adduct (27; R = F_3CCO) which, by successive treatment with base and then



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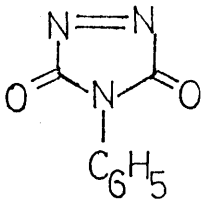

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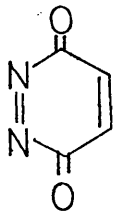

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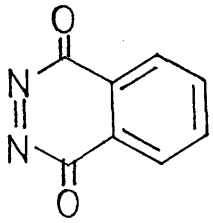

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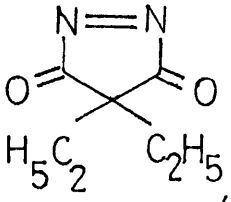

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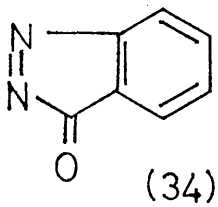

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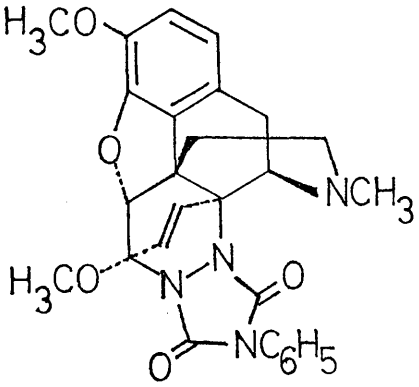

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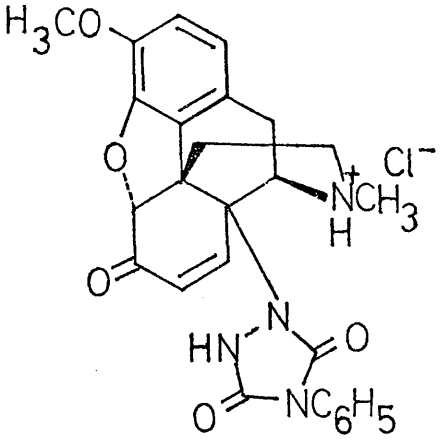

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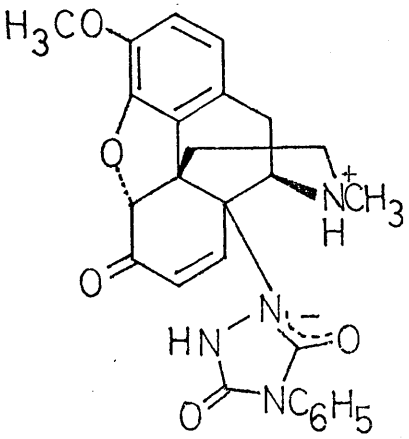

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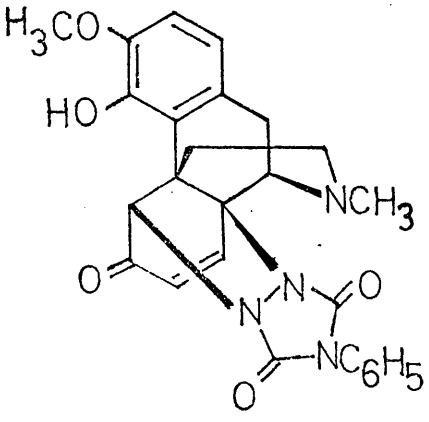


(38)

acid, gave (28), tautomeric with (29). This could be converted with acid and formaldehyde into (24).

Obviously the above reactions did not provide an easy synthetic route to the 14-nitrogen substituted opiates. Since azodicarboxylates exist mainly in the trans configuration, and this in certain circumstances may hinder or preclude the formation of Diels-Alder adducts, the building of the azo-system into a ring, thus restraining it in a cisoid configuration should provide more powerful dienophiles. Thus 4-phenyl-1,2,4-triazoline-3,5-dione (30) is an excellent dienophile[34]. It has been found to react with thebaine in a Diels-Alder fashion, as have the other cisoid azo-oxo-dienophiles[35]. (31,32,33 and 34).

The chemistry of the adduct (35) of Cookson's dienophile (30) with thebaine has been studied in depth[36]. Attempted formation of its hydrochloride resulted in (36), the free base of which, obtained by merely warming in water, was shown to exist, in the solid at least, with the betaine structure (37). Attempted crystallisation of this betaine from ethanol resulted in the phenol (38). The sequence (35)→(36)→(38) is analogous to the sequences (11; R = C_6H_5)→(12)→(13) and (11; R = CH_3CO)→(15; R = CH_3CO)→(16; R = H) in the chemistry of the thebaine adducts with nitrosoarenes[16,17], and C-nitrosocarbonyl-compounds[25] respectively, vide supra. Again reduction of the adduct (35), with diimide, gave the corresponding 7,8-dihydro-compound which gave a normal hydrochloride.

Nitration of the methoxy-diene system of thebaine at C-14 was also considered as a route to 14-aminocodeinone derivatives.

As thebaine readily undergoes rearrangement in strong acid, conventional nitrating agents could not be used. Tetranitromethane $\left[C(NO_2)_4\right]$ was considered ideal as it was a mild nitrating agent which could be used in neutral or basic media. A preliminary communication[30], vide supra, reported that, like bromination, nitration with methanolic tetranitromethane resulted in C-14 substitution to give 14-nitrocodeinone dimethyl ketal (21; R = NO_2). Further studies[37] reported that 14 nitrocodeinone dimethyl ketal could be reduced to 14-aminocodeinone (15; R = H). They also reported that the yield of 14-nitrocodeinone dimethyl ketal was low (25%), primarily because the bulk of the thebaine precipitated out of solution as the bright yellow nitroform salt, but also because a second crystalline product, of similar chromatographic properties to the ketal (21; R = NO_2), of unknown and unusual structure was formed in the reaction.

The objects of the present investigations were to study the mechanism of nitration with the aim of controlling the reaction in a desired direction, if necessary developing an alternative procedure and to investigate the structure and properties of the second unidentified nitration product.

B. THE CHEMISTRY OF TETRANITROMETHANE

Tetranitromethane was first made by boiling a solution of trinitromethane in fuming nitric acid and concentrated sulphuric acid. The trinitromethane was made from the reaction of trinitroacetonitrile with hydrogen sulphide. Tetranitromethane was put to use as a very sensitive test reagent for unsaturated compounds[39] with which it gave deep brown colourations. The structure of four nitro groups symmetrically placed about a central carbon atom was initially accepted but later called into doubt. Willstätter and Hottenroth[40] studied the following reactions of polynitromethanes with potassium hydroxide and concluded that two of the nitro groups in polynitromethanes must have a peculiar position,

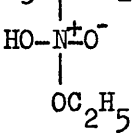
1)[41] $CBr_2(NO_2)_2 \longrightarrow CBr(NO_2)_2K$

2)[42] $CClBr(NO_2)_2 \longrightarrow CCl(NO_2)_2K$

3)[43] $Cl_3CCBr(NO_2)_2 \longrightarrow H_3CC(NO_2)_2K$

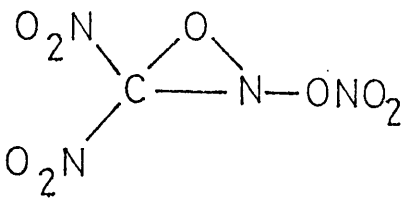
4)[44] $C(NO_2)_4 \longrightarrow C(NO_2)_3K$

5)[45] $H_3CC(NO_2)_3 \longrightarrow H_3CC(NO_2)_2K$

6)[46] $H_3CC(NO_2)_3 \longrightarrow$ 

(Reaction 6) with potassium ethoxide in ethanol)

The trinitromethane $(H_3CC(NO_2)_3)$ was made from tetranitromethane by forming the silver salt of trinitromethane $(AgC(NO_2)_3)$ and reacting that with methyl iodide. To account for the



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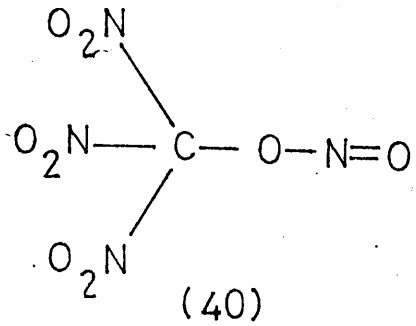

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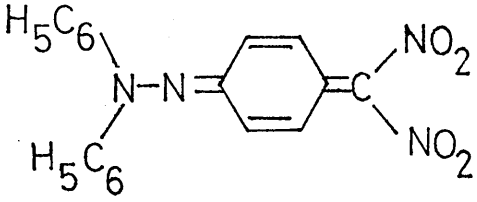

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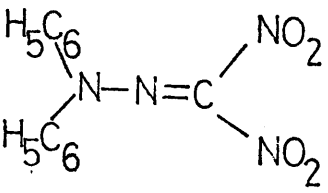

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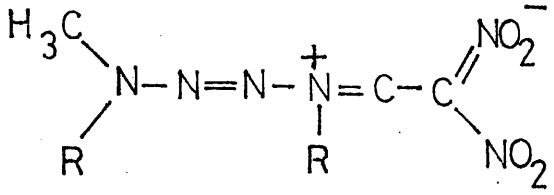


(43)

reactions 1) to 6) Willstätter and Hottenroth postulated[40] that tetranitromethane and other polynitro derivatives of methane had the part structure (= $\underline{C}ON - ONO_2$). This gave tetranitromethane structure (39).

Schmidt[47] found that tetranitromethane could also be decomposed by aqueous alkali in the following manner:

7) $$3C(NO_2)_4 + 6KOH \longrightarrow 4KNO_2 + K_2CO_3 + {}_3H_2O$$

The relative extent of each reaction, 4) and 7) was dependent upon the concentration of alkali. Noting that iodonitroform $\left[IC(NO_2)_3\right]$ in aqueous potassium hydroxide gave[48] only potassium nitroform $\left[KC(NO_2)_3\right]$ iodide and periodate, Schmidt held that reaction 7) depended on the fourth "nitro" group. As potassium nitrite was formed he believed that structure (40) best fitted his observations, although he believed it might be in equilibrium with the structure (39) proposed by Willstätter and Hottenroth[40].

Early spectrophotometric investigations into the colours given by tetranitromethane with aromatic compounds tended to support Schmidt's structure (40) by showing[49] that the spectra were more similar to those from alkyl nitrite - aromatic complexes than those from alkyl nitrate - aromatic complexes.

Reduction of tetranitromethane in acid conditions was known[50] to give guanidine $\left[(NH_2)_2CNH\right]$. Reduction in basic conditions resulted[51] in the easy removal of one nitro group, claimed to be evidence for a 'nitroite' part structure. When the reduction to guanidine was studied[52] quantitatively, it was

found that only 18 equivalents and not 24 were required for the reduction. Trinitromethane was reduced to guanidine with the consumption of 18 equivalents. This was cited as evidence for one labile 'nitro' group in tetranitromethane, and hence as evidence for Schmidt's structure (40).

Preliminary X-ray diffraction data suggested[53] that Schmidt's structure (40) was correct but in 1932, an investigation into dipole moments of a series of nitro compounds fairly conclusively proved that tetranitromethane must have a symmetric structure[54].

Notwithstanding this, Hungarian workers in 1936 proposed[55] yet another structure $\left[(NO_2)_2\ CN(O)OONO\right]$. They claimed that no other proposed structure satisfactorily explained why tetranitromethane was an oxidising agent. They also claimed their structure satisfied the known reactions of tetranitromethane such as trinitromethane and guanidine formation.

Their arguments were summarily dealt with by Robinson[56]. He claimed that the small dipole moment of tetranitromethane was absolutely convincing evidence for a symmetrical structure. He also showed how the strong inductive effect of four nitro groups would mean that tetranitromethane should act as an electron acceptor and it was therefore not surprising that it should be an oxidising agent. He explained that there was not one labile nitro group in the molecule (as supporters of Schmidt's structure proposed) but that the removal of one nitro group entirely altered the environment of the carbon atom and it was not untoward that trinitromethane had different properties from tetranitromethane.

Three years later an electron diffraction study proved[57] Robinson correct. However as late as 1966 tetranitromethane

was sometimes being assigned the structure (39) of Willstätter and Hottenroth.

The ready elimination of a nitro group in the reaction of tetranitromethane with bases usually leads to the formation of nitroform salts; products of nitrosation or nitration of the base may be produced in conjunction with the salt formation.[47,58,59] Thus tertiary amines are oxidised to nitrosamines, e.g. N-dimethylaniline gives N-methylphenylnitrosamine and formaldehyde[59]. (For a review of this type of reaction as a means of preparing secondary amines see reference 60a and for a postulated but unlikely mechanism see reference 60b).

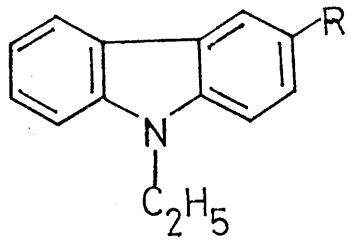
Although the reduction of tetranitromethane by phenylhydrazine proceeded beyond the nitroform stage to nitromethane[61] (and benzene and nitrogen), the action of 1,1,2-triphenylhydrazine on tetranitromethane gives[62] 4-(dinitromethylene)-2,5-cyclohexadien-1-one diphenylhydrazone (41). Recently free radical species derived from tetranitromethane were detected[63] when it was reduced in basic media. The reaction of tetranitromethane with 1,1-diphenylhydrazine has been reported[64] not to proceed to the nitromethane stage, as was the case with phenylhydrazine, but gave 1,1-dinitro-2,3-diazo-3,3-diphenylpropene (42). Evidence was cited for a free radical mechanism.

Tetranitromethane has been found[65] to react with tetraalkyl-2-tetrazines to give yellow crystalline solids characterised as dipolar ions of trialkyl-(β,β-dinitrovinyl)-2-tetrazines (43). The predominant resonance structure associated with these ions had the cationic portion derived from the

2-tetrazine and a 1,1-dinitro carbanionic portion stablised through charge separation and conjugation.

Tetranitromethane was investigated as a nitrating agent for reactive aromatic compounds by Schmidt and Fischer[58]. It was reported that high yields of mono nitrated aniline derivatives were obtained from reactions of anilines carried out in a pyridine-ethanol solution. Reaction of p-cresol under similar conditions[58] was reported to provide a 60 per cent yield of 4-methyl-2-nitrophenol. Tetranitromethane appeared to be a rather specific nitrating agent for phenols and aromatic amines, although under similar conditions, azulene gave[66] 1-nitroazulene in 81 per cent yield. Because of its specificity, tetranitromethane has been employed for the nitration of the tyrosyl side chains in proteins and peptides[67], although a reported drawback in this use is its capability of oxidising cysteine and the formation of products arising from crosslinking of tyrosine residues. (See reference 68 for a review of the nitration of proteins by tetranitromethane and reference 69 for a discussion of the mechanism with respect to the spatial constraints of the tertiary structure of the protein). It has been suggested that the nitration of aromatic compounds might proceed through the nitronium ion[67] or through nitrosation then oxidation[70].

Tetranitromethane acts as an initiator in the cationic polymerisation of N-vinylcarbazoles, acting as an electron acceptor.[71] Electron transfer to tetranitromethane results in dissociative capture $\left(\text{yielding } {}^{\bullet}NO_2 \text{ and } {}^{-}C(NO_2)_3\right)$. Bruice[69,72]



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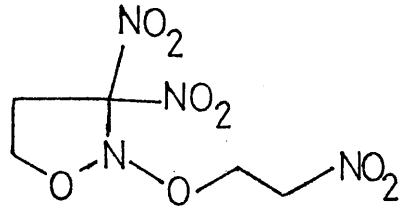

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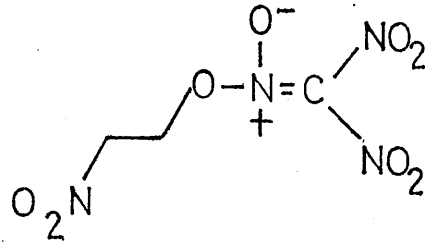


(46)

and co-workers have confirmed this process for the nitration of phenols in basic media. They showed that the rate of nitration was given by the equation:

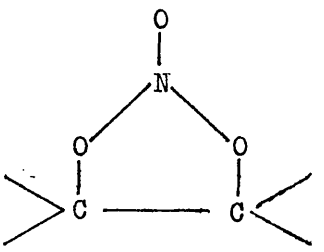
$$\text{rate} = k \left[\text{phenoxide ion}\right] \left[\text{tetranitromethane}\right]$$

All the products of the reaction were shown to arise from the reactions of a single intermediate, the formation of which was rate determining. The products isolated were the nitroform anion (ca. 100%), nitrite ion, nitrophenols and phenol coupling products (e.g. Pummerer's ketone) which could only have arisen via phenoxide free radical intermediates. They proposed initial charge transfer complex formation between phenoxide ion and tetranitromethane followed by the rate determining step of electron transfer to tetranitromethane and production of $\left[ArO^{\cdot} + \dot{N}O_2 + {}^{-}C(NO_2)_3\right]$. The presence of nitro radicals and radicals derived from trinitromethane have been detected[63] in solutions of tetranitromethane containing unsaturated substances and alkali or pyridine.

Without alkali or pyridine present nitration of aromatic compounds was very slow. Thermal reaction between tetranitromethane and N-ethylcarbazole (44; R = H) in enert solvent gave[73] 3-nitro-N-ethylcarbazole (44; R = NO_2) in 90% yield after 4 weeks at room temperature but with irradiation the reaction went quickly to give yields>90% in ca. 90 minutes. High yields of nitrocarbazoles were obtained only when the concentrations of carbazole and tetranitromethane were sufficient to give a concentration of charge transfer complex in excess of 2×10^{-2} molar, otherwise the tetranitromethane was destroyed by photochemical side reactions.

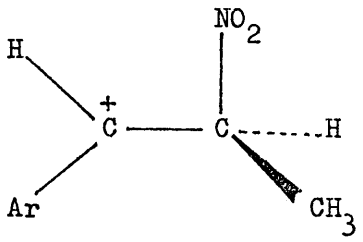
Further studies[74] have shown that the first stage of interaction of aromatic compounds with tetranitromethane in solution were charge transfer complexes of the Mulliken type. Under the action of a quantum of light total electron transfer of the electron from the aromatic compound to tetranitromethane took place.

Considerable confusion has existed in the literature as to the part played by tetranitromethane in its reactions with olefins. It was known to be an effective colour test reagent for unsaturation[39]. Macbeth[75] and co-workers concluded from spectroscopic evidence that an organic nitrite was developed transiently in the reaction whereas other workers[76] have advocated the presence of charge transfer complexes. Lagercrantz[77] et al. have shown that, with light inducement, free radicals are formed in the reaction of tetranitromethane with cyclohexene. Again it has been suggested[78] that a chemical bond might be formed as shown:



Notwithstanding these observations, most of the reactions of tetranitromethane with olefins are best explained by an ionic mechanism involving initial formation of a charge transfer complex followed by transfer of one of the nitro groups to the olefin, i.e. effectively attack on the olefin by the nitronium ion NO_2^+, to give a β-nitrocarbonium ion and the trinitromethane anion.

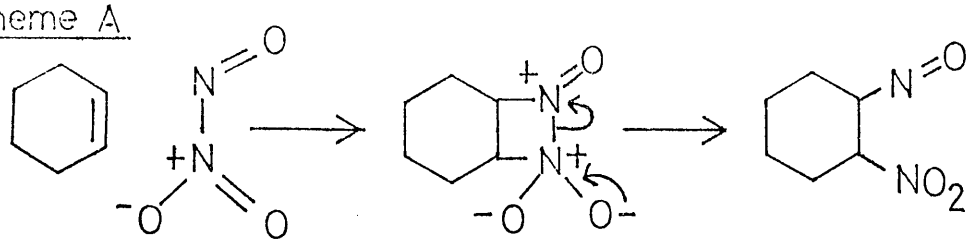
Schmidt[79] was the first to investigate the products of the reaction with olefins. He found that nitration occurred at double bonds next to an aromatic nucleus, e.g. from anethole, p-$H_3COC_6H_4CH{:}CHCH_3$, he obtained either p-$H_3COC_6H_4CH{:}C(NO_2)CH_3$ in an enert solvent or p-$H_3COC_6H_4CH(OCH_3)CH(NO_2)CH_3$ in methanol but he found no reaction with 3,4-methylenedioxyallylbenzene. These observations were in accord with an ionic intermediate of the type:



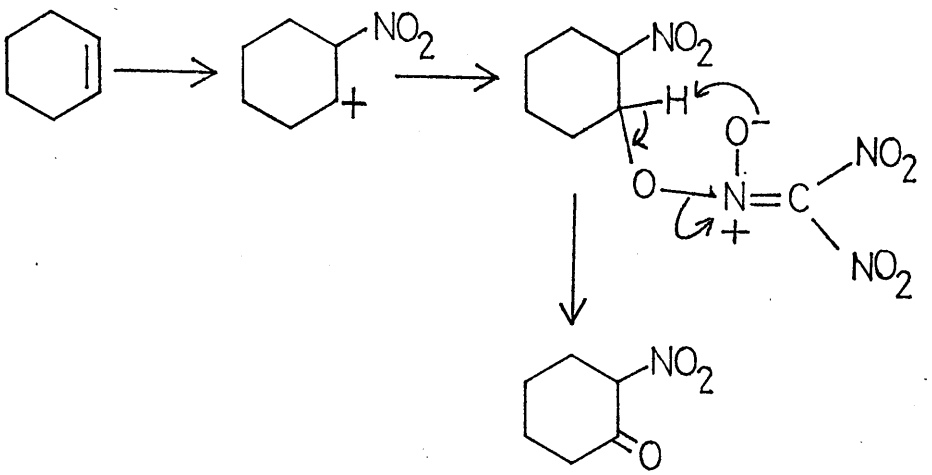
Later workers[80] investigated the products of the reaction of ethylene with tetranitromethane. They obtained in 49% yield the isoxazolidine (45) which on base hydrolysis gave 3,3-dinitropropan-1-ol. They rationalised the formation of the isoxazolidine (45) by postulating nitration and trinitromethylation through oxygen of the ethylene to give (46) which underwent 1,3 dipolar addition to another ethylene molecule.

This nitration-trinitrocyclomethylation reaction was extended to a series of olefins[81,82]. In all cases except cyclohexene and stilbene, 3,3-dinitro-2-(nitroethoxy) isoxazolidines were formed. The conversion of reactants was 90 - 98%, very little trinitromethane was formed and the use of radical or ionic initiators had no substantial effect on the yields of the products. In many cases the main reaction product was

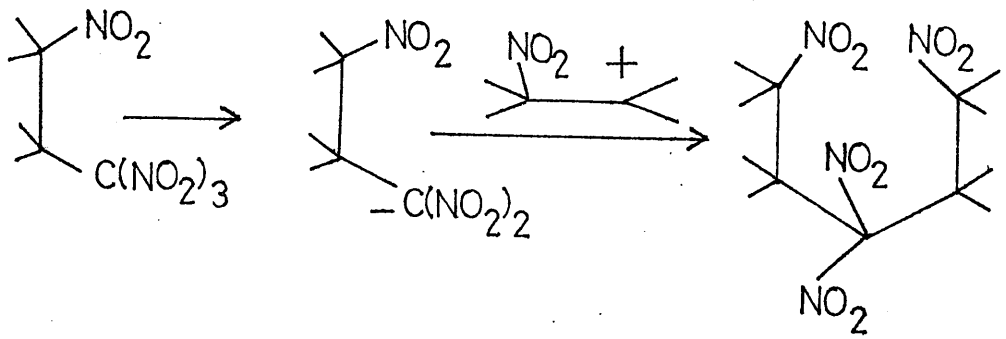
Scheme A

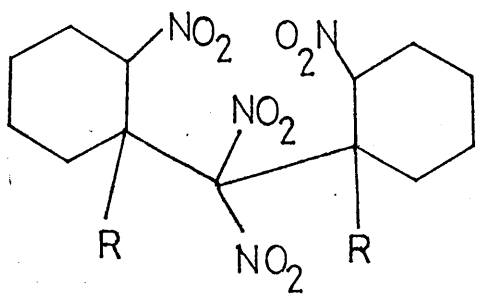


Scheme B

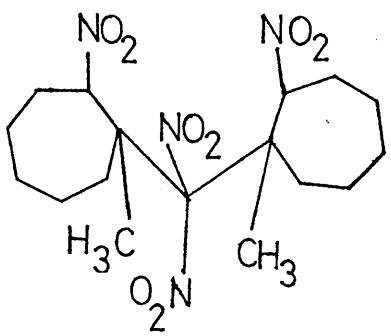


Scheme C

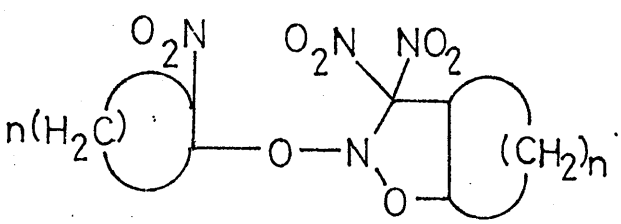



NO2
O2N
NO2
R
NO2
R

(47)


NO2
NO2
NO2
H3C
CH3
O2N

(48)


O2N
O2N
NO2
n(H2C)
O
N
O
(CH2)n

(49)

accompanied by small amount of 1-nitro-2-nitrosoalkanes. With stilbene 2-nitro-2-phenylacetophenone was obtained in 61% yield and cyclohexane gave adipic acid in 30 - 40% yield, an indication of the oxidising properties of tetranitromethane.

The reaction of tetranitromethane with cyclohexene had also been studied by Bradshaw[83] who obtained substantially different results. He obtained a water soluble solid in ca. 5% yield which readily isomerised to 1-nitro-2-nitrosocyclohexane. He also obtained 2-nitrocyclohexanone, 2-nitrosocyclohexanone, 1,2-dinitrocyclohexane and a compound which he identified as (47; R = H) all in ca. 15% yield. He postulated that the nitrocompounds arose from attack of N_2O_3 (from decomposition of tetranitromethane) as in scheme A. He also proposed that the ketonic products arose through scheme B. As a test of this proposal, 1-methylcyclohexene was treated with tetranitromethane and only 2 - 5% of ketonic products were produced, the main product (60 - 70%) being identified as (47; R = CH_3). 1-methylcycloheptene gave the corresponding compound (48) in 80% yield. The compounds (47) and (48) were postulated as having arisen from nitration followed by trinitromethylation through carbon, then decomposition as in scheme C.

It was rather strange that Bradshaw did not observe adipic acid in the cyclohexene reaction, particularly as he found that cyclooctene, presumably under the same reaction conditions gave suberic acid in 45% yield. Moreover his reaction mechanism was at odds with previous investigations (vide supra).

However it was only a year later that Torsel[84] showed that the structures (47) and (48) assigned by Bradshaw, were erroneous

and that the proper structures were (49) arising from nitration and trinitromethylation through oxygen followed by a 1,3-dipolar addition to another molecule of olefin to give the isoxazolidines (49) entirely analogous to those investigated by Altukhov[81,82] et al. from the reaction of tetranitromethane with other olefins. In 1971 the Russian workers[86] investigated the cyclohexene reaction with similar results as obtained by Torsel.

Schmidt's work on the reaction of tetranitromethane with olefins has been reinvestigated[85] by Swarc and co-workers. The reaction of 1,1-diphenylethylene was proven to go through the intermediate β-nitrocarbonium ion $(C_6H_5)_2\overset{+}{C}CH_2NO_2$, giving 1,1-diphenyl-2-nitroethylene in an enert solvent. No trinitromethylation and subsequent dipolar addition was reported. The work of Schmidt on the nitration of anethole has also been investigated. Schmidt did not report any products arising from trinitromethylation but the Russian workers reported[87] the formation of $p\text{-}CH_3OC_6H_4CH\ ON(O)C(NO_2)_2\ CH(NO_2)CH_3$ as the major product.

The confusion as to whether a trinitromethane anion would combine with the intermediate carbonium ion in the nitration of olefins led the Russians to investigate[88] the reaction with a series of substituted ethylenes. It appeared that steric factors exerted a substantial influence on the reaction. The intermediate β-nitrocarbonium ions formed from 1,1-diphenylethylene and triphenylethylene were sterically hindered and gave the nitroalkenes 1,1-diphenyl- and 1,1,2-triphenyl-2-nitroethylene. (Reaction 8; R = H and C_6H_5).

8) $RCH{:}\ C(C_6H_5)_2 \longrightarrow RCH(NO_2)\overset{+}{C}(C_6H_5)_2 \longrightarrow RC(NO_2){:}C(C_6H_5)_2$

The less hindered β-nitrocarbonium ions from β-methyl- and ββ-dimethylstyrene combined, through oxygen, with the trinitromethane anion (reaction 9; R = H and CH_3) to form the nitronic esters which, because of steric hindrance, did not form isoxazolidines by 1,3-dipolar addition with another olefin molecule, but decomposed to the α-nitroketones (Reaction 9; R = H or CH_3).

9) $R(CH_3)C{:}\ CHC_6H_5 \longrightarrow R-\underset{\displaystyle CH_3}{\overset{\displaystyle NO_2}{C}}-\overset{\displaystyle O}{\overset{\|}{C}}-C_6H_5$

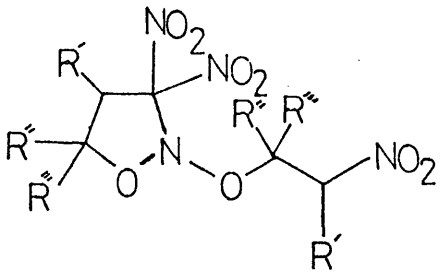
This is a characteristic reaction of nitronic esters[89] (Hass reaction). The isonitrosodinitromethane $\left[HON{:}\ C(NO_2)_2\right]$ formed in reaction 9) decomposed to nitrogen trioxide (N_2O_3) resulting in the formation of nitronitroso- derivatives of the starting alkenes (c.f. Bradshaws results with cyclohexene). Replacement of the hydrogen by methyl in the α-carbon atom of β-methylstyrene rendered the ester of aci-trinitromethane incapable of decomposing to the α-nitroketone. The structure of the stable ester obtained was confirmed by basic hydrolysis to the potassium salt of trinitromethane and 2,3-diphenyl-3-nitroprop-1-ene (Reaction 10).

10) $C_6H_5CH{:}\ C(CH_3)C_6H_5 \longrightarrow C_6H_5CH(NO_2)C(CH_3)[ON(O)C(NO_2)_3]C_6H_5$

$\downarrow$ KOH/EtOH

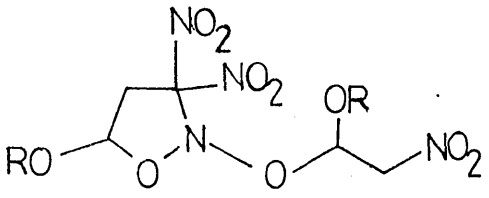
$C_6H_5\ CH(NO_2)C(C_6H_5){:}\ CH_2$

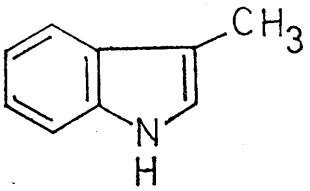
Those ethylenes with less bulky substituents on the double bond, e.g. alkyl groups (either symmetrically or asymmetrically placed) or a benzene nucleus and alkyl group (asymmetrically placed) gave substituted isoxazolidines by 1,3-dipolar addition of a second olefin molecule to the intermediate aci-trinitromethane ester formed (Reaction 11; $R'R''R'''$ = H, CH_3, C_6H_5 or iso-$C_3H_7CH_3CH_3$).

11) $R'CH{:}CR''R''' \longrightarrow$ 

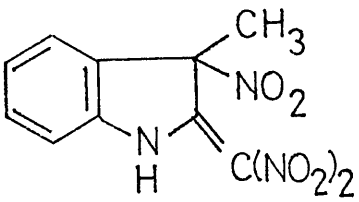
The relative stability of the β-nitrocarbonium ions did not appear to be important as p-$CH_3OC_6H_5CH{:}\ CH_2$ is trinitromethylated but $(p\text{-}CH_3OC_6H_5)_2C{:}\ CH_2$ is not and yields[90] the olefin $(p\text{-}CH_3OC_6H_5)_2C{:}\ CHNO_2$. (See reference 91 for similar reactions of this sort).

This reaction of nitration-trinitromethylation has been extended to dienes and unsaturated ethers. Ethers of the type $H_2C{:}\ CHOR$ were found[92] to give, under mild conditions (15°C for 3 days), isoxazolidines of the type:

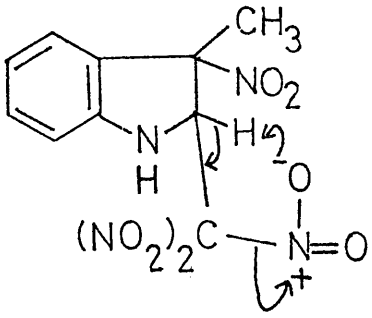




(50)

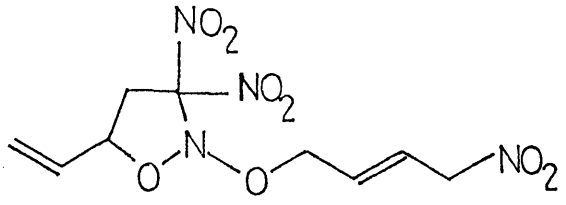


(51)



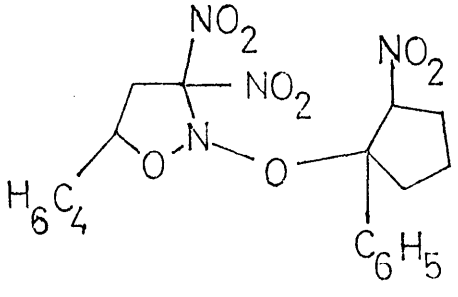
(52)

Butadiene gave[95] the isoxazolidine;



but the more sterically hindered dimethylpentadiene, $H_2C{:}\ CCH_3CH{:}\ C(CH_3)_2$ gave only $O_2NCH_2CHCH_3{:}\ C(CH_3)_2ON(O)C(NO_2)_2$ which did not cyclise[95].

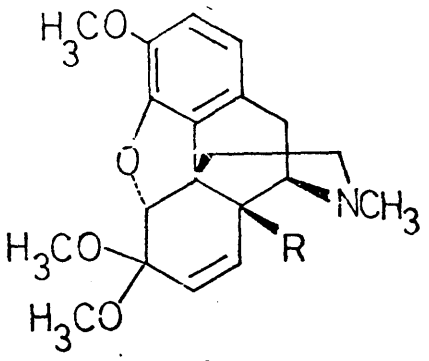
There are few reported cases of nitration followed by trinitromethylation through carbon in the reactions of tetranitromethane with olefins. When skatole (50) was nitrated[93] with tetranitromethane the major product was (51) which was postulated as having resulted from attack of the trinitromethane anion at C-2 to give (52), followed by loss of nitrous acid as shown. Dinitromethylation has also been observed in the reaction of tetranitromethane with 1,1,3-triphenylhydrazine and 1,1-diphenylhydrazine (vide supra). The reactions of tetranitromethane with 1,phenylcyclohexene and 1-phenylcyclopentene, which are sterically hindered for 1,3-dipolar addition reactions, gave[86] 1-phenyl-2-nitro-1-trinitromethylcyclohexane and 1-phenyl-2-nitro-1-trinitromethylcyclopentene. Strangely, the reaction of 1-phenylcyclopentene with tetranitromethane in the presence of hexene gave[86] the isoxazolidine:



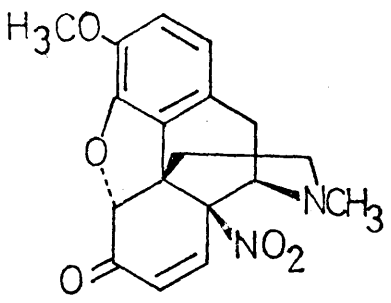
This suggested that the initially formed aci-trinitromethane ester was converted, as a result of a thermodynamically controlled reaction, into the tetranitroalkane.

Tetranitromethane also gave trinitromethyl and dinitromethyl compounds with the cyclic ethers tetrahydrofuran and tetrahydropyran. By a radical, but not a chain process, tetranitromethane reacted[94] with the cyclic ethers to give firstly 2-trinitromethyl-derivatives which, again by a radical process, gave 2-dinitromethyl-analogues. This might cast doubt on the postulated reaction mechanism for the nitration of skatole.

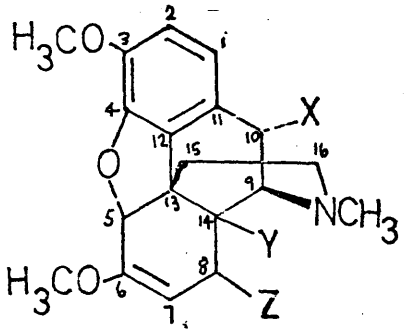
DISCUSSION



(21)



53



(54) At least one of

$X, Y, Z = NO_2$

A. THE REACTION OF TETRANITROMETHANE WITH THEBAINE

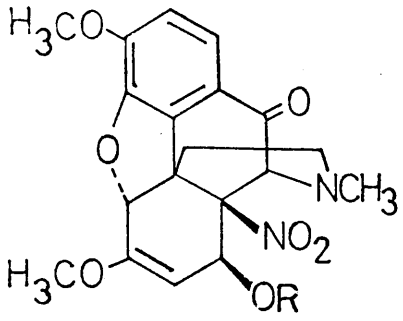
It was known[37] that the reaction of tetranitromethane with thebaine in methanol gave mainly thebaine nitroform $\left(\text{thebaine.H}^{+}\ {}^{-}C(NO_2)_2\right)$ as a bulky yellow precipitate. Left in solution were 14β-nitrocodeinone dimethyl ketal (21; R =NO_2) along with an unidentified nitration product, with similar chromatographic properties, and a trace of 14β-nitrocodeinone (53). By using alumina chromatography followed by fractional crystallisation the unknown compound has been isolated in a pure state.

Attempts to find the molecular weight and elemental composition of the compound were frustrated by its behaviour in the mass spectrometer and its defiance of all attempts at microanalysis. The highest peaks in the mass spectrum were of variable intensity (m/e 388, 389 and 390) and it was not found possible by varying the ionising voltage and temperature to obtain a convincing molecular ion. The base peak in the spectrum was at m/e 342.1340, corresponding to the ion $C_{19}H_{20}NO_5^{+}$. The base peaks in the spectra of 14β-nitrocodeinone, its dimethyl ketal and other 14β-nitro-derivatives prepared later arose from loss of $NO_2^{\bullet}$ from the molecular ion. If the same fragmentation pattern were assumed for the unknown compound it would lead to a molecular formula of $C_{19}H_{20}N_2O_7$ and a molecular weight of 388 a.m.u. Vapour phase osmometry gave molecular weight values of 412, 420 and 428 a.m.u. which precluded the possibility of a dimeric structure. Microanalysis gave variable results although on one occasion analysis for C, H, N, and O gave values (see experimental) not too far removed from those calculated for $C_{19}H_{20}N_2O_7$.

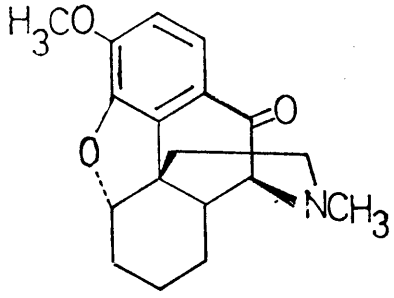
The i.r. spectrum of the unknown compound was very similar to that of 14β-nitrocodeinone dimethyl ketal (21; R = NO_2) with absorption at 1644, 1551 and 1350cm^{-1} indicating the presence of a double bond and a nitro group. The proton n.m.r. spectrum showed three methyl singlets in similar positions to those in the spectrum of thebaine, and two pairs of doublets at τ 4.58 and 5.78 (J = 3.5Hz) and τ 5.05 and 5.41 (J = 6Hz), each doublet integrating for one hydrogen. With the assumption that no skeletal rearrangement had taken place we considered that a structure such as (54) could best explain these data.

As the N-methyl resonance frequency was not much changed (7.46) from that of thebaine (7.60) it seemed probable that the C-10 substituent X was trans to the nitrogen bridge. Taking the doublets at τ 4.58 and 5.78 to arise from H-10 and H-9 respectively the assignment of X had to explain the very low chemical shift of H-10. The resonances at τ 5.05 and 5.41 were assigned to H-8 and H-7.

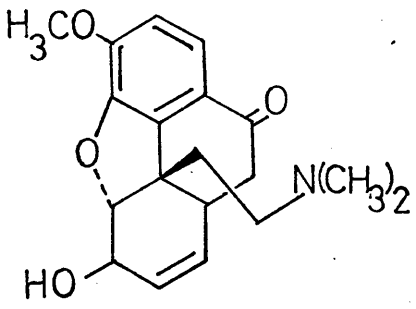
On treatment with base the unknown compound yielded a yellow crystalline substance with a molecular formula of $C_{19}H_{20}N_2O_7$ (by analysis and accurate mass measurement) which was assigned structure (55; R = H) on the following evidence. The u.v. spectrum of the compound strongly indicated a C-10 ketonic function on comparison with the published spectra of 10-oxodihydrodesoxycodeine (56) and 10-oxocodeine methine (57).


H3CO
O
O
NCH3
NO2
H3CO
OR

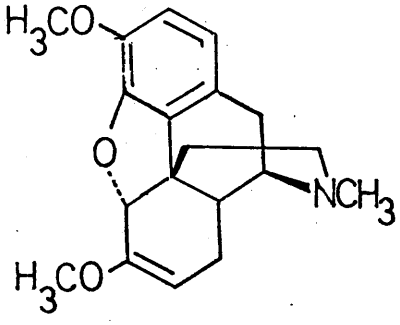
(55)


H3CO
O
O
NCH3

(56)


H3CO
O
O
N(CH3)2
HO

(57)


H3CO
O
NCH3
H3CO

(58)

TABLE 1

(57) Ref. 97		(56) Ref. 97		(55; R = H)	
λ n.m. max		λ n.m. max		λ n.m. max	
244	1.86×10^4	245	1.66×10^4	241	1.24×10^4
284	1.10×10^4	289	1.20×10^4	288	1.10×10^4
323	4.90×10^3	322	5.75×10^3	320	6.90×10^3

This part structure was supported by i.r. absorption at $1680cm^{-1}$, wide separation of the aromatic proton n.m.r. signals, and a singlet n.m.r. resonance for H-9.

The n.mr. spectrum also showed the presence of a secondary hydroxylic proton giving a doublet (τ 6.8) coupled (J = 7.5Hz), which was in turn, coupled to a signal at τ 5.41. The resonances at τ 5.41 and τ 5.61 were assigned to H-7 and H-8 respectively. The hydroxyl group was intramolecularly hydrogen bonded ($3585cm^{-1}$ with no change in dilution) and, assuming that nitration had occurred at C-14 as in the other products of the reaction, this hydroxyl was considered to be in the C-8 position, cis to the nitro group and hydrogen bonded to it. The cis stereochemistry was supported by the small coupling of 1Hz between H-7 and H-8, the dihedral angle being close to 90° when the C-8 substituent is β.

Further evidence for structure (55; R = H), and in particular for the assignment of the signals (H-7 and H-8) was gained from the proton n.m.r. of the acetylated product (55; R = CH_3CO). It was expected that the resonance assigned to H-8 should shift downfield by around 1 p.p.m. on acetylation and the resonance was indeed

found to move from τ 5.61 to 4.47 becoming a multiplet on acetylation. It was shown to be coupled to H-5 and H-7 (J_5 = 1.25, J_7 = 1H_z) but H-7 was not coupled to H-5. This long-range coupling was further proof of the enol ether part structure.

The ^{13}C n.m.r. spectra of the nitro-compound and (55; R = H) were obtained as well as those of thebaine, codeine, 8,14-dihydrothebaine (58) and 14β-nitrocodeinone dimethyl ketal (21; R = NO_2) as standards (See table 2). Assignments were made with the help of reference 96. A very recent publication[104] by Japanese workers has reported and assigned the ^{13}C n.m.r. spectra of thebaine, 8,14-dihydrothebaine and substituted codeinones. Their assignments are in agreement with ours except for C-10 and C-15 which are interchanged. They did not report any spectra of C-10 or C-15 functionalised compounds. Our assignments are upheld by the proton n.m.r. and u.v. spectra of C-10 functionalised derivatives reported in table 2 .

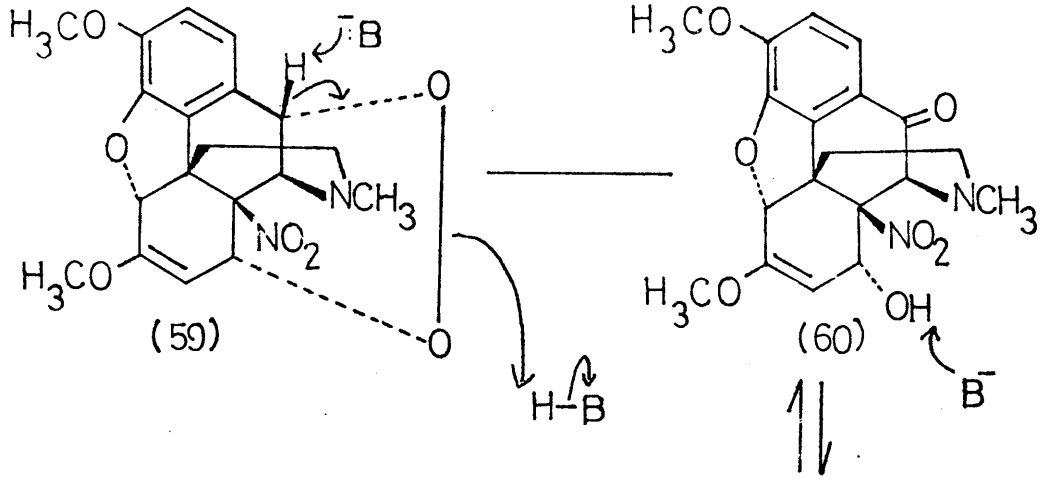
The ^{13}C n.m.r. spectrum of the base degradation product (55; R = H) was in accord with the proposed structure, the resonances assigned to C-6 and C-7 corresponding closely to those of C-6 and C-7 in dihydrothebaine (58). The spectrum of (55; R = H) showed all 19 resonances but the initially obtained spectrum of the unknown compound showed only 18 resonances. As the fragmentation ion in its mass spectrum had composition $C_{19}H_{20}NO_5$, the ^{13}C n.m.r. was re-run to reveal a very weak resonance for C-13. Another peculiar feature of the spectrum was the very wide separation of the olefinic resonances arising

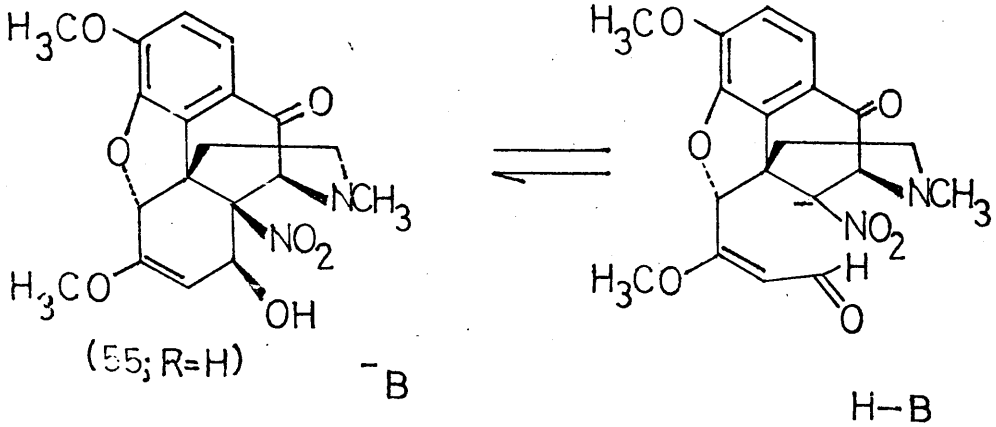
from C-6 and C-7 (160.15 and 90.15 p.p.m. downfield from T.M.S.). Further examination showed that C-10 was in a different environment to that of the other alkaloids. The C-8 resonance at 78.84 p.p.m. was not that of an olefinic carbon (c.f. thebaine and codeine) nor that of a methylenic carbon (c.f. dihydrothebaine) and so substitution at C-8 was indicated. With resonances of 78.84 and 76.26 p.p.m., C-8 and C-10 were thought to be linked to oxygen.

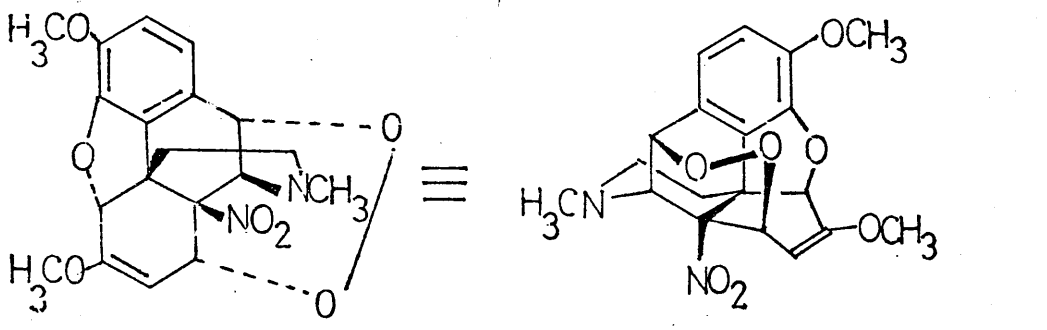
By plotting the apparent coupling constants in the ^{13}C n.m.r. spectrum against the off-resonance frequency and extrapolating to zero coupling it is possible to correlate a ^{13}C n.m.r. resonance with the resonance of the hydrogen on that carbon. It was assumed that an off-resonance frequency of 44800 Hz corresponded to the proton frequency in trimethylsilane. With this assumption, τ values were calculated for the three unambiguously identified methyl signals in the proton n.m.r. Comparison of these calculated values with the observed values gave a correction factor for the above assumption. This technique was used to show that the lowfield resonance in the proton n.m.r. of the unknown compound was that of H-10 and that the widely separated olefinic ^{13}C resonances were correctly assigned. The calculated values for H-5, H-7, H-8, H-9 and H-10 (τ 4.77, 5.45, 5.02, 5.80, and 4.65 respectively) agreed very well with the observed values (τ4.73, 5.41, 5.05, 5.78 and 4.58), thus providing further confirmation of structure (54).

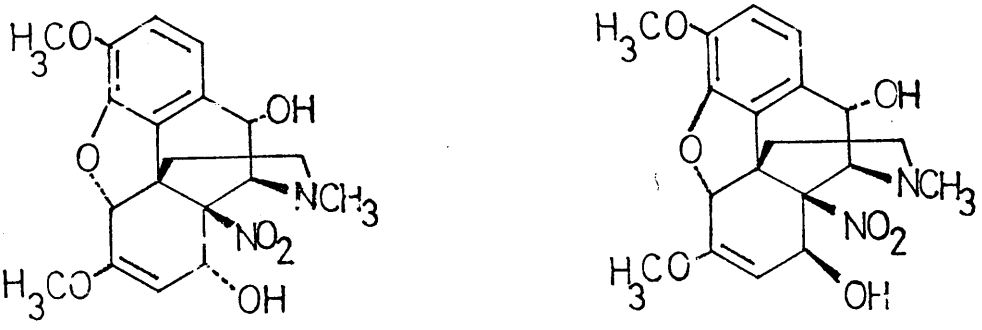
Consideration of various structures which, with mild base, would give (55; R = H) and which would satisfy the above spectral data, led us to believe that structure (59)should be considered for this mysterious nitro compound. The low chemical shift of H-10 could be explained by the peroxide ring constraining it to lie in

Scheme D


H3CO
B
H
O
NCH3
NO2
H3CO
(59)
H3CO
O
NCH3
NO2
H3CO
OH
(60)
H–B
B


H3CO
O
NCH3
NO2
H3CO
OH
(55; R=H)
B
H3CO
O
NCH3
NO2
H3CO
H
O
H–B


H3CO
O
NCH3
NO2
H3CO
O
OCH3
H3CN
O
O
O
OCH3
NO2


H3CO
OH
O
NCH3
NO2
H3CO
OH
(61)
H3CO
OH
O
NCH3
NO2
H3CO
OH
(62)

the plane of the aromatic ring. This structure also explained the similarity of the C-8 and C-10 resonances in the ^{13}C n.m.r. spectrum, and being isomeric with (55; R = H) was consistent with the observation that the mass spectra of (59) and (55; R = H) were very similar. Base could open the peroxide ring to (60) which could epimerise, via a ring-opened aldehyde, to (55; R = H) under basic conditions. Presumably the quasi-equatorial configuration of the 8β hydroxyl group and the strong hydrogen bonding between it and the nitro group makes the 8β-epimer more stable than the α-epimer (60). (Scheme D).

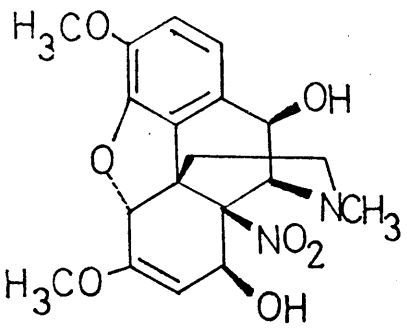
If the nitro compound did have structure (59) then it was believed that treatment with iodide should effect a reduction to the diol (61) and that subsequent treatment with base should give the C-8 epimer (62).

Accordingly, treatment of the compound with sodium iodide in acetic acid gave the diol (61) in good yield. The proton n.m.r. spectrum showed that the H-10 signal had moved upfield to τ4.97 and had now become a doublet. This upfield shift was as expected, as opening the peroxide ring should allow H-10 to move out of the plane of the aromatic ring. Double irradiation experiments showed H-10 to be coupled (J = 12.5Hz) to an exchangeable proton absorbing at τ5.54. Support for the stereochemistry at C-10 came from the absence of coupling between H-9 and H-10 as the dihedral angle is close to 90° when H-10 is cis to the nitrogen bridge. Moreover, if the hydroxyl group had been cis to the bridge the N-methyl resonance would have been expected to shift downfield, but this was not observed. The H-8

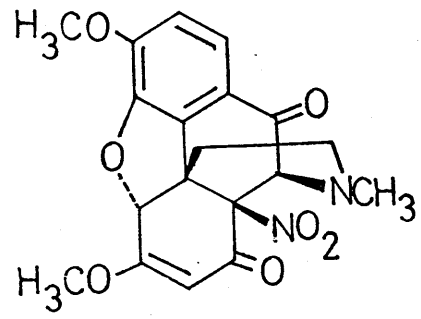
resonance was a doublet of doublets (τ 5.30, J = 9Hz, J = 6Hz) which collapsed to a doublet (J = 6Hz) on addition of D_2O. The C-8 hydroxyl group must be in the α configuration (i.e. OH trans to the nitro group) to explain the large coupling between H-8 and H-7 (vide supra). Further evidence for the 8α, 10α-dihydroxy configuration is that both hydroxyls are strongly intramolecularily hydrogen bonded (i.r. 3570 and 3500cm^{-1} and large n.m.r. coupling constants).

If the postulated peroxide structure (59) was correct then (61) should epimerise with base at C-8 to give (62). This must occur to rationalise the formation of (55; R = H) from the unknown compound. Treatment of (61) in ethanol with aqueous hydroxide did give the C-8 epimeric diol (62). In the n.m.r. spectrum of this compound H-7 and H-8 gave singlets (τ 5.32 and 5.78 respectively), indicating a H-7 to H-8 dihedral angle close to 90° and therefore that the C-8 hydroxyl was β i.e. cis to the nitro group. As there was now no hydrogen bonding between the two hydroxyls, H-10 gave a singlet (τ 4.82) as did H-9 (τ 5.94) which, with there being no significant change in the N-methyl resonance frequency, confirmed that the trans stereochemistry at C-10 had been retained. The infra-red spectrum showed the presence of free and intramolecularily hydrogen bonded hydroxyls (3610 and 3540cm^{-1}).

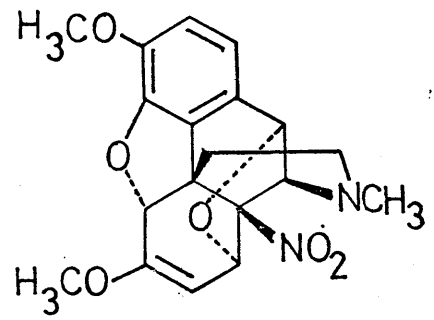
Sodium borohydride reduction of 10-oxo-derivatives of codeine was known[97] to produce the 10β alcohols. As a check on the argument used in assigning stereochemistry at C-10 in the diols (61) and (62), the base degradation product (55; R = H) was reduced with sodium borohydride to the corresponding 10β-diol (63).


H3CO
OH
O
NCH3
NO2
H3CO
OH

(63)


H3CO
O
O
NCH3
NO2
H3CO
O

(64)


H3CO
O
O
NCH3
NO2
H3CO

(65)

As expected, the N-methyl resonance was now downfield [τ 7.24, c.f. τ 7.49 for (61) and τ 7.45 for (62)] and coupling of 6Hz was now observed between H-9 and H-10 (τ 5.71 and 4.96). The resonances for H-7 and H-8 remained virtually unchanged at τ 5.55 and 5.71 indicating that no change in the stereochemistry of ring C had taken place. The i.r. spectrum showed both free and intramolecularily hydrogen bonded hydroxyl absorptions (3600 and 3560cm^{-1}) and the continued presence of the nitro group (1542cm^{-1}). The compound was unstable and was slowly oxidised back to (55; R = H). That 10β-hydroxy-derivatives were more readily oxidised than 10α-hydroxy-derivatives was originally commented on by Rapoport and workers[97].

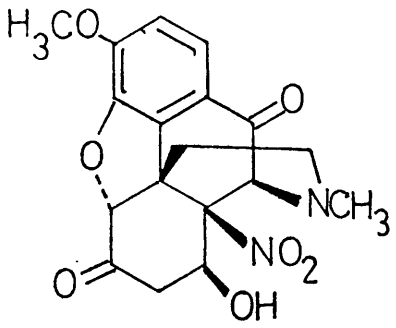
The diols (61), (62) and (63) were all oxidised to the same diketone (64) with mangenese dioxide, as was (55; R = H), as a check that no other sites in the molecule had been affected in the reductions and epimerisation. The i.r. spectrum showed absorption at 1691, 1623 and 1544cm^{-1}, indicating the presence of the unsaturated ketone groups, double bond and nitro group. The C-10 ketonic function was detected by wide separation of the aromatic protons, spectrum signals and the singlet resonance for H-9 (τ 5.56) in the proton n.m.r. spectrum (as well as the typical u.v. spectrum [λ_{max} 220n.m. (ε = 1.52 x 10^4), 238 n.m. (1.62 x 10^4), 280 n.m. (1.11 x 10^4) and 318 n.m. (5.11 x 10^3) c.f. Table 1]. Although this spectrum indicated the presence of the C-10 ketone it was anomalous in that Woodward's rules as modified by Fieser and Scott[98], predicted a maximum at 257 n.m. for the enone system, and the spectrum exhibited a minimum at 258 n.m. The presence of the adjacent nitro group was probably responsible for this

disparity. The ^{13}C n.m.r. spectrum was totally compatible with structure (64)(See Table 2).

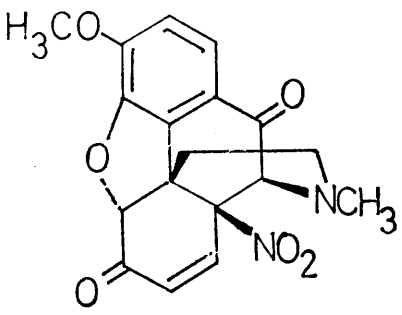
The reduction of the unknown compound with iodide (vide supra) was studied quantitatively to ascertain the number of equivalents being reduced and hence check the feasibility of the peroxide structure (59). Unfortunately the results were anomalous and consistently so. Assuming a molecular weight of 388 a.m.u. for the unknown compound; one mole was found to react with iodide liberating 0.37 moles of iodine measured by thiosulphate titration. Although iodometric analysis of peroxides is a standard procedure, in the presence of olefins or other functional groups it is unreliable owing to other interfering reactions. However the diol (61) was produced in high yield in this reaction, no explanation is offered for these irregular results.

Trialkylphosphines have been known since 1927 to react with peroxides, giving ethers, or diols in the presence of water, and the measurement of liberated trialkyl phosphine oxides has become a sensitive analytical technique[99]. It was thought that the reaction would give a more reliable estimation of the equivalent of the unknown compound and the resulting ether (65) should display interesting spectroscopic properties. In particular the H-10 n.m.r. signal was thought likely to move further downfield as ring contraction would pull it further into the plane of the aromatic ring.

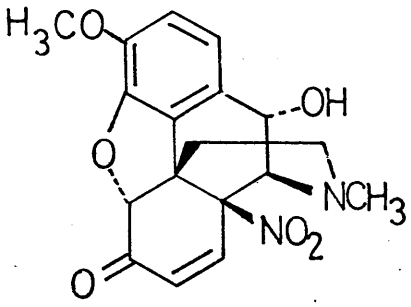
The compound (59) with an equimolar amount of triphenylphosphine gave the ether (65) in 84% yield and triphenylphosphine oxide in 98% yield. The proton n.m.r. spectrum of the ether (65) showed H-7 and H-8 had become magnetically equivalent and gave a two-proton singlet at τ 5.20. Unexpectedly, the H-10


H3CO
O
O
NCH3
NO2
O
OH

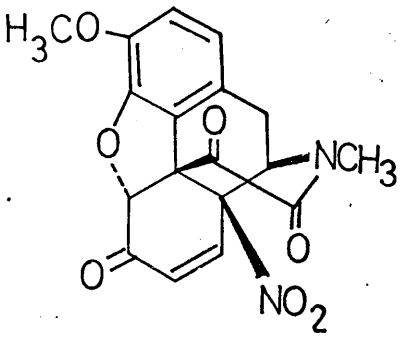
(66)


H3CO
O
O
NCH3
NO2
O

(67)


H3CO
O
OH
NCH3
NO2
O

(68)


H3CO
O
O
NCH3
O
O
NO2

(69)

resonance had moved upfield (τ4.95 from τ 4.58). Models showed the ring contraction moved H-10 further away from the aromatic ring as well as into the plane of the aromatic ring and it was more shielded as a result. The ^{13}C n.m.r. of (65) was extremely similar to that of the originally unknown compound (59), implying that no great change in the substitution pattern on the carbon skeleton had taken place (see Table 2). The ether (65) gave a correct elemental analysis for $C_{19}H_{20}N_2O_6$ and, since (59) quantitatively oxidised one molar equivalent of triphenylphosphine, this confirmed the composition $C_{19}H_{20}N_2O_7$ for (59).

The base degradation product (55; R = H) was stable to 5M-hydrochloric acid at room temperature (recoverable after one hour) but at elevated temperatures hydrolysed to the alcohol (66) and the diketone (67). The alcohol (66) was an unstable yellow oil which rapidly gave (67). The i.r. spectrum of (66) showed the presence of the aryl and aliphatic keto-groups (1683 and 1744cm^{-1}) and an intramolecularly hydrogen bonded hydroxyl group (3610 and 3450cm^{-1}). The wide separation of the aromatic resonances in the proton n.m.r. (τ2.56 and 3.10; J = 9Hz) confirmed the presence of the C-10 ketone. The C-8 hydroxyl proton gave a multiplet at τ6.42. The stereochemistry at C-8 could only be deduced by the strong intramolecular hydrogen bonding characteristic of the C-8β-hydroxyls in this series.

The diketone (67) was a stable crystalline solid. The proton n.m.r. showed two AB quartets for the aromatic (τ2.57 and τ3.14; J = 8.5 Hz) and olefinic (τ3.46 and τ 3.74; J = 10 Hz) protons. The u.v. spectrum was consistent with the C-10 ketone function [242 n.m. ($\varepsilon = 1.12 \times 10^4$), 293 n.m. ($\varepsilon = 8.47 \times 10^3$),

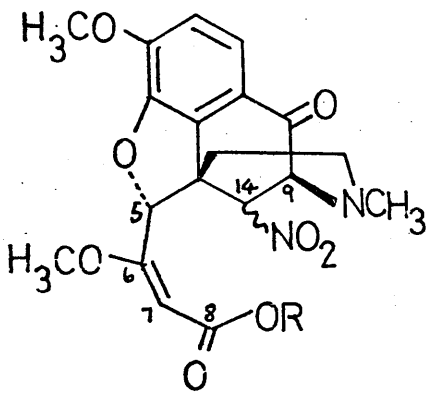
324 n.m. ($\varepsilon = 4.72 \times 10^3$) and the two ketone absorptions were resolved in the i.r. spectrum (1690 and 1686cm^{-1}).

The compound (67) was also prepared by acid hydrolysis, then oxidation, of the ether (65) obtained by triphenylphosphine reduction of (59). The acid hydrolysis of (65) gave (68), a yellow crystalline solid, in high yield - presumably by a concerted process. The i.r. spectrum showed the presence of a hydroxyl group (3610cm^{-1}) and a conjugated ketone (1698cm^{-1}). The C-7, C-8 double bond was indicated by the AB quartet for H-7 and H-8 in the proton n.m.r. spectrum (τ3.06 and τ3.83; J = 10Hz). H-10 gave a broad singlet (τ4.78) which sharpened with addition of deuterium oxide. The α-OH configuration at C-10 was again established by the N-methyl resonance which was virtually unchanged at τ7.42. Oxidation with manganese dioxide gave the corresponding C-10 ketonic compound (67), identical to that prepared by base catalysed hydrolysis of (59) then acid hydrolysis.

Attempts were made to oxidise the known 14β-nitrocodeinone (53) to compound (67) as confirmation of structure. With aqueous chromic acid, under the conditions used by Rapoport and co-workers[97] to oxidise codeine (2) and dihydrodesoxycodeine to their 10α-hydroxy-derivatives, the 14α-nitrocodeinone gave an insoluble salt which did not react further. Under more vigorous conditions the oxidation gave mixtures of starting material and intractable tars. Using chromium trioxide in acetic anhydride with trifluoroacetic acid a colourless crystalline compound (69) was isolated in low yield. The mass spectrum of this compound gave a molecular ion

of m/e 370.079 corresponding to the composition $C_{18}H_{14}N_2O_9$, i.e. the oxidation reaction had replaced four protons with two oxygens. The u.v. spectrum [208 n.m. (end absorption), 265 n.m. (ε = 3.76 x 10^3)] did not show the expected absorption for a C-10 ketone, neither did the i.r. spectrum (1756 and 1689cm^{-1}). The n.m.r. spectrum showed two AB quartets for the aromatic (τ3.15 and τ3.29; J = 9Hz) and olefinic (τ3.26 and τ3.80; J = 10Hz) protons. The most noticeable features of the n.m.r. spectrum were the singlet, low-field (τ4.04) resonance assigned to H-5, and the low-field resonance of H-9 (τ5.09). The H-9 resonance was a doublet of doublets, indicating the presence of two hydrogens on C-10. Thus, as the two methyl signals were still present (τ6.14 and τ6.78), the four protons which were lost in the reaction must have been those on C-15 and C-16, which made (69) the only tenable structure for the oxidation product. The proximity of H-5 to the C-15 carbonyl explains its low chemical shift and the amide function explains the low chemical shift of H-9. The i.r. absorption at 1756cm^{-1} may be ascribed to the C-15 keto-group although its frequency is high for a 6-membered ring. The presence of a nitro-group in the 14β-nitrocodeinone makes the nitrogen less basic, and less likely to be protonated, and hence C-16 more liable to oxidation in an acid medium. Oxidation at C-16 activates C-15 for further oxidation.

Other oxidising agents such as dichloro-dicyano-quinone, selenium dioxide, ceric ammonium nitrate and manganese dioxide proved of no use. Proof of structure was also attempted by reduction of the C-10 carbonyl group in (55; R = H) to a C-10 methylene group. Triethylsilane (Et_3SiH), which was known to



(70)

reduce aromatic carbonyls to methylenes[100], did not react at all. Reductive routes through the p-toluenesulphonylhydrazone could not be attempted owing to the persistent refusal of the compound (55; R = H) to form this derivative.

The compound (64), from the manganese dioxide oxidation of (55; R = H), did not give the expected u.v. spectrum for the ring C enone system (vide supra). The effect of base on this compound was therefore explored to confirm the presence of an α-nitro-ketone group. It was expected that base would leave ring C between C-8 and C-14 if the carbonyl was at C-8. The reaction of (64) with sodium hydroxide in methanol and ethanol gave compounds of composition $C_{20}H_{22}N_2O_8$ and $C_{21}H_{24}N_2O_8$ tentatively assigned structures (70; R = CH_3 and C_2H_5). Discussion will be confined to the ethoxy-derivative. The i.r. spectrum showed the presence of two carbonyl functions (1713 and 1682cm^{-1}) and a nitro group (1556cm^{-1}). The i.r. absorption at 1713cm^{-1} and the interconversion of the ethoxy- and methoxy- derivatives under the reaction conditions indicated the ester functionality. The u.v. spectrum gave evidence that the C-10 carbonyl was still present {237 n.m. ($\varepsilon = 2.29 \times 10^4$) 287 n.m. ($\varepsilon = 1.06 \times 10^4$), 3.23 n.m. ($\varepsilon = 4.91 \times 10^3$)}. The proton n.m.r. spectrum showed the usual low field AB quartet (τ2.95 and τ3.12; J =9Hz) for the aromatic protons and also a low-field, one-proton singlet at τ2.84. There were three other resolved, one-proton resonances; a singlet at τ4.93 removable by exchange with deuterioxide; a doublet of doublets at τ5.06 (J = 3.5 and < 1Hz) removable with deuterioxide; and a doublet at τ6.02 which collapsed to a singlet with deuterioxide. The proton resonating at τ5.06 was shown to be derived from the solvent by carrying out the reaction in an n.m.r. tube using ethanol OD

as solvent. The low-field singlet at τ2.84 led us to believe that a double bond had formed between C-9 and C-14 with concommitant opening of the nitrogen bridge. However the ^{13}C n.m.r. spectrum (see Table 2) showed there was only one double bond outside the aromatic ring, that of the enol ether part structure. Off-resonance decoupling showed there were eight quaternary, six tertiary, three secondary and four primary carbons in the molecule, which made structure (70; R = C_2H_5) the most likely on ^{13}C n.m.r. data.

In this structure the protons H-5, H-7 and H-14 could all, theoretically have exchanged with deuterioxide but H-9 could have collapsed from a doublet to a singlet with dueterioxide. We therefore assigned the proton resonances at τ5.06 and τ6.02 to H-14 and H-9 respectively. As a consequence, either H-5 or H-7 had to give the low-field resonance at τ2.84, which we considered to be abnormally low for either proton.

To elucidate which proton was resonating at τ2.84 we used the technique of single frequency off resonance decoupling of the ^{13}C n.m.r. spectrum to correlate the ^{13}C resonances with the resonances of protons on particular carbons (vide supra). As there was no ambiguity over the ^{13}C n.m.r. assignments for C-5, C-7, C-9 and C-14, the low field resonance at τ2.84 was shown to arise from H-5 (calculated τ2.79), the multiplet at τ5.06 from H-14 (calculated τ5.07), the singlet at τ4.93 was from H-7 (calculated τ4.97) and the doublet τ6.02 was from H-9 (calculated τ6.07).

The very low resonance of H-5 could only be explained by the ring C residue being very much hindered in rotation and being

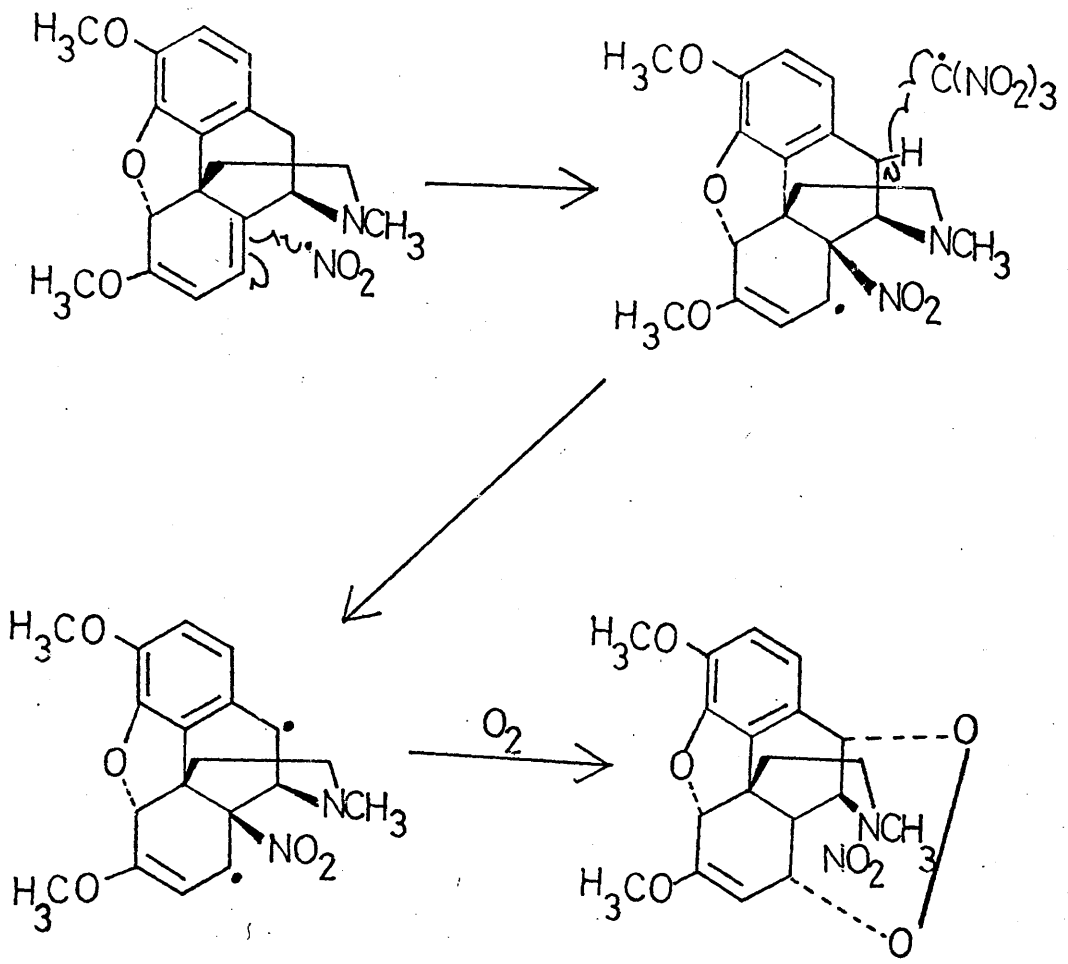
restrained to lie in such a position that H-5 is strongly deshielded by the ester carbonyl. However no change in the proton n.m.r. was observed on heating to 60°C.

The stereochemistry at C-14 could not be deduced directly from the proton n.m.r. spectrum as in either configuration, the H-9, H-14 dihedral angle was the same. However, if the nitro group was in the α position i.e. axial to ring C and equatorial to the nitrogen bridge, then the ring C residue at C-5 would encounter much more severe steric restraint and thus explain the abnormal H-5 resonance. The stereochemistry at C-14 in ring C cleaved derivatives has not been discussed in the literature[101].

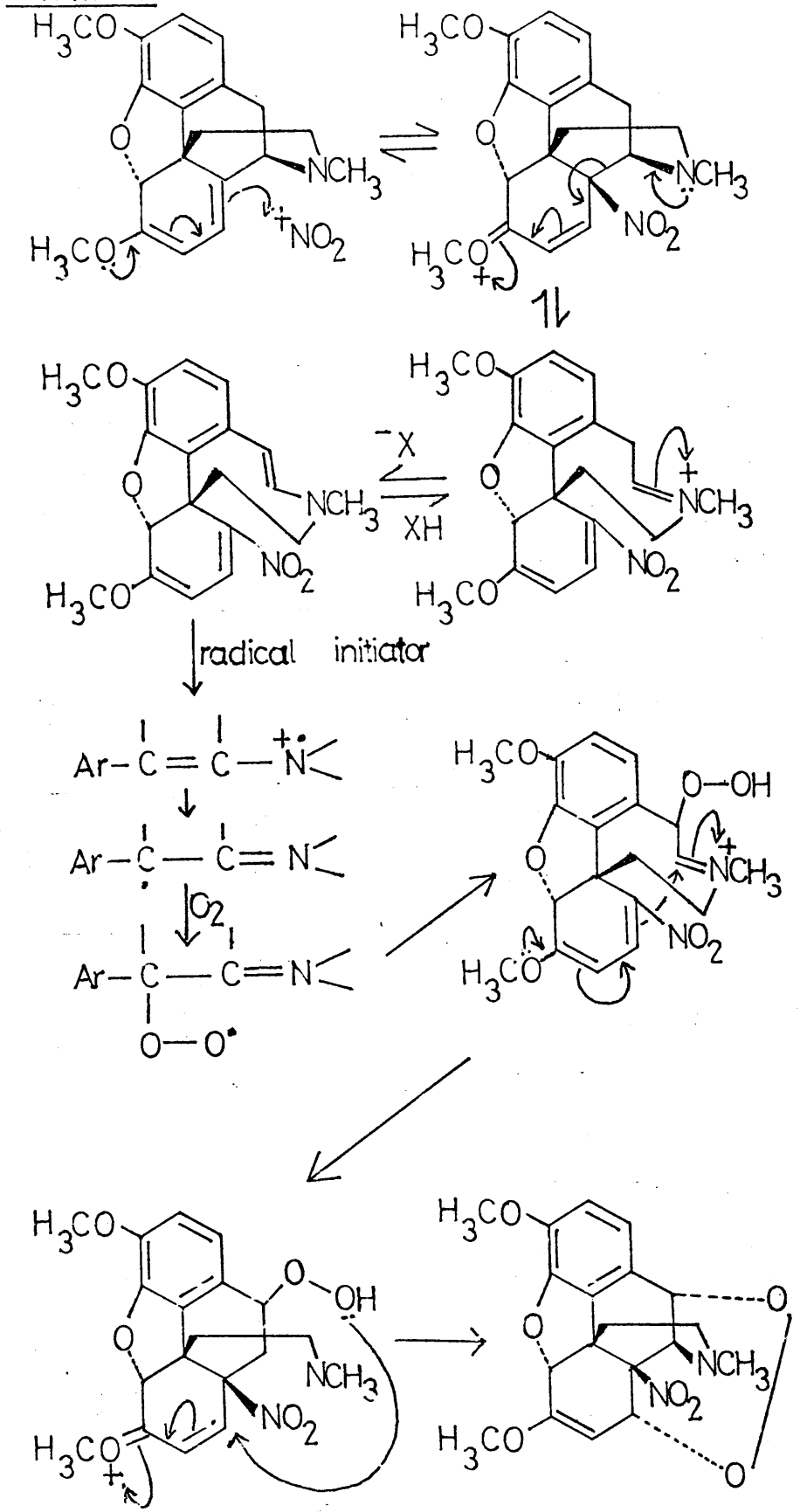
In order to obtain confirmatory evidence for the peroxide structure of (59) and to optimise its yield, the reaction conditions for its formation were investigated. The yields of the reaction were found to be very variable and hence conclusions were hard to draw. It was found that oxygen was essential for the formation of (59) but that very rigorous scavenging for oxygen was required before (59) was no longer produced. Conditions were found with the presence of the radical initiator 2,2'-azobis-2-methylpropionitrile, in which (59) was formed to the exclusion of 14β-nitrocodeinone or its ketals and it was shown that oxygen was not just acting as a radical initiator. The formation of (59) was, in the presence of radical initiators, independent of conditions of light or dark.

Formation of 14β-nitrocodeinone or its ketals was assumed to proceed via attack by the nitronium ion on the methoxy-diene

Scheme E


H3CO
O
NCH3
NO2
H3CO
C(NO2)3
H
O
NCH3
NO2
H3CO
H3CO
O
NCH3
NO2
H3CO
O2
H3CO
O
O
NCH3
NO2
H3CO
O

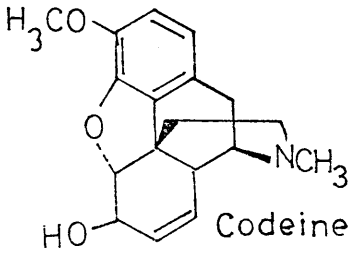
Scheme F



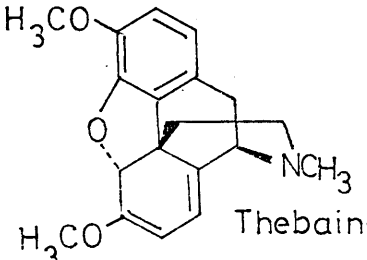
system of thebaine, but the above results suggested that (59) was formed by initial attack of the nitro-radical on the methoxy-diene system as in scheme E. However a mechanism whereby (59) was formed through the same ionic nitration step as 14β-nitro-codeinone was also possible (scheme F). No evidence has been obtained which would distinguish between these two pathways. However scheme E does not explain our observations that neopine, 14β-nitrocodeinone and its dimethyl ketal are not attacked appreciably by $C(NO_2)_4$ although they all possess benzylic methylene groups.

Other reagents for introducing a nitro-group at C-14 were investigated without success. Dinitrogen tetroxide gave an intractable gummy precipitate and nitryl chloride ($ClNO_2$) gave a multicomponent mixture, the proton n.m.r. of which suggested the presence of 14-chloro- as well as 14-nitro- codeinones and their dimethyl ketals, but the reaction was not investigated further as it offered no improvement on the tetranitromethane reaction. Nitric acid was known[102] to nitrate codeine at C-1 but the reaction with thebaine was investigated. Using two molar equivalents of fuming nitric acid in acetic acid a very low yield of 14β-nitrocodeinone was obtained. Also isolated from the reaction mixture was a small amount of material identified as 1-nitrothebaine. The proton n.m.r. of this compound was practically identical to that of thebaine except for the absence of the aromatic AB quartet. The one aromatic proton resonated at τ2.13. The reaction was not investigated further owing to the small yield of 14β-nitrocodeinone.

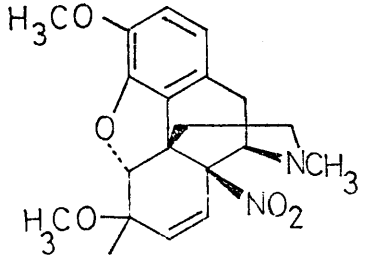
For a compilation of the proton n.m.r. spectra of 14β-nitro-compounds see Table 3.



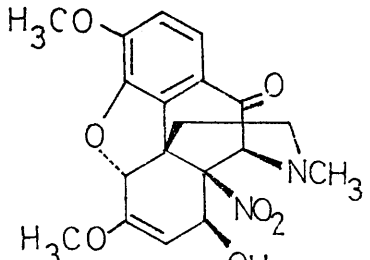
Codeine
(2)



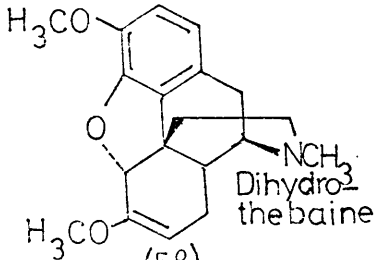
Thebaine
(4)



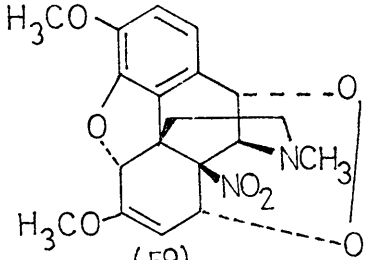
(21;R=NO_2)



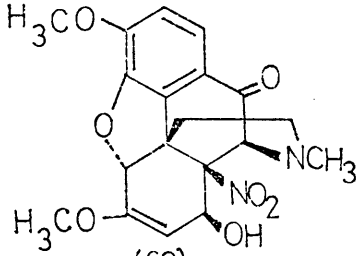
(55;R=H)



Dihydro-thebaine
(58)



(59)



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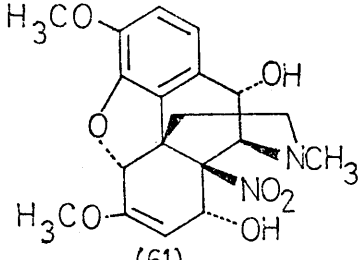

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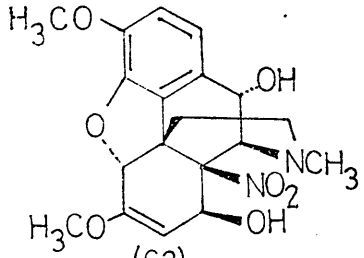

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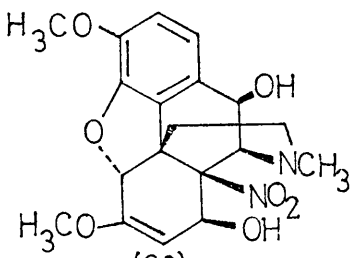

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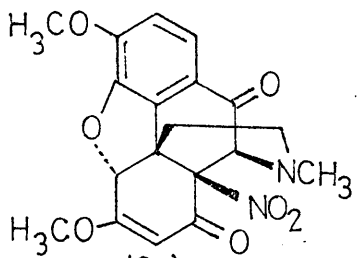

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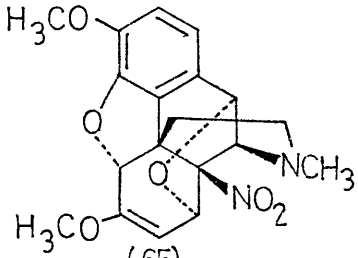

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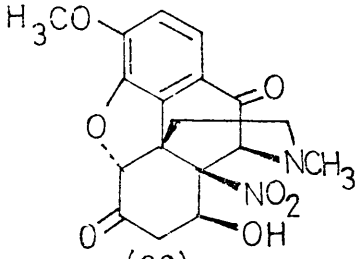

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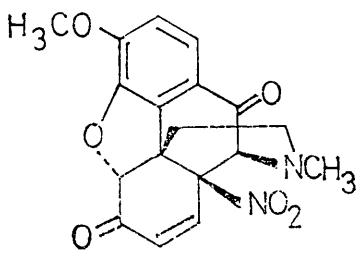

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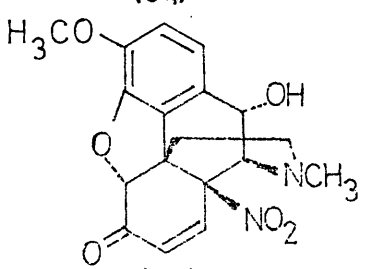

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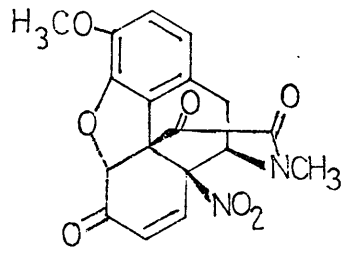


(69)

TABLE 2

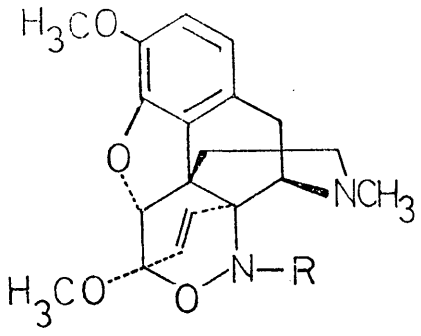
Chemical Shifts are quoted p.p.m. downfield from T.M.S.

	Codeine	Thebaine	Dihydro thebaine	(21; R=NO_2)	(55; R=H)	(59)	(65)	(64)	(70; R=Et)
C-1	119.31	119.06	118.40	118.63	119.15	120.11	118.66	120.10	118.61
C-2	112.91	113.10	113.78	115.53	114.56	114.05	114.67	115.33	114.54
C-3	141.20	142.68	143.00	142.58	143.67	142.00	144.00	142.70	145.61
C-4	146.31	144.71	145.17	144.18	150.92	146.16	196.47	150.47	149.26
C-5	91.38	89.47	88.47	90.79	87.46	86.08	85.82	86.07	86.76
C-6	66.43	152.42	152.22	195.85	153.00	160.15	155.82	170.35	165.74
C-7	133.25	95.85	97.98	138.26	197.80	90.15	97.35	101.54	96.19
C-8	128.10	113.32	23.64	128.26	67.76	78.84	76.93	183.19	165.99
C-9	58.80	60.85	59.01	62.81	67.08	62.21	67.41	66.84	67.73
C-10	35.75	37.06	35.76	130.66	190.06	76.26	76.28	188.62	190.48
C-11	127.10	127.64	126.92	125.03	124.05	124.07	127.78	124.58	124.57
C-12	131.00	133.30	129.21	131.57	134.81	132.66	132.5	133.88	136.34
C-13	42.96	46.07	42.49	47.38	46.33	44.21	46.09	46.38	47.41
C-14	40.70	132.36	39.80	89.30	93.96	87.36	89.90	94.47	82.94
C-15	20.44	29.61	20.31	22.08	29.91	28.87	26.37	28.95	31.44
C-16	46.37	46.07	46.46	45.56	45.26	45.25	46.35	45.38	45.90
OCH_3	56.26	56.45	56.52	57.10	56.61	56.22	56.55	57.05	56.70
OCH_3	–	54.81	54.24	49.69	55.18	55.26	55.12	56.67	55.70
OCH_3	–	–	–	48.87	–	–	–	–	–
NCH_3	42.96	42.37	43.02	42.96	43.25	42.27	43.04	43.34	43.32
CH_2CH_3	–	–	–	–	–	–	–	–	60.30
CH_2CH_3	–	–	–	–	–	–	–	–	14.26

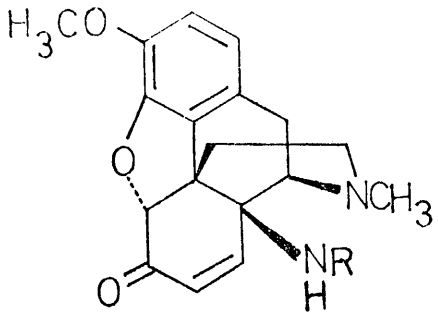
TABLE 3

Proton n.m.r. chemical shifts (τ)

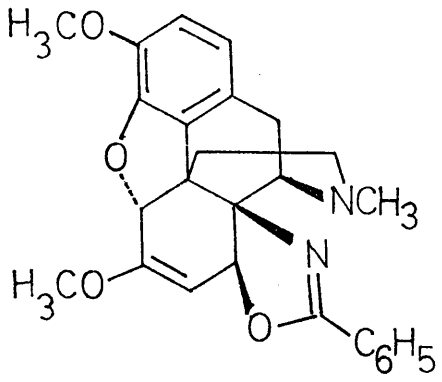
	(55)	(59)	(61)	(62)	(63)	(64)	(65)	(66)	(67)	(68)	(69)	(70; R=Et)
H-1 and H-2	2.52 3.08	3.03 3.16	2.96 3.13	3.05 3.08	2.96 3.17	2.54 3.08	3.22	2.56 3.10	2.57 3.14	3.03 3.16	3.15 3.29	2.59 3.12
H-5	4.64	4.73	4.82	4.74	4.84	4.64	4.66	4.92	4.78	4.84	4.04	2.84
H-7	5.41	5.41	5.11	5.32	4.96	4.39	5.20	–	3.46	3.83	3.26	4.93
H-8	5.61	5.05	5.30	5.78	5.71	–	5.20	7.22	3.74	3.06	3.60	–
8-OH	6.81	–	4.8/5.4	7	–	–	–	6.42	–	–	–	–
H-9	5.78	5.78	6.04	5.94	5.71	5.56	5.30	5.76	5.92	5.87	5.09	6.02
H-10	–	4.58	4.97	4.82	–	–	4.95	–	–	4.78	–	–
10-OH	–	–	5.54	7	–	–	–	–	–	–	–	–
3-OCH_3	5.99	6.13	6.09	6.16	6.11	6.02	6.11	5.98	6.08	6.10	6.14	6.06
6-OCH_3	6.38	6.45	6.44	6.53	6.46	6.23	6.51	–	–	–	–	6.58
NCH_3	7.48	7.46	7.49	7.45	7.24	7.48	7.41	7.53	7.51	7.42	6.78	7.61
H-14	–	–	–	–	–	–	–	–	–	–	–	5.06



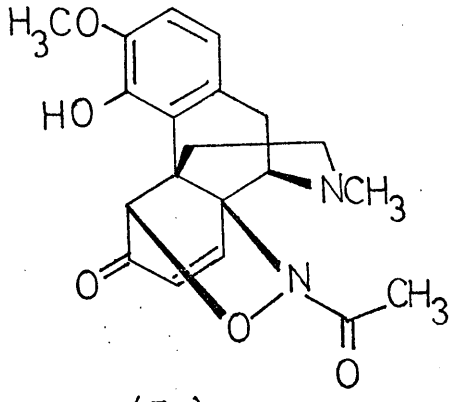
(11)



(15)

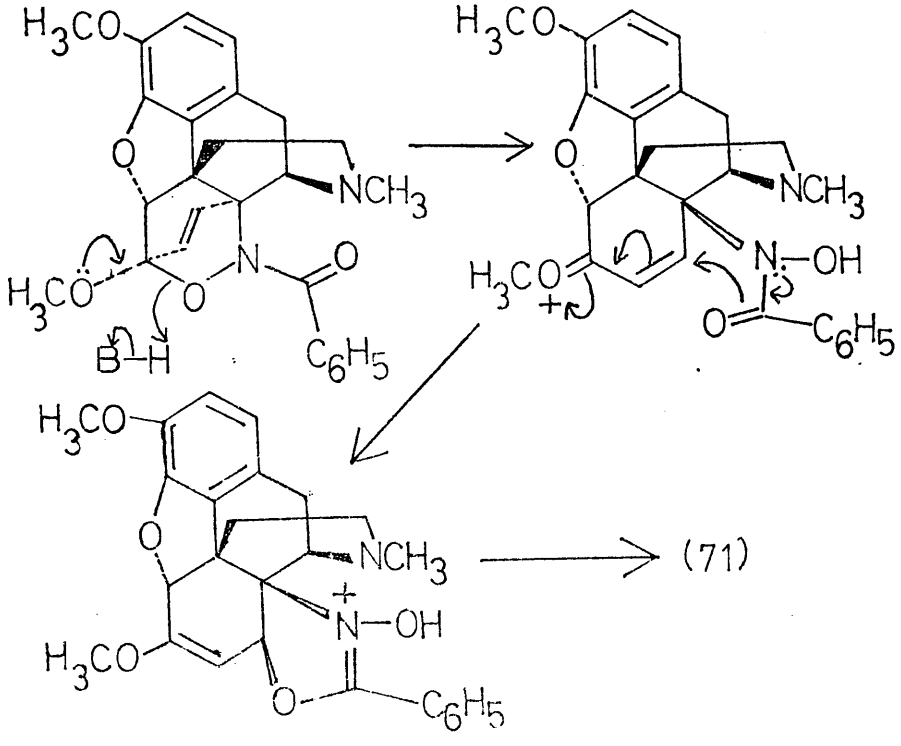


(71)



(72)

Scheme G



B. SOME REACTIONS OF 14β-AMINO-DERIVATIVES OF CODEINE AND THEBAINE.

It was known[25] that catalytic hydrogenation of the adduct (11; R = CH_3CO) formally derived from thebaine and nitroso-carbonylmethane, did not reduce the oxygen-nitrogen bond but the 7,8-double bond. Replacement of the methyl group by phenyl was thought likely to make the oxygen-nitrogen bond more susceptible to reduction and give a new route to 14β-aminocodeinones. (Previous preparations[25] of (11; R = C_6H_5CO) utilised tetraethylaminonium periodate as an oxidant for the benzohydroxamic acid, because of its solubility, but we found sodium periodate to work satisfactorily providing the reaction was well stirred). All attempts at catalytic reduction of the phenyl compound (11; R = C_6H_5CO) failed to produce any reaction whatever. As an alternative procedure we employed zinc in acetic acid and isolated a colourless crystalline compound identified as (71).

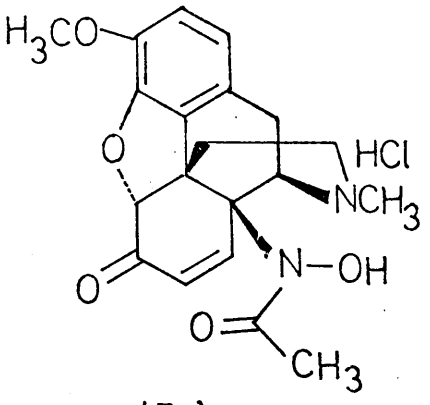
Weak absorption in the i.r. spectrum of (71) at 1681cm^{-1} showed the presence of a C=N linkage and absorption at 1682cm^{-1} the presence of a double bond. The mass spectrum (m/e = 430) indicated the loss of oxygen from the starting material and the proton n.m.r. confirmed that all three methyl groups were still present. The pattern of the proton n.m.r. spectrum was very reminiscent of that found in the 8β-hydroxy-14β-nitro- compounds (from the reaction of thebaine with tetranitromethane) and suggested a similar substitution pattern in ring C. H-5 gave a singlet (τ5.06) and H-7 and H-8 an AB quartet (τ5.21 and 5.41; J = 3Hz). This coupling of 3Hz was larger than that normally

seen between H-7 and H-8α, and resulted from distortion of ring C by the fused oxazoline ring.

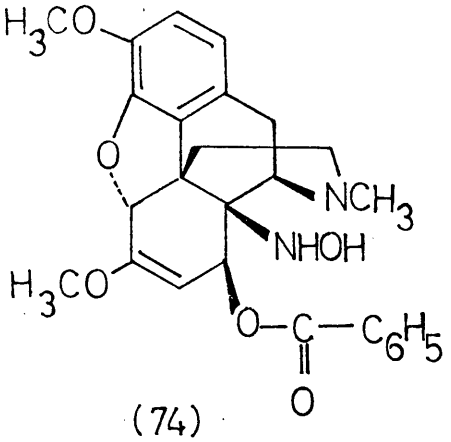
The oxazoline ring was envisaged as resulting from reduction of the protonated form of its N-oxide, which was formed by a reversible, acid-catalysed rearrangement of the starting adduct (scheme G). Further evidence for this rearrangement's taking place before the reductive step, was obtained from acid hydrolysis studies on the adduct (vide infra). The adducts (11; R = CH_3CO and R = C_6H_5: CHCO) did not undergo this reaction giving only low yields of thebaine or starting material depending on the severity of the conditions. Thebaine was a byproduct in the formation of the oxazoline (71) from (11; R = C_6H_5CO).

Further chemical evidence was sought for the oxazoline structure of (71) from acid hydrolysis. Methanolic hydrochloric acid cleanly hydrolysed (71) to N-benzoyl-14β-aminocodeinone (15; R = C_6H_5). This was identified by its i.r. spectrum (3360, 1682 and 1658cm^{-1}) which indicated the presence of the enone and secondary amide part structures and by its proton n.m.r. spectrum, which showed loss of the 6-methoxy signal and the presence of one exchangeable proton (τ2.35). The olefinic protons (H-7 and H-8) appeared as a two proton singlet at τ3.79, consistent with the spectra of known N-acyl-14β-aminocodeinones prepared[37] by R. M. Allen.

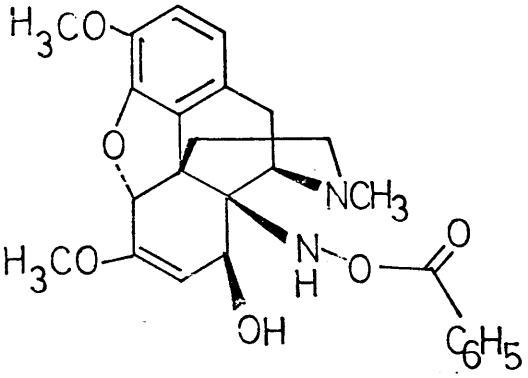
In a further attempt to reduce the oxygen-nitrogen bond, the adduct (11; R = CH_3CO) was treated with stannous chloride in methanol and hydrochloric acid. This gave a product, upon work up with sodium bicarbonate, whose n.m.r. spectrum showed loss of


H3CO
O
HCl
NCH3
O
N–OH
O
CH3

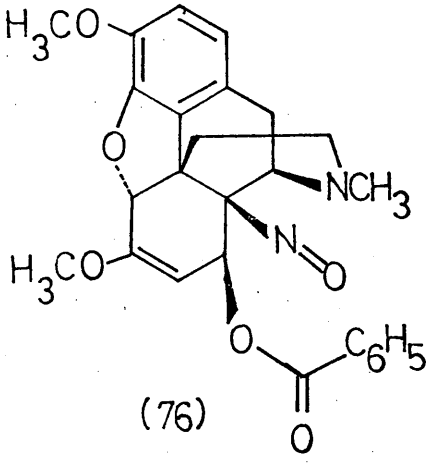
(73)


H3CO
O
NCH3
NHOH
H3CO
O–C–C6H5
O

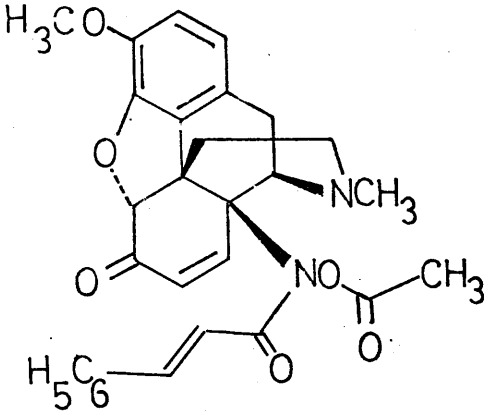
(74)


H3CO
O
NCH3
H3CO
N
H
O
O
OH
C6H5

(75)


H3CO
O
NCH3
N
O
H3CO
O
C6H5
O

(76)


H3CO
O
NCH3
O
NO
CH3
O
O
H5C6

(77)

the 6-methoxy signal and whose i.r. spectrum showed the presence of an enone ($1690cm^{-1}$) system and an acetyl group ($1675cm^{-1}$). The compound was shown to be identical to (72), previously prepared by the action of sodium methoxide on (73; R = CH_3), the previously reported acid hydrolysis product of (11; R = CH_3CO).[25]

Before it was realised that this reaction was merely an acid catalysed hydrolysis the adduct (11; R = C_6H_5CO) was subjected to the same reaction conditions. The product of this reaction surprisingly did not exhibit enone absorption in the infra-red and had a 6-methoxy signal in the proton n.m.r., 0.5 p.p.m. down-field (τ6.50) form that in the starting material, and also twodeuterium oxide exchangeable protons at τ4.91. The carbonyl absorption in the i.r. spectrum indicated a benzoyloxy part structure. The similarity between the proton n.m.r. of this structure and that of (55; R = CH_3CO) persuaded us that structure (74) was correct. The signal for H-8 was downfield (t4.52) and coupled to H-5 (τ4.99; J = 1.4Hz) and H-7 (τ5.41; J = 1.8Hz). By the same argument as in the case of (55; R = CH_3CO) the configuration at C-8 of the benzoyloxy function had to be β. This compound (74) could be hydrolysed to the previously reported[25] hydrolysis product, the hydrochloride of (15; R = OH), from the adduct (11; R = C_6H_5CO). The omission of stannous chloride from this reaction gave similar yields of (74).

It was hard to visualise a reaction mechanism to account for the benzoyloxy function at C-8 in (74) which did not utilise an oxazoline like intermediate, but the phenyloxazoline (71) under the conditions of this reaction was hydrolysed, as before, to N-benzolyl-14β-aminocodeinone (15; R = C_6H_5).

The yield of (74) from the hydrolysis of the adduct (11; R = C_6H_5CO) was variable and occasionally a different product, shown to be (75), was obtained. Elemental analysis showed this to be an isomer of (74). The i.r. spectrum showed absorption due to a strongly hydrogen bonded hydroxyl (3440cm^{-1}), a hydrogen on nitrogen (3230cm^{-1}) and a high carbonyl absorption at 1735cm^{-1}. Normal benzoates absorb around 1720cm^{-1} but benzozloxy groups on nitrogen have been reported as having high frequency absorption[103] (e.g. $C_6H_5CO_2NEt_2$ absorbs at 1740cm^{-1} (liquid)). The n.m.r. spectrum showed the N-H proton as an exchangeable singlet at t1.56. H-5 gave a singlet with fine coupling to H-8 while H-7 (τ5.39) gave a doublet with coupling to H-8 (τ6.04) which gave a broad singlet sharpening with deuterium oxide. This compound (75) was rather unstable, especially in solution, slowly turning pink and no interpretable mass spectrum was obtained.

14β-Hydroxyaminocodeinones were known[32] to acylate on oxygen and so, to check whether the i.r. absorption of 1735cm^{-1} was reasonable for (75), 14β-hydroxylaminocodeinone (15; R = OH) was treated with benzoyl chloride to give 14β-benzoyloxyamino-codeinone (15; R = $C_6H_5CO_2$). This compound had the expected proton n.m.r. with one exchangeable proton at t0.80 and an AB quartet for H-7 and H-8 (τ3.41 and 2.78; J = 10Hz). The i.r. absorption showed the presence of a hydrogen on nitrogen (3200cm^{-1}) but, paradoxically, the carbonyl absorption was lower than expected at 1723cm^{-1}. This compound, like (75) was unstable and slowly turned pink.

The occasional formation of (75) in the acid hydrolysis of the adduct (11; R = C_6H_5CO) indicated it was an artifact from the

basic work-up. However, initial attempts to isomerise (74) to (75) with mild base (e.g. triethylamine) were unsuccessful. Eventually (74) was found to isomerise to (75) in high yield in an ethyl acetate-ethanol-water emulsion in the presence of sodium bicarbonate; exactly the conditions occasionally encountered in the work-up of the acid hydrolysis of the adduct (11; R = C_6H_5CO).

As (74) had a similar substitution pattern on ring C as the 14β-nitro series of compounds (vide supra), an attempt was made to oxidise (74) to the corresponding nitro compound. With both manganese dioxide and tetraethylammonium periodate an unstable turquoise compound was formed. This was assigned the nitroso structure (76). Crystallised from benzene the compound had composition $C_{26}H_{26}N_2O_6$ by elemental analysis but the highest peak in the mass spectrum at m/e 478.172 corresponded to the ion of composition $C_{26}H_{26}N_2O_7$. No peak was seen at m/c 462, which would correspond to the molecular ion of the nitroso compound (76) and the fragmentation pattern was similar to that of a nitro compound. However the i.r. spectrum showed no absorption corresponding to a nitro group and the u.v. spectrum was indicative of a nitroso group $\left(681 \text{ n.m. } (\varepsilon = 46) \right)$.

The compound (55; R = C_6H_5CO) was prepared from (55; R = H) as a model compound for n.m.r. studies and, as expected, its n.m.r. spectrum was very similar to that of the previously prepared and discussed acetoxy compound (55; R = CH_3CO) and had some similarity with that of (76). In (55; R = C_6H_5CO), H-5, H-7 and H-8 resonated at τ4.68, τ5.54 and τ4.35 respectively with fine coupling.

In the nitroso compound (76), H-5, H-7 and H-8 resonated at τ4.92, τ5.90 and τ4.21 respectively with fine coupling between H-5 and H-8 and between H-7 and H-8. This similarity was confirmatory evidence for the substitution pattern on ring C. In the n.m.r. spectrum of (76) there was also a one-proton doublet of doublets (J = 5.5 and 1Hz) at τ4.41. No similar signal was seen in the spectrum of the nitro-compound (55; R = C_6H_5CO). Irradiation at τ6.7 resulted in the multiplet collapsing to a fine doublet (J 1Hz) which suggested that this signal was due to H-9. A 14β-nitro function was never observed to bring H-9 so low, but H-9 did appear as a broad doublet at τ5.20, τ5.08 and τ5.06 in the adducts (11; R = CH_3CO, C_6H_5CO, and C_6H_5:CHCO). This was taken as good evidence that the functionality at C-14 was not nitro but nitroso. The anomalous mass spectrum of (76) may be due to a trace of the nitro compound as an impurity and the nitroso-compound not giving a molecular ion or it may be due to a gas phase reaction in the mass spectrometer. Unfortunately, attempts to obtain a value for the molecular weight by vapour phase osmometry were inconclusive owing to concentration variation of the result. A value of 412 was obtained for a 16.8g/litre solution and a value of 565 for a 2.29g/litre solution.

Attempts made to further oxidise (76) to the corresponding nitro-compound and to reduce it to the corresponding amino-compound failed, due to its extreme instability in solution.

The different behaviour of the adducts (11; R = CH_3CO and C_6H_5CO) under acid hydrolysis led us to prepare the adduct (11; R = C_6H_5CH:CHCO) and investigate its behaviour with acid.

This adduct was prepared in an entirely analogous manner to the other two and had similar spectral properties. It was found to give, under both vigorous and mild acid conditions, the hydrochloride (73; R = $C_6H_5CH{:}CH$). The proton n.m.r. spectrum of this compound was very similar to that of (73; R = CH_3) prepared from the adduct (11; R = CH_3CO) for comparison purposes. The spectrum (DMSO-d_6) showed hydroxyl proton absorption at τ-1.48 and signals for H-8 and H-7 as an AB quartet at τ3.07 and τ3.80. H-9 resonated at low field (τ4.57) because of the quaternised nitrogen and H-5 resonated at τ4.98. The corresponding resonances in (73; R = CH_3) were τ-1.11, τ3.16, τ3.84, τ4.70 and τ5.01.

The n.m.r. spectrum of the free base of (73; R = $C_6H_5CH{:}CH$) was different in that the H-7 and H-8 signals became a singlet at τ3.81. This was probably due to a different orientation of the side chain. The effect of the orientation of this bulky side chain was investigated by forming the acetylated compound (77). The i.r. spectrum showed the expected high absorption of the acetoxy-nitrogen carbonyl at 1804cm^{-1} and the conjugated carbonyl absorption at 1693cm^{-1}. At 30° the proton n.m.r. spectrum of (77) was poorly resolved with H-8 appearing as a broad singlet at τ3.84 and with a broad envelope of ten protons between τ7.3 and 8.0. However at 60° a sharp spectrum was obtained showing H-7 and H-8 as an AB quartet (τ3.90 and 3.52; J = 9.5Hz) and the two 'missing' methyl signals at τ7.63 and τ7.78.

The adducts (11; R = CH_3CO and $C_6H_5CH{:}CHCO$) both hydrolysed in a similar manner but the adduct (11; R = C_6H_5CO) hydrolysed through a different path, giving 14β-hydroxylaminocodeinone <u>via</u>

8β-benzoyloxy-compounds. It was noticeable that the n.m.r spectra of all three adducts were very similar except for the position of the 6-methoxy signal. In both the adducts (11; R = CH_3CO and $C_6H_5CH{:}CHCO$) the 6-methoxy methyl resonated at τ6.44 while the same methyl in the adduct (11; R = C_6H_5CO) resonated at τ7.04.

EXPERIMENTAL

M.p.'s were taken on a Kofler hot-stage apparatus. Proton n.m.r. spectra were measured, unless otherwise stated, in deuteriochloroform at 60MHz and 100MHz. ^{13}C n.m.r. spectra were measured on a Varian F.T. 100 machine at 100.1 MHz in deuteriochloroform. I.r. spectra were taken in chloroform solution unless otherwise stated and mass spectra at an ionising voltage of 70 eV. U.v. spectra were taken in ethanol. Column chromatography utilised Woelm alumina (neutral, grade III) and t.l.c. was carried out over Merck GF_{254} alumina.

The preparation of tetranitromethane was exactly that of P. Liang[105].

The preparation of benzohydroxamic acid was exactly that of Hauser and Renfrow[106].

PREPARATION OF 14β-NITRO-DERIVATIVES OF THEBAINE WITH TETRANITROMETHANE:-

The following general procedure illustrates the general method used to nitrate thebaine in the 14β-position with tetranitromethane. The thebaine was dissolved in solvent and an equimolar amount of tetranitromethane added slowly. The resultant brown solution was stirred at room temperature and after approximately thirty minutes a bulky yellow crystalline precipitate (thebaine nitroform salt) appeared from which thebaine could be recovered, in ca. 70% yield, by partitioning between chloroform and aqueous bicarbonate. The filtrate was subject to column chromatography over alumina (neutral, grade III). Elution with benzene-chloroform (1:1) generally only partly separated the

nitration product (59) from 14β-nitrocodeinone dimethyl ketal (21; R = NO_2) but satisfactorarily separated 14β-nitrocodeinone (53) from its dimethyl ketal. Fractional crystallisation from ethanol of suitable combinations of fractions yielded the pure products. Some typical results are shown below

A) To thebaine (3.11g, 0.01 mole) in benzene (150 ml) with 2,2'-azobis-2-methylpropionitrile (50 mg) under oxygen in the dark was added slowly a solution of tetranitromethane (1.96g, 0.01 mole) in benzene (25 ml). After 2.5h the reaction mixture was treated as above to give (59), (1.05 g, 28%).

B) The same reaction conditions as A) but in daylight gave (59) (1.18 g, 31%) and 14β-nitrocodeinone (0.20g, 6%).

C) The same reaction conditions as B) but under oxygen free nitrogen gave 14β-nitrocodeinone (53) (4.93mg, 14%) and its dimethyl ketal (21; R = NO_2) (629mg, 16%) and only slight traces of (59).

D) The same reaction conditions as C) but without the radical initiator gave 14β-nitrocodeinone (53) (0.80g, 23%) and its dimethyl ketal (21; R = NO_2), (1.08g, 28%).

E) Using the same molar quantities as before but in methanol in conditions of oxygen and light and radical initiator the reaction gave (59) (820mg, 21%) with only traces of the ketal.

F) As in E) but in the dark the reaction gave (59), (620mg, 16%).

G) As in E) but without radical initiator the reaction gave the ketal (21; R = NO_2), (1.29g, 33%).

H) Tetranitromethane (1.96g, 0.01 mole) was added to a solution of thebaine (3.11g, 0.01 mole) and concentrated ammonia (1ml) in dioxan. After 2h the reaction gave after crystallisation from ethanol, 14β-nitrocodeinone (53), (1.40g, 41%).

CHARACTERISATION OF 14β-NITROCODEINONE (53):-

Obtained by the above methods and crystallised from ethanol to give pale yellow plates, m.p. 172°C (Lit.[37] 172.5 - 173°C), ν max 1690 and 1548cm^{-1}; τ 3.32 (2H:s: H-1 and H-2), 3.38 and 3.82 (2H:AB_q: J = 10Hz: H-7 and H-8), 4.86 (1H:s:H-5), 5.92 (1H:d: $J_{10\alpha}$ = 6Hz: H-9), 6.18(3H:s:3-OCH_3), 6.50 (1H:d: $J_{10\alpha}$ = 18Hz: H-10β), 7.44 (1H:dofd: J_9 = 6Hz and $J_{10\beta}$ = 18Hz: H-10α), and 7.60 (3H:s:NCH_3); m/e 342 (M+) 295 and 253.

CHARACTERISATION OF 14β-NITROCODEINONE DIMETHYL KETAL (21; R = NO_2):-

Crystallised from ethanol to give white needles, m.p. 227°(Lit 37, 227 - 227.5°C); ν_{max} 1546cm^{-1}; τ 3.34 and 3.48 (2H:AB_q: J = 8Hz: H-1 and H-2), 4.13 (2H:s: H-7 and H-8), 4.96 (1H:S: H-5), 6.14 (3H:s:3-OCH_3), 6.57 (3H:s:6-OCH_3), 6.94 (3H:s: 6-OCH_3) and 7.56 (3H:s:NCH_3); m/e 388 (M^+) 342 and 310. ^{13}C n.m.r. spectrum - see Table 2.

CHARACTERISATION OF 8,14-DIHYDRO-8α,10α-EPIDIOXY-14β-NITROTHEBAINE (59):-

Crystallisation from ethanol gave long needles, m.p. 159 - 159.5°C; R_F 0.70 (c.f. 14β-nitrocodeinone 0.68 and its dimethyl ketal 0.75) for t.l.c. over Merck GF_{254} alumina (benzene-chloroform 1:1); ν_{max} 1644 and 1551cm^{-1}; λ_{max} 221 n.m. (end absorption), 283 n.m. (ε = 2.10 x 10^3) and 289 n.m. (ε = 2.13 x 10^3); τ 3.02 and 3.16 (2H:AB_q: J = 8Hz: H-1 and H-2), 4.58 (1H:d: J = 3.5Hz: H-10), 4.73(1H:s: H-5), 5.05(1H:d: J = 6.4Hz: H-7), 5.41(1H:d: J = 6.4Hz: H-8), 5.78(1H:d:J = 3.5Hz: H-9), 6.13(3H:s:3-OCH_3), 6.45(3H:s: 6-OCH_3) and 7.46(3H:s:NCH_3); m/e 390, 389, 388 and 342.1340 (base peak), $C_{19}H_{20}NO_5$ requires 342.1341. Vapour phase osmometry of benzene solutions of (59) gave molecular weights of

412, 420 and 428 (calibration with benzene solutions of thebaine). N.m.r. spectroscopy of a solution of 20.91mg of the compound (59) and 16.05mg of symmetric trinitrobenzene gave, by integration values for the molecular weight ranging from 336 to 383 averaging 355. Elemental analysis of (59) was inconsistent:-

	%C	%H	%N	%O
Analysis (1)	57.98	5.32	10.24	-
Analysis (2)	58.96	5.25	8.33	-
Analysis (3)	59.65	5.37	7.15	28.05
$C_{19}H_{20}N_2O_7$ requires (M = 388)	58.76	5.19	7.21	28.84

For the ^{13}C n.m.r. spectrum see Table 2.

BASE HYDROLYSIS OF (59):-

The compound (59) (220mg) was dissolved in minimum amount of ethanol and a few drops of 4N-sodium hydroxide were added. After 1.5h the solution was neutralised with dilute hydrochloric acid (2.5M), reduced in volume under reduced pressure and then poured into brine and extracted repeatedly with chloroform. The combined chloroform extracts were dried (Na_2SO_4) and evaporated to give (55; R = H), 8,14-dihydro-8β-hydroxy-14βnitro-10-oxothebaine, (207mg, 94%) as a yellow foam which was usually used directly or could be crystallised to give a yellow crystalline solid (158mg, 72%), m.p. 219°C', ν_{max} 3585, 1680, 1619 and 1547cm^{-1}; λ_{max} 241 n.m. ($\varepsilon = 1.24 \times 10^4$), 288 n.m. ($\varepsilon = 1.10 \times 10^4$) and 320 n.m. ($\varepsilon = 6.90 \times 10^3$); τ 2.52 and 3.08 (2H:AB_q: J = 9Hz: H-1 and H-2), 4.64(1H:s:H-5), 5.41(1H:D:J_8 <1Hz:H-7), 5.61(1H:d of d: J = 7.5Hz and J_7 <1Hz:H-8), 5.78(1H:s:H-9), 5.99(3H:s:3-OCH_3),

6.38(3H:s:6-OC$\underline{H}_3$), 6.81(1H:d:J = 7.5Hz: C-8-OH), 7.48(3H:s: NC$\underline{H}_3$); m/e 388.1265 ($C_{19}H_{20}N_2O_7$ required 388.1270), 342 and 326. (Found: C, 58.77; H, 5.35; N, 7.29% $C_{19}H_{20}N_2O_7$ requires C, 58.76; H, 5.19; N, 7.21%) For the ^{13}C n.m.r. spectrum see Table 2.

ACETYLATION OF (55; R = H):-

The compound (55; R = H) (60mg) in pyridine (3ml) was treated with three drops of acetic anhydride and left overnight, the poured into brine (25ml) and extracted with chloroform. The combined chloroform extracts were washed with aqueous sodium bicarbonate, dried ($MgSO_4$)and evaporated to dryness. The remaining acetic acid was azeotroped off using toluene, then benzene then ether to give a yellow solid (43mg, 55%) after crystallisation from ethyl acetate-petrol (b.p. 60°-80°C). Recrystallisation of this material (20mg) from ethanol gave (55; R = CH_3CO), 8β-acetoxy-8,14-dihydro-14β-nitro-10-oxothebaine, (11mg), m.p. 241.5°C; ν_{max} 1683, 1557 and 1552cm^{-1}; λ_{max} 243 n.m. (ε=1.39 x 10^4), 289 n.m. (ε= 1.16 x 10^4 and 321 n.m. (ε = 7.05 x 10^3); τ 2.41 and 3.02(2H:AB_q: J = 9Hz:H-1 and H-2), 4.47(1H:m: H-8), 4.62(1H:d: J = 1.25Hz: H-5), 5.56(1H:d: J < 1Hz: H-7), 5.96(3H:s:3-OC$\underline{H}_3$), 6.04(1H:s:H-9), 6.37(3H:s:6-OC$\underline{H}_3$), 7.47(3H:s: NC$\underline{H}_3$) and 7.81(3H:s:OC(O)C$\underline{H}_3$); m/e 430(M^+), 384 and 341. (Found: C, 58.67; H, 5.18; N, 6.19%. $C_{21}H_{22}N_2O_8$ requires C,58.60; H, 5.15; N, 6.51%)

BENZOYLATION OF (55; R = H):-

The compound (55; R = H) (50mg) was dissolved in benzene (10ml) containing a catalytic amount of pyridine. A few drops

of benzoyl chloride were added and after 1h., the solution was diluted with benzene (20ml) and washed copiously with aqueous sodium bicarbonate and brine. The benzene layer was then dried (Na_2SO_4) and evaporated under reduced pressure to an oil which crystallised on the addition of methanol to give off-white (55; R = C_6H_5CO), 8,14-dihydro-8β-benzoyloxy-14β-nitro-10-oxothebaine, (49mg, 77%) m.p. 243°C; ν_{max} (KBr) 1716, 1682, 1548 and 1344cm^{-1}; λ_{max} 240n.m. (ε =2.34 x 10^4), 286 n.m. (ε = 1.12 x 10^4) and 323 n.m. (ε = 6.14 x 10^3); τ 2.03(2H:m:m aromatics), 2.48 and 3.10(2H:ABq: J = 9Hz: H-1 and H-2), 2.6(3H:m:o and p aromatics), 4.35(1H:bs: H-8), 4.68(1H:d: J = 1Hz: H-5), 5.54(1H: d: J = 1Hz: H-7), 6.04 (3H:s:3-OCH_3), 6.44(3H:s: 6-OCH_3) and 7.58(7.58:s:NCH_3); m/e 492 (M^+). This compound has not yet been successfully analysed.

REDUCTION OF (59) WITH IODIDE:-

(59) (50mg) in acetic acid (10ml) was treated with sodium iodide (115mg,five fold molar excess) in acetic acid (3ml) under nitrogen at room temperature. After 16h the reaction mixture was poured onto ice-water (25ml) and brought to pH8 by addition of aqueous sodium bicarbonate. The resultant solution was extracted with chloroform and the extracts combined and washed consecutively with 2.5N-sodium thiosulphite, aqueous sodium bicarbonate, and brine. The chloroform solution was then dried ($MgSO_4$) and reduced in volume to give a white solid (46mg, 96%) which after crystallisation from ethanol gave (61), 8,14-dihydro-8α,10α-dihydroxy-14β-nitrothebaine, (23mg, 46%),

m.p. 175 - 177°C; ν_{max} 3570, 3500 and 1545cm^{-1}; λ_{max} 219 n.m. (end absorption), 279 n.m. (ε 2.13 x 10^3) and 284 n.m. (ε = 2.19 x 10^3); τ 2.96 and 3.13(2H:Abq: J = 8Hz:H-1 and H-2), 4.82(1H:s:H-5), 4.97(1H:d: J = 12Hz:H-10), 5.11(1H:d: J_8 = 6Hz: H-7), 5.30(1H:dofd; J = 9Hz and J_7 = 6Hz:H-8), 5.54(1H:d: J = 12Hz: 10-OH), 6.04(1H:s:H-9), 6.09(3H:s:3-OCH_3), 6.44(3H:s:6-OCH_3) and 7.49(3H:s:NCH_3); m/e 390 (M^+) and 344. (Found: C, 57.82; H, 6.48; N, 6.64%. $C_{19}H_{22}N_2O_7$. C_2H_6O requires C, 57.79; H, 6.47; N, 6.42%).

ESTIMATION OF LIBERATED I_2:-

(59) (50.3mg) in acetic acid (10ml) was added to a solution of sodium iodide(114mg) in acetic acid (3ml) under nitrogen. A control solution of sodium iodide (114mg) in acetic acid (13ml) was prepared. After 17h both solutions were taken to pH6 with 5N-sodium hydroxide and made up to 250ml with water. Aliquots (10ml) were titrated with 10^{-3}N-sodium thiosulphate. Titres required: 7.84, 7.84, 7.83, and 7.88ml, average 7.85ml, for the reaction mixture. The control gave no colour with starch indicator Result:- 1 molar equivalent of (59) reacted with iodide to give 0.376 molar equivalents iodine. The estimation was repeated without nitrogen and without neutralisation, the titrations being carried out at pH4. Result:- 1 molar equivalent of (59) reacted with iodide to give 0.368 molar equivalents of iodine.

EPIMERISATION OF (61):-

(61) (70mg) was dissolved in ethanol (10ml) and treated with a few drops of 4N-sodium hydroxide. After 0.5h the solution was poured into brine and extracted with chloroform. The

chloroform extracts were dried (Na_2SO_4) and reduced to a clear oil which was crystallised from methanol to give colourless (62), 8,14-dihydro-8β,10α-dihydroxy-14β-nitrothebaine, (41mg, 59%), m.p. 210 - 211°C with decomposition; ν_{max} 3610, 3500 (broad), 1651, 1623, 1539 and 1441cm^{-1}, τ 1.05 and 1.08(2H:ABqH-1 and H-2), 4.74(1H:s:H-5), 4.82(1H:s:H-10), 5.32(1H:s:H-7), 5.78(1H:s:H-8) 5.94(1H:s:H-9), 6.16(3H:s:3-OC$\underline{H}_3$), 6.53(3H:s:6-OC$\underline{H}_3$), 7.0(2H:m:8-OH and 10-OH) and 7.45(3H:s:NC$\underline{H}_3$). (Found: C, 58.69; H, 5.71; N, 7.44%. $C_{19}H_{22}N_2O_7$ requires C, 58.45; H, 5.68; N, 7.18%).

SODIUM BOROHYDRIDE REDUCTION OF (55; R = H):-

(55; R = H) (40mg) was dissolved in methanol (3ml) and added to a solution of excess sodium borohydride in aqueous methanol (2ml) at 0°C and left to come to room temperature overnight. 1N-Sodium hydroxide (0.5ml) was added, the solution was reduced in volume and poured into water. The solution was extracted with chloroform and the combined chloroform extracts were washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure to give a white solid (31mg, 78%) which was crystallised from benzene-hexane (with difficulty), to give (63), 8,14-dihydro-8β,10-β dihydroxy-14β-nitrothebaine, (17mg, 43%), m.p. 237 - 238°C; ν_{max} 3605, 3560, 1652, 1536 and 1447cm^{-1}; τ 2.96 and 3.17 (2H:ABq: J = 8.3Hz:H-1 and H-2), 4.84(1H:s:H-5), 4.96(1H:d: J = 6Hz:H-10), 5.55(1H:s:H-7), 5.71(1H:d:J = 6Hz:H-9), 5.7(1H:broad m: H-8), 6.11(3H:s:3-OC$\underline{H}_3$), 6.46(3H:s:6-OC$\underline{H}_3$) and 7.24(3H:s:NC$\underline{H}_3$); m/e 390 (M^+). This compound was unstable and did not give a correct analysis.

OXIDATION OF (55; R = H):-

(55; R = H) (25mg) was dissolved in benzene (30ml) and treated with a large excess of activated manganese dioxide[109] for four hours, then filtered through celite, and evaporated under reduced pressure to give a yellow oil (23mg) which crystallised from ether to give yellow (64), 8,14-dihydro-8,10-dioxo-14β-nitrothebaine, (19.5mg, 78%) m.p. 232 - 233°C; ν_{max} (KBr) 1691, 1623, 1602 and 1554cm^{-1}; λ_{max} 220 n.m. (ε = 1.52 x 10^4), 238 n.m. (ε = 1.62 x 10^4, 280 n.m. (ε = 1.11 x 10^4) and 318 n.m. (ε = 5.11 x 10^3); τ 2.44 and 2.98 (2H:ABq: J = 8.5Hz:H-1 and H-2) 4.27(1H:s:H-7), 4.55(1H:s:H-5), 5.46(1H:s: H-9), 5.92(3H:s:3-OC$\underline{H}_3$), 6.13(3H:s:6-OC$\underline{H}_3$) and 7.21(3H:s:NC$\underline{H}_3$); m/e 386 (M^+), 340 and 308. (Found: C, 59.06; H, 4.70; N, 7.25%. $C_{19}H_{18}N_2O_7$ requires C, 59.05; H, 4.71; N, 7.26%). For ^{13}C n.m.r. spectrum see Table 2.

OXIDATION OF THE DIOLS (61), (62) and (63):-

The diols (61) and (62) (in benzene) and (63) (in chloroform) were each oxidised in similar manner to give (64) in high yield.

REACTION OF (64) WITH ETHANOLIC BASE:-

(64) (47mg) was dissolved in ethanol (25ml) at 50°C. A few drops of 4N-sodium hydroxide were added and after 5 minutes the now bright yellow solution was poured into brine and extracted with chloroform. The combined chloroform extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give a foam (53mg) which was crystallised from ethanol to give an ester,

tentatively assigned structure (70; R = C_2H_5), (42mg, 80%), m.p. 172°C; ν_{max} 1713,1682, 1642, 1623, 1556, 1449 and 1287cm^{-1}; λ_{max} 237 n.m. (ε = 2.29 x 10^4), 287 n.m. (1.06 x 10^4) and 323 n.m. (4.19 x 10^3); τ 2.59 and 3.12(2H:ABq: J = 8Hz: H-1 and H-2), 2.84(1H:s:H-5), 4.93(1H:s:C$\underline{H}$CO$_2$Et), 5.06 (1H:dofd: J_9= 3.5Hz and J = 1.2Hz:C$\underline{H}$NO$_2$), 5.81(2H:q:OC$\underline{H}_2$CH$_3$), 6.02(1H:d: J_{14} = 3.5Hz:H-9), 6.06(3H:s:3-OC$\underline{H}_3$), 6.58(3H:s:6-OC$\underline{H}_3$), 7.61(3H:s:NC$\underline{H}_3$) and 8.79(3H:t:OCH$_2$C$\underline{H}_3$); m/e 432 (M+), 402, 386 and 243. For ^{13}C n.m.r. see Table 2. (Found: C, 58.16; H, 5.81; N, 6.74%. $C_{21}H_{24}N_2O_8$ requires C, 58.33; H, 5.59; N, 6.48%)

REACTION OF (64) WITH METHANOLIC BASE:-

(64) (100mg) was treated exactly as above but using methanol as solvent. The crude product (61mg) was purified by preparative t.l.c. over alumina (chloroform) followed by crystallisation from methanol to give the methyl ester (70; R = CH_3), (36mg, 33%), m.p. 199 - 200°C; ν_{max}(KBr) 1707, 1684, 1644, 1617, 1598, 1550 and 1443cm^{-1}; τ 2.60 and 3.12(2H:ABq: J = 8Hz:H-1 and H-2), 2.86(1H:s: H-5), 4.92(1H:s:C$\underline{H}$CO$_2$Me), 5.09(1H:dofd: J = 5Hz and J< 1Hz:C$\underline{H}$NO$_2$), 6.02(3H:s:3-OC$\underline{H}_3$), 6.28(3H:s:CO$_2$C$\underline{H}_3$), 6.55(3H:s:6-OC$\underline{H}_3$), and 7.59(3H:s:NC$\underline{H}_3$); m/e 418 (M+) and 312 (base peak). A correct analysis has not yet been obtained for this compound.

ACID HYDROLYSIS OF (55; R = H):-

(55; R = H) was dissolved in 5M-hydrochloric acid (15ml) and heated under reflux for 10 minutes, then left to cool to room temperature and taken to pH8 with saturated sodium bicarbonate and extracted with chloroform. The combined cloroform extracts

were washed with brine, then dried (Na_2SO_4) and evaporated under reduced pressure to give a clear oil (178mg) which was subjected to preparative t.l.c. over alumina (chloroform-benzene, 1:1). The major product (R_F0.85) was crystallised from ethanol to give bright yellow crystalline (67), 14β-nitro-10-oxocodeinone, (43mg, 28%) m.p. 205 - 207°C; ν_{max} 1690, 1686, 1608, 1586, and 1549cm^{-1}; λ_{max} 215 n.m. (end absorption), 242 n.m. (ε = 1.17 x 10^4), 293 n.m. (8.47 x 10^3) and 324 n.m. (4.72 x 10^3); τ 2.57 and 3.14(2H:ABq: J = 8.5Hz:H-1 and H-2), 3.46 and 3.74(2H:ABq: J = 10Hz: H-7 and H-8), 4.78(1H:s:H-5), 5.92(1H:s:H-9), 6.08(3H:s:3-OC$\underline{H}_3$) and 7.51(3H:s:NC$\underline{H}_3$); m/e 356 (M^+) and 310. (Found: C, 60.59; H, 4.64; N, 8.35%. $C_{18}H_{16}N_2O_6$ requires C, 60.67; H, 4.53; N, 7.86%).

The other product (R_F0.15) was isolated as a viscous unstable yellow oil (66), 7,8-dihydro-8β-hydroxy-14β-nitro-10-oxocodeinone, (34mg, 18%); ν_{max} 3610, 3450, 1744, 1683, 1622 and 1554cm^{-1}; τ 2.56 and 3.10 (2H:ABq: J = 9Hz:H-1 and H-2), 4.92(1H:s:H-5), 5.76(1H:s:H-9), 5.98(3H:s:3-OC$\underline{H}_3$), 6.42(1H:bd: J = 8Hz:8-OH) and 7.53(3H:s:NC$\underline{H}_3$); m/e 374:1112 ($C_{18}H_{18}N_2O_7$ requires 374.1114), 356, 328 and 310 (base peak).

OXIDATION OF 14β-NITROCODEINONE (53):-

14β-Nitrocodeinone (108mg, 0.36m.mole) was suspended in acetic anhydride (0.4ml) and trifluoroacetic acid was added dropurise until the solution was homogenous. To this was added chromium trioxide (100mg, 1m.mole) in acetic anhydride (0.45ml) such that the temperature did not exceed 10°C. The mixture was then poured onto ice, taken to pH8 with aqueous

sodium bicarbonate solution and extracted with chloroform. The combined chloroform extracts were washed with brine, then dried (Na_2SO_4) and evaporated under reduced pressure to a yellow multicomponent oil. Preparative t.l.c. over alumina (chloroform) followed by crystallisation from ethyl acetate gave (69) 14β-nitro-15,16-dioxocodeinone, (14mg, 12%), m.p. 215°C with decomposition; R_F0.50 (alumina:chloroform); ν_{max} 1756, 1689 and 1567cm^{-1}; λ_{max} 208 n.m. (end absorption) and 265 n.m. (ε = 3.76 x 10^3); τ 3.15 and 3.29(2H:ABq: J = 9Hz:H-1 and H-2), 3.26 and 3.60(2H: Abq: J = 10Hz: H-7 and H-8), 4.04(1H:s:H-5), 5.09(1H:dofd: $J_{10\alpha}$ =5Hz, $J_{10\beta}$ = 1Hz:H-9), 6.14(3H:s:3-OC$\underline{H}_3$) and 6.78(3H:s:NC$\underline{H}_3$); m/e 370.0792 ($C_{18}H_{14}N_2O_7$ requires 370.0801).

REDUCTION OF (59) WITH TRIPHENYLPHOSPHINE:-

(59) (97mg, 0.25m.mole) was dissolved in benzene (25ml) along with triphenylphosphine (65.6mg, 0.25m.mole) and the solution heated under reflux overnight. The solution was evaporated under reduced pressure and the three-component oil separated by preparative t.l.c. over alumina (benzene-chloroform, 1:1). Elution of the first band (R_F0.8 to 0.9) gave a mixture of starting materials (6.5mg). Elution of the band R_F0.2 to 0.4 gave triphenylphosphine oxide (68.5mg, 98%). Elution of the band R_F0.4 to 0.6 gave (65), 8,14-dihydro-8α,10α-epoxy-14β-nitrothebaine,(78mg, 84%), m.p. 131 - 132°C (ex methanol); ν_{max} 1640 and 1549cm^{-1}; τ 3.22(2H:s:H-1 and H-2), 4.66(1H:s: H-5), 4.95 and 5.30(2H:ABq:H-10 and H-9), 5.20(2H:s:H-7 and H-8), 6.11(3H:s:3-OC$\underline{H}_3$), 6.51(3H:s:6-OC$\underline{H}_3$) and 7.41(3H:s:NC$\underline{H}_3$); m/e 372 (M^+), 326 (base peak), 310, 294, 282 and 269. For the

^{13}C n.m.r. spectrum see Table 2.(Found: C, 61.53; H, 5.44; N, 7.80%. $C_{19}H_{20}N_2O_6$ requires C, 61.28; H, 5.41; N, 7.52%).

ACID HYDROLYSIS OF (65):-

(65) (74.4mg) was dissolved in 5M-hydrochloric acid (20ml) and left at room temperature for 2h. The solution was brought to pH8 with aqueous sodium bicarbonate and extracted with chloroform. The chloroform extracts were washed with brine, dried (Na_2SO_4) and reduced in volume under reduced pressure. The resultant oil was subjected to preparative t.l.c. over alumina (chloroform) and the major fraction (R_F0.3) eluted to give (68) 10α-hydroxy-14β-nitrocodeinone, (43mg, 60%), m.p. 206 - 7°C (ethanol); ν_{max} 3610, 1698 and 1555cm^{-1}; λ_{max} 280 n.m. (ε = 189); τ3.03 and 3.16(2H:ABq: J = 8Hz: H-1 and H-2), 3.06(1H:d: J = 10Hz:H-8), 3.83(1H:d: J = 10Hz:H-7), 4.78(1H:bs: sharpens with D_2O:H-10), 4.84(1H:s:H-5), 5.87(1H: bs:H-9); 6.10(3H:s:3-OCH_3) and 7.42(3H:s:NCH_3); m/e 358 (M+), 312 (base peak) and 294. (Found: C, 60.39; H, 5.10; N, 7.51%. $C_{18}H_{18}N_2O_6$ requires C, 60.33; N, 5.06; N, 7.82%).

Elution of that fraction with R_F0.8 yielded starting material (3mg).

OXIDATION OF (68):-

(68) (12mg) was dissolved in benzene (10ml) and excess active manganese dioxide[109] added and the suspension stirred overnight. The mixture was filtered through celite and evaporated under reduced pressure to give (67) 14β-nitro-10-oxocodeinone, (8mg, 66%) identical to that previously prepared.

PREPARATION OF ACETOHYDROXAMIC ACID[107]:-

To a solution of sodium hydroxide (16g, 0.4mole) in water (100ml) at 0°C was added hydroxylamine hydrochloride (28g, 0.4mole). As soon as all had dissolved acetic anhydride (40g, 0.4mole) was added and the mixture left to stand overnight. The solution was reduced to an oil-solid mixture under reduced pressure at 40°C. This mixture was taken up in ethanol, filtered to remove NaCl and concentrated to an oil which was crystallised from ethyl acetate (≃ 1l) to give acetohydroxamic acid (14.3g, 47%) m.p. 86 -89°. (Lit.[108] m.p. 88°C).

PREPARATION OF POTASSIUM CINNAMOYLHYDROCHLORIDE:-

Solutions of hydroxylamine hydrochloride (46.7g, 0.67mole) in methanol (240ml) and potassium hydroxide (56.1g, 1mole) in methanol (140ml) were mixed at 0°C. After 5 minutes ethyl cinnamate (50g, 0.28moles) was added and the potassium chloride filtered off. After 48h filtration gave the bright yellow crystalline potassium salt of cinnamoylhydroxamic acid (24.5g, 46%).

PREPARATION OF THE THEBAINE-NITROSOCARBONYL ADDUCT[110] (11; R = CH_3CO):-

Thebaine (2.00g, 6.4m.mole) in ethyl acetate (100ml) was added to a solution of tetraethylammonium periodate (3g, 9.1m.mole) in 0.2M-acetic acid buffer (100ml) at approximately pH6, and the two phase solution stirred vigorously at 0°C. Acetohydroxamic acid (2.00g, 27m.mole) was added over 5 minutes and the solution stirred for 1h. The ethyl acetate layer was then separated off

and the aqueous layer basified with aqueous sodium bicarbonate and extracted with ethyl acetate. The combined ethyl acetate layers were washed with sodium bisulphite solution, then brine, then dried (Na_2SO_4) and evaporated under reduced pressure to a clear oil which crystallised from ethyl acetate - petrol (b.p. 60 - 80°C) to give (11; R = CH_3CO), (0.77g, 32%) m.p. 194-6°C; (Lit.[110] 194 -6°C); ν_{max} (KBr) 1670 and 1495cm^{-1}; τ 3.31 and 3.47 (2H:ABq: J = 9Hz:H-1 and H-2), 3.89 and 4.03(2H:ABq: J = 9Hz:H-7 and H-8), 5.20(1H:bd: J = 7Hz:H-9), 5.22(1H:s:H-5), 6.21(3H:s:3-OCH_3), 6.44(3H:s:6-OCH_3), 7.52(3H:s:NCH_3) and 8.01(3H:s:CH_3CON); m/e 384 (M^+) and 386.

PREPARATION OF THE THEBAINE-NITROSOCARBONYL ADDUCT (11; R = C_6H_5CO):-

Thebaine (5g, 0.016 mole) in ethyl acetate (250ml) was added to a suspension of sodium periodate (5.44g, 0.23mole) in 0.2M-acetic acid buffer (pH6). The mixture was cooled to 0°C and benzohydroxamic acid added, with vigorous stirring, over 10 minutes. After a total of 1h solid sodium metabisulphite was added until the mixture was a light yellow. Filtration of the two phase system gave the white solid hydroiodide of (11; R = C_6H_5CO) (8.7g, 94%), m.p. 207 - 209°C, which was partitioned between chloroform and aqueous sodium bicarbonate. The combined chloroform extracts were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure to give a clear oil which crystallised from benzene-petrol (b.p. 60 - 80°) to give (11; R = C_6H_5CO), (4.01g, 57%), m.p. 170 - 2°C; ν_{max} (KBr) 1662, 1603, 1500 and 1445cm^{-1}; λ_{max} 218 n.m. (end absorption),

226 n.m. (inflexion, ε = 2.06 x 10^4) and 275 n.m. (inflexion, ε = 4.79 x 10^3); τ 2.26(2H:m:m-aromatics), 2.63(3H:m:o-and p-aromatics), 3.30 and 3.44(2H:ABq: J = 8Hz:H-1 and H-2), 3.70 and 4.07(2HABq: J = 9Hz:H-7 and H-8), 5.08(1H:d: J = 7Hz:H-9), 5.41(1H:s with fine coupling:H-5), 6.20(3H:s:3-OCH_3), 7.04(3H:s: 6-OCH_3) and 7.51(3H:s:NCH_3); m/e 446 (M^+).

PREPARATION OF THE THEBAINE-NITROSOCARBONYL ADDUCT (11; R = $C_6H_5CHCHCO$):-

Thebaine (5g, 0.016mole) in ethyl acetate (250ml) was added to a suspension of sodium periodate (5.44g, 0.23mole) in 0.2M-acetic acid buffer (250ml) at pH6. Potassium cinnamoyl-hydroxamate (5.95g, 0.37mole) was added to the mixture at 0°C with vigorous stirring over 10 minutes. After 1h in total at 0°C, solid sodium metabisulphite was added until a yellow colouration persisted. The ethyl acetate and aqueous phases were decanted leaving an oily gum which was partitioned between chloroform and aqueous sodium bicarbonate. The ethyl acetate and aqueous phases were separated, the aqueous phase brought to pH9 and extracted with chloroform. This chloroform extract was added to the other chloroform extract. The ethyl acetate phase was washed copiously with aqueous sodium bicarbonate and then combined with the chloroform extracts. The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give a white solid, which after crystallisation from benzene gave the adduct (11; R = C_6H_5 CHCHCO), (5.53g, 73%) m.p. 198 - 5°C with decomposition; λ_{max} 214 n.m. (end absorption) and 287 n.m. (ε = 2.85 x 10^4); ν_{max} 1662, 1618, 1607, 1585, 1497 and 1448cm^{-1}; τ 2.43 and 2.99(2H:ABq: J = 15.5Hz:-CHCHCO-), 2.6(5H:bm: aromatics), 3.32 and

3.44(2H:ABq: J = 4.5Hz:H-1 and H-2), 3.79 and 4.02(2H:ABq: J = 5Hz:H-7 and H-8), 5.06(1H:bd:J = 6Hz:H-9) 5.36(1H:s:H-5), 6.20 (3H:s:3-OC$\underline{H}_3$), 6.44(3H:s:6-OC$\underline{H}_3$) and 7.48(3H:s:NC$\underline{H}_3$); m/e 472 (M^+) and 455 (base peak). (Found: C, 71.02; H, 5.82; N, 5.65%. $C_{28}H_{28}N_2O_5$ requires C, 71.17; H, 5.97; N, 5.93%).

HYDROLYSIS OF THE ADDUCT (11; R = CH_3CO)[110]:-

The adduct (100mg) was dissolved in 1M-hydrochloric acid (0.5ml) and left for 30h at room temperature and then filtered to give crystalline (73; R = CH_3) N-acetyl-14β-hydroxyamino-codeinone hydrochloride, (51mg, 43%), m.p. 205 - 7°C; ν_{max}(KBr) 3410 (broad) 1684 and 1504cm^{-1}; τ (dimethylsulphoxide-d_6)-1.11 (1H:s:N-O$\underline{H}$), 0.2 to 0.3(1H:envelope:$N^+\underline{H}$), 3.14 and 3.28(2H:ABq: J = 8Hz:H-1 and H-2), 3.16(1H:d:J=11H:H-8),3.84(1H:d:J = 11Hz:H-7), 4.70(1H:bs:H-9), 5.01(1H:s:H-5), 6.26(3H:s:3-OC$\underline{H}_3$), 7.07(3H:bs: $N^+C\underline{H}_3$) and 7.85(3H:s:C$\underline{H}_3$CON); m/e 370 (M^+ - HCl), 353 and 279 (base peak).

REDUCTION OF THE THEBAINE ADDUCT (11; R = C_6H_5CO):-

The adduct (3.00g) was dissolved in glacial acetic acid (30ml). Zinc dust (4.58g, ten fold excess) was added and the misture heated with stirring at 70 - 80°C for 2h, then filtered hot, neutralised with aqueous sodium bicarbonate and extracted with chloroform. The chloroform extracts were washed with brine, dried (Na_2SO_4), reduced in volume and subjected to column chromatography over alumina (neutral, grade III, 200g). Elution with benzene-chloroform (1:1) gave, after crystallisation from ethanol, the oxazoline (71), (820mg, 28%), m.p. 176 - 8°C,

λ_{max} 202 n.m. (end absorption) and 232 n.m. (ε = 2.06 x 10^3); ν_{max} 1661 and 1638cm^{-1}; τ 1.97(2H:m:m-aromatics), 2.57(3H:m:o- and p-aromatics), 3.23 and 3.32(2H:ABq: J = 8.5Hz:H-1 and H-2), 5.06(1H:s:H-5), 5.21 and 5.41(2H:ABq: J = 3Hz: H-7 and H-8), 6.21(3H:s:3-OCH_3), 6.54(3H:s:6-OCH_3) and 7.57(3H:s:NCH_3); m/e 430 (M^+), 415, 325 and 310 (base peak). (Found: C, 72.85; H, 6.35; N, 6.37%. $C_{26}H_{26}N_2O_4$ requires C, 72.54; H, 6.09; N, 6.51%).

HYDROLYSIS OF THE OXAZOLINE (71):-

The oxazoline (71) (200mg.) was dissolved in methanol under reflux and concentrated hydrochloric acid (0.5ml:32% w/w) added. After 3h the solution was cooled, neutralised with aqueous sodium bicarbonate and extracted with chloroform. The combined chloroform extracts were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure to give, after preparative t.l.c. over alumina (chloroform) (15; R = C_6H_5CO), N-benzoyl-14β-aminocodeinone, (140mg, 72%), m.p. 252 - 3°C; ν_{max} 3360, 1682 and 1658cm^{-1}; τ 2.10 to 2.15(2H:m:m-aromatics), 2.5(3H:m:o- and p-aromatics), 2.35(1H:bs:removed by D_2O:C_6H_5CONH), 3.28 and 3.47 (2H:ABq: J = 8Hz:H-1 and H-2), 3.79 (2H:s:H-7 and H-8), 4.99(1H:s:H-5), 6.16(3H:s:3-OCH_3), 6.84(1H:bs:H-9) and 7.52(3H:s:NCH_3); m/e 416 (M^+), 295, 254, 238 and 229 (base peak). (Found: C, 70.72; H, 6.06; N, 6.63%. $C_{25}H_{24}N_2O_4 \cdot 0.5CH_3OH$ requires C, 70.81; H, 6.06; N, 6.47%).

MILD ACID HYDROLYSIS OF THE THEBAINE ADDUCT (11; R = CH_3CO):-

The adduct (200mg) was dissolved in ethanol (11ml) and concentrated hydrochloric acid (1.5ml) added. After 2h at room

temperature solid sodium bicarbonate was added, the solution poured into water and the pH adjusted to 8. Chloroform extracts of this solution were dried (Na_2SO_4) and subjected to preparative t.l.c. over alumina (chloroform) to give the phenol (72), identical with an authentic sample, (67mg, 33%); m.p. 221°C (with decomposition. Lit. 221°C); ν_{max} 3540, 3350, 1690 and 1675cm^{-1}; τ 2.84(1H:d: J_7 = 10Hz:h-8), 3.33(2H:s:H-1 and H-2), 4.01(1H:d ofd:J_8 = 10Hz, J_5 = 2Hz:H-7), 4.84(1H:bs:H-5), 5.72(1H:bd: $J_{10\alpha}$ = 5Hz:H-9), 6.20(3H:s:3-OC$\underline{H}_3$), 7.89(3H:s:NC$\underline{H}_3$), 7.92(3H:s: C$\underline{H}_3$CON), 6.41(1H:bd: $J_{10\beta}$ = 18Hz:H-10α) and 7.26(1H:broad d ofd: $J_{10\alpha}$ =18Hz, J_9 = 5Hz: H-10β).

MILD ACID HYDROLYSIS OF THE THEBAINE ADDUCT (11; R = C_6H_5CO):-

The adduct (100mg) was dissolved in ethanol (20ml) and concentrated hydrochloric acid (1.5ml) added. After 2h at room temperature the reaction was worked up in an exactly analogous manner to the above hydrolysis to give solid (74), 8,14-dihydro-8β-benzoyloxy-14β-hydroxyaminothebaine, (85mg, 85%). Crystallisation from methanol gave material with m.p. 129 - 30°C; ν_{max} 3200 - 3300 and 1710cm^{-1}; τ 1.94(2H:m:m-aromatics), 2.56(3H: m:o- and p-aromatics), 3.28 and 3.38(2H:ABq: J = 9Hz:H-1 and H-2), 4.52(1H:dofd: J_7 = 1.8Hz and J_5 = 1.4Hz:H-8), 4.6(2H:broad envelope: removed with D_2O:N$\underline{H}$O$\underline{H}$), 4.99(1H:d:J_8 = 1.4Hz:H-5), 5.41(1H:d: J_8 = 1.8Hz:H-7), 6.15(3H:s:3-OC$\underline{H}_3$), 6.50(3H:s:6-OC$\underline{H}_3$) and 7.67(3H:s: NC$\underline{H}_3$); m/e 354, 342 (M^+ less benzoic acid), 122 and 105 (base peak). (Found: C, 66.95; H, 6.07; N, 5.97%. $C_{26}H_{28}N_2O_6$ requires C, 67.22; H, 6.08; N, 6.03%.)

ISOMERISATION OF (74):-

The 8-benzoyloxy-compound (74) (70mg) was dissolved in ethanol (20ml) then poured into water (40ml). Ethyl acetate (≃ 20ml) was added slowly with vigorous shaking until an emulsion had formed. Solid sodium bicarbonate was added to the emulsion such that the emulsion was saturated, and then the mixture was shaken for 2h. It was then poured into water (150ml) and extracted with ethyl acetate. The ethyl acetate extracts were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure to give (75), 14β-benzoyloxyamino-8,14-dihydro-8β-hydroxythebaine, (66mg, 94%), m.p. 144.5°C with decomposition (exmethanol); ν_{max} 3440, 3230, 1735, 1663 and 1607cm^{-1}; τ1.56 (1H:s:removed with D_2O:N-H), 2.04(2H:dofd: J = 8Hz, J = 1Hz:m-aromatics), 2.51(3H:m:o- and p- aromatics), 3.26 and 3.38(2H:ABq: J = 7.5Hz:H-1 and H-2), 5.09(1H:d: J_8 < 1Hz:H-5), 5.39(1H:d: J_8 = 1.5Hz:H-7), 6.04(1H:m:sharpens with D_2O:H-8), 6.15(3H:s:3-OCH_3) 6.68(1H:bd:H-9), 6.88(3H:s:6-OCH_3) and 7.57(3H:s:NCH_3), irradiation at τ6.04 results in doublets at τ5.09 and 5.39 collapsing to singlets; m/e 311 (M^+ less water and C_6H_5CON). (Found: C, 66.98; H, 6.02; N, 5.92%. $C_{26}H_{28}N_2O_6$ requires C, 67.22; H, 6.08; N, 6.03%).

OXIDATION OF 8,14-DIHYDRO-8β-BENZOYLOXY-14β-HYDROXYAMINOTHEBAINE (74):-

(74) (65mg) was dissolved in benzene (8ml) and treated with a large excess of active manganese dioxide[109]. After stirring for 8h the slurry was filtered through celite and then percolated through alumina (grade III) with chloroform. The

bright green eluate was collected and evaporated down under reduced pressure at 40°C to give (76), 8,14-dihydro-8β-benzoyloxy-14β-nitrosothebaine (56mg, 81%); m.p. 116°C with decomposition, weeping from 104°C (crystallised from benzene-ether); λ_{max} 209 n.m. (end absorption), 283 n.m. (ε = 1.09 x 10^4), and 681 n.m. (ε =46, in chloroform); ν_{max} 1716 and 1666cm^{-1}; τ 2.06(2H:m:m-aromatics), 2.57(3H:m:o-and p-aromatics), 3.29(2H:s:H-1 and H-2), 4.21(1Hbs:H-8), 4.41(1H:dofd: $J_{10\alpha}$ = 5.5Hz, $J_{10\beta}$ < 1Hz: irradiation at τ6.7 removed larger coupling:H-9), 5.90(1H:d: J_8 = 2Hz: irradiation at τ4.2 removes coupling:H-7), 6.16(3H:s:3-OC$\underline{H}_3$), 6.57(3H:s:6-OC$\underline{H}_3$) and 7.61(3H:s:NC$\underline{H}_3$); m/e 478.1724 (M^+ + 16; $C_{26}H_{26}N_2O_7$ requires 478.1740), 432; vapour phase osmometry gave molecular weights of 412 (concentration of 16.8g/l) and 565(2.71g/l). (Found: C, 67.39; H, 5.69; N, 6.13%. $C_{26}H_{26}N_2O_6$ requires C, 67.52; H, 5.67; N, 6.06%)

STRONG ACID HYDROLYSIS OF THE THEBAINE ADDUCT (11; R = C_6H_5CO):-

The adduct (500mg) was dissolved in methanol (5ml), water (5ml) and concentrated hydrochloric acid (1ml) and the resulting solution heated under reflux for 1h then reduced in volume and left to cool to room temperature. Filtration gave the hydrochloride of (15; R = OH), 14β-hydroxyaminocodeinone hydrochloride (327mg, 96%), m.p. 240 - 243°C with decomposition from 288°C; ν_{max} (KBr) 1679cm^{-1}; i.r. spectrum identical with that of authentic sample[110].

STRONG ACID HYDROLYSIS OF (74):-

The benzoate (74) (50mg) was dissolved in methanol (2ml) and

concentrated hydrochloric acid (2 drops) added. After heating 1h at just under reflux temperature the solution was reduced to half its volume under nitrogen and left to crystallise. The 14β-hydroxyaminocodeinone hydrochloride, (15; R = OH), obtained in this way was identical by its i.r. spectrum and mixed m.p. to that obtained previously from the hydrolysis of (11; R = C_5H_5CO).

BENZOYLATION OF 14β-HYDROXYAMINOCODEINONE HYDROCHLORIDE (15; R = OH):-

The hydrochloride of (15; R = OH) (100mg) was dissolved in pyridine at 0°C and excess benzoyl chloride added (0.1ml) and the solution left for 2h and then poured into ice water (100ml). The pH of this solution was taken to 8 with concentrated ammonia and the extracted with ethyl acetate. The extracts were washed copiously with aqueous sodium bicarbonate, water and brine then dried (Na_2SO_4) and evaporated under reduced pressure. After preparative t.l.c. over alumina (chloroform) the main component was isolated to give (15; R = C_6H_5CO), 14β-benyoyloxyaminocodeinone (42mg, 35%), m.p. 104 with decomposition; ν_{max} 3200, 1713 and 1692cm^{-1}; τ 0.80(1H:bs: removed with D_2O:NH), 2.18(2H:m:m-aromatics), 2.53(3H:m:o- and p-aromatics), 3.33(2H:s:H-1 and H-2), 3.41(1H:d: J = 10Hz:H-7), 2.78(1H:d: J = 10Hz:H-8), 5.30(1H:s:H-5), 6.18(3H:s:3-OCH_3) and 7.56(3H:s:NCH_3); m/e 432. (Found: C, 69.60; H, 5.57; N, 6.40%. $C_{25}H_{24}N_2O_5$ requires C, 69.43; H, 5.59; N, 6.48%)

ACID HYDROLYSIS OF THE ADDUCT (11; R = C_6H_5CH:CHCO):-

The adduct (500mg) was dissolved in methanol (5ml) and concentrated hydrochloric acid (3ml) and the solution heated under

reflux for 1h, allowed to cool and white crystalline (73; R = $C_6H_5CH:CH$) 14β-(N-cinnamoyl)hydroxyaminocodeinone hydrochloride was filtered off. (403mg, 77%), m.p. 196°C with decomposition; λ_{max} 222 n.m. (end absorption) and 289 n.m. (ε = 1.00 x 10^4); ν_{max} 3620, 3340, 2720, 1684 1660 and 1615cm^{-1}; τ (dimethylsulphoxide-d_6) -1.48(1H:s: removed with D_2O:N-OH), 0.33(1H:bs: N^+H), 2.38(2H:m:m-aromatics), 2.56(4H:m: o and p-aromatics and CH:CHCO), 2.77(1H:d: J = 16Hz: CH:CHCO), 3.12 and 3.24(2H:ABq: J = 9Hz: H-1 and H-2), 3.07 and 3.80(2H:ABq: J = 10Hz: H-7 and H-8), t 4.57(H1:bs:H-9), 4.98(1H: s:H-5), 6.23(3H:s:3-OCH_3) and 7.02(3H:s:NCH_3); m/e 458 (M^+). This compound has not been successfully analysed. Partition of this material between chloroform and aqueous sodium bicarbonate yielded the free base of (73; R = $C_6H_5CH:CH$) which on crystallisation from ethanol had m.p. 210 - 211°C; ν_{max} 1692 and 1648cm^{-1}; τ 2.40(3H:m:m-aromatics and ArCH:CH), 2.73(4H:m: o- and p-aromatics and ArCH:CH), 3.29 and 3.42(2H:ABq: J = 8Hz: H-1 and H-2), 3.81(2H:s:H-7 and H-8), 4.86(1H:s:H-5), 6.16 (4H:s:3-OCH_3 and NOH) and 7.43(3H:s:NCH_3); m/e 458.

ACETYLATION OF (73; R = $C_6H_5CH:CH$):-

The hydrochloride (73; R = $C_6H_5CH:CH$) (55mg) was dissolved in dry pyridine (5ml), treated with excess acetic anhydride and left at room temperature overnight. The solution was then poured into chloroform and washed copiously with aqueous sodium bicarbonate, water and brine. The chloroform solution after drying and evaporation under reduced pressure afforded crystalline (77),

N-acetoxy-N-cinnamoyl-14β-aminocodeinone (53mg, 95%), m.p. 182 - 49° with decomposition; λ_{max} 215 n.m. (end absorption), and 284 n.m. ($\varepsilon = 2.41 \times 10^4$); ν_{max} 1804, 1693,1655 and 1618cm^{-1}; τ(60°C) 2.40(1H:d:J = 15Hz: ArCH:CH), 2.66(6H:m: CH:CHC$_6$H$_5$), 3.36 and 3.42(2H:ABq:J = 7Hz:H-1 and H-2), 3.50(1H: d:J = 9.5Hz:H-8, 3.92(1H:d: J = 9.5Hz:H-7), 4.97(1H:bs:H-5), 6.18(4H:s:3-OCH$_3$ and H-9), 7.63(3H:s:6-OCH$_3$) and 7.78(3H:s:NCH$_3$); m/e 500 (M$^+$), 440 and 309 (base peak). (Found: C, 69.80; H, 5.55; N, 5.72%. $C_{29}H_{28}N_2O_6$ requires C, 69.58; H, 5.64; N, 5.60%).

NITRATION OF THEBAINE WITH NITRIC ACID:-

Thebaine (1g, 3.2m.mole) was dissolved in acetic acid (5ml) and fuming nitric acid (0.37g, 6.4m.mole) added at 0°C. After 5h the reaction mixture was poured into ice-water, neutralised with aqueous sodium bicarbonate and extracted with chloroform. The combined chloroform extracts were washed with brine, dried (Na_2SO_4) and reduced in volume. Column chromatography over alumina (benzene-chloroform 1:1) gave 14β-nitrocodeinone (53), (101mg, 9 %) identical to that previously prepared. Further elution gave 1-nitrothebaine (43mg, 4%) after crystallisation from ethanol m.p. 196 - 7°C; ν_{max} 1612 and 1520cm^{-1}; τ 2.13(1H:s:H-2), 4.22 and 4.73(2H:ABq: J = 7Hz:H-7 and H-8), 4.44(1H:s:H-5), 5.94(3H:s:3-OCH$_3$), 6.27(3H:s:6-OCH$_3$), 7.46(3H:s:NCH$_3$); m/e 356 (M$^+$). (Found: C, 64.11; H, 5.79; N, 7.88%. $C_{19}H_{20}N_2O_5$ requires C, 64.03; H, 5.66; N, 7.86%).

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