SYNTHESIS OF NOVEL MORPHINANS FROM THEBAINE

A Thesis presented to the University of Glasgow

for the Degree of

Doctor of Philosophy

by

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SUMMARY

The synthesis of codeinone enol ethers from thebaine, via acetals of 14β-bromocodeinone, has been successfully carried out. These enol ethers have, in turn, been converted into 6-alkoxy-6-desmethoxy-19-alkylthevinols, which have been shown to be analgesics of potency comparable to that of morphine.

The reduction of 14β-bromocodeinone dimethyl acetal to thebaine has been investigated, and it has been proved that the reaction leads to highly selective loss of the 6β-methoxy group.

The synthesis of 14β-alkylthionorcodeinones has been accomplished by reaction of N-t-butoxycarbonylnorthebaine with sulphenyl chlorides, followed by deprotection. Thebaine itself does not undergo sulphenylation under these conditions and has proved unreactive towards other sulphur reagents. However, 14β-(2-phenylethyl)thiocodeinone has been produced by N-methylation of the corresponding nor base. These alkylthiocodeinone derivatives have been tested for analgesic potency and have been found to be analgesics of moderate to high activity. Some reactions of the alkylthionorcodeinones, including their oxidation to 14β-alkylsulphonylnorcodeinones, have been investigated.

Thebaine has been found to react with certain sulphenyl chlorides in the presence of triethylamine to give Diels-Alder type adducts, whose formation is consistent with generation of thioaldehydes *in situ*. The formation of these adducts, the first of their kind, and some of their reactions have been investigated.

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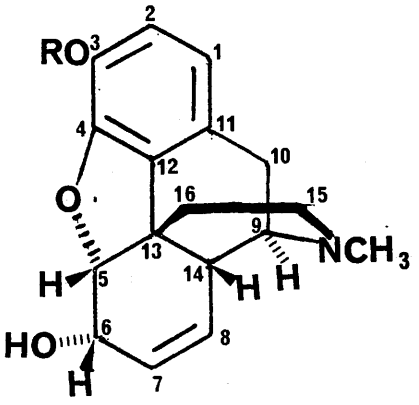
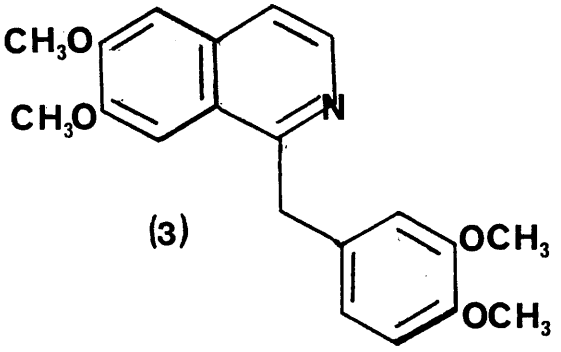
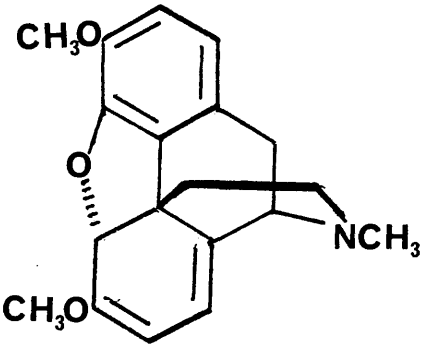

RO
HO
O
NCH3
H
H
H
H
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16

(1) R = H

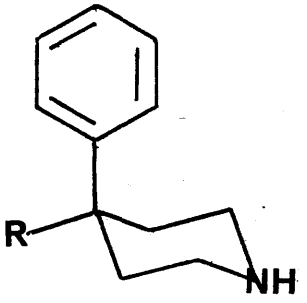
(2) R = CH_3


CH3O
CH3O
N
OCH3
OCH3

(3)


CH3O
O
NCH3
CH3O

(4)



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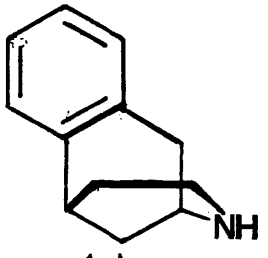

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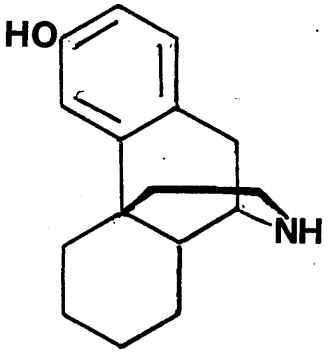
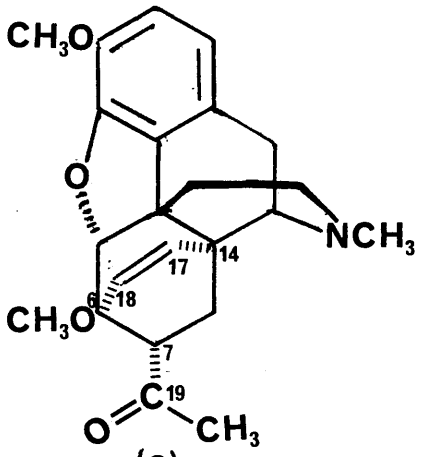


(7)

Increased potency is not the only objective of chemists in this field. Morphine itself is a potent analgesic, is relatively long-lasting, and is readily available in quantity. Despite this, its clinical use is limited by a range of undesirable side effects, including respiratory depression, euphoria and disphoria, nausea and constipation. Besides this, there is a considerable risk of both physical and psychological addiction. The goal of a great deal of research has been to separate analgesic activity from the undesirable effects of the opiates. One strategy employed was based on the concept of an active 'core' in the molecule, responsible mainly for analgesia, with other functional groups causing or enhancing the side effects of morphine. Such an approach led to synthesis of compounds such as the 4-phenylpiperidines (5),[3] the benzomorphans (6)[4] and the 3-hydroxymorphinans (7)[5] which possessed some of the structural features of morphine. Many of these compounds are active analgesics; however, they also share the side-effects of morphine.

An alternative approach is based on the idea that a more rigid molecule than morphine might, because of its more restricted conformation, interact more specifically with opiate receptor sites in the brain, giving selectivity in favour of particular effects. On this basis, Bentley and coworkers prepared Diels-Alder adducts of thebaine (4) with substituted alkenes, giving 6,14-etheno bridged



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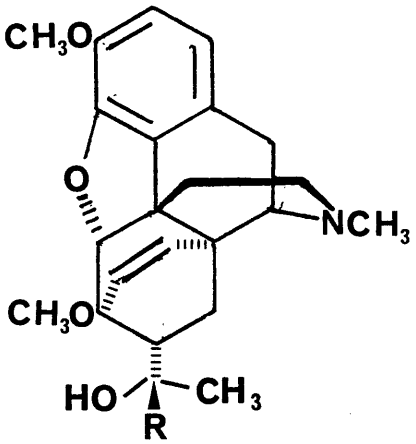

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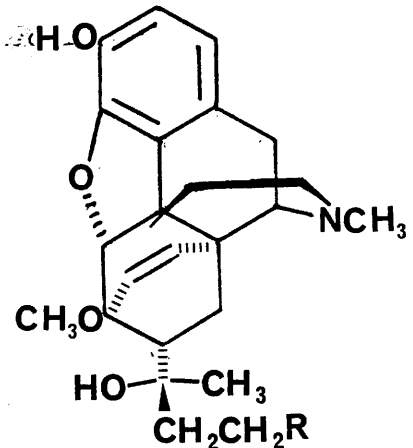


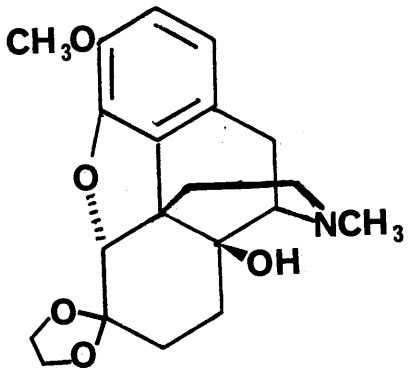
(10)

a. R = CH_3

b. R = Ph

compounds.[6] One adduct in particular, the methyl ketone (8) from thebaine and methyl vinyl ketone, proved to have analgesic potency comparable with that of morphine. Subsequently, Grignard reactions of this ketone gave tertiary alcohols (9) with very high stereoselectivity,[7] and these compounds exhibited analgesic activities up to several hundred times that of morphine. Further synthetic modification led to phenolic derivatives such as etorphine (10a),[8] an analgesic approximately 10^4 times as potent as morphine. A number of such compounds are known, and their structure-activity relationships have been investigated; the greatest activity is associated with the phenylethyl derivative (10b).[9] The geometry of the tertiary alcohol centre and the position of the hydrophobic benzene ring relative to the rest of the molecule are critical factors in the activity of these compounds. Enhanced analgesic activity has also been observed in codeinone derivatives carrying hydrophilic substituents at the 14-position, such as 14 β-hydroxycodeinones.[10] For example, the dihydrocodeinone derivative (11) is more potent than morphine and has the additional advantage of being active when given orally.

A combination of the above factors - a hydrophilic substituent at the 14 β-position, together with a hydrophobic residue attached to ring C of the alkaloid molecule - is found in the 14 β-acylamino-codeinones (12a). These compounds have been synthesised recently,[11,12] and are active analgesics;



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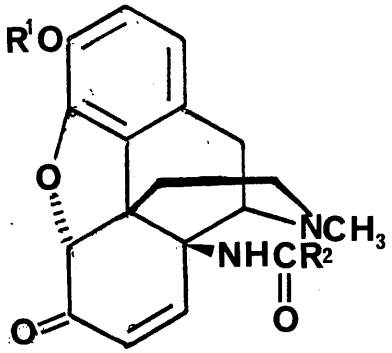
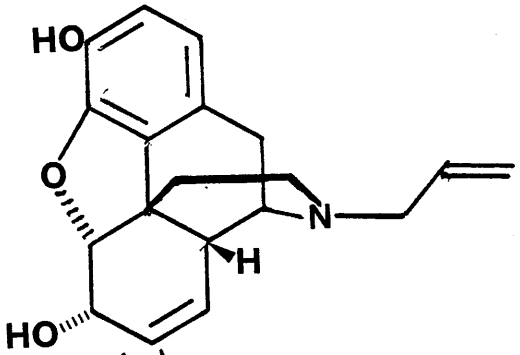


(12)
a. $R^1 = CH_3$
b. $R^1 = H$



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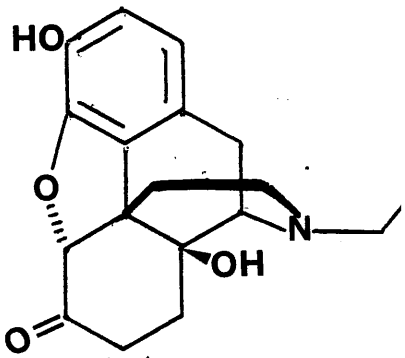
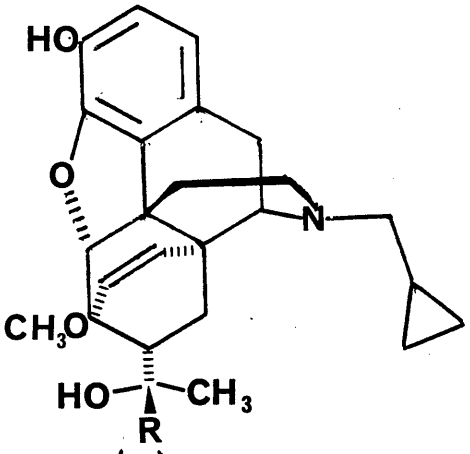


(14)

the derived morphinones (12b) have extremely high potencies, the most active being ca. 10^4 times as active as morphine. As in the 6,14-bridged compounds (10), the maximum potency is found where R^2 is a 2-phenylethyl group.[12]

Perhaps of even greater importance than the synthesis of high-potency opiate analgesics was the discovery that replacement of the N-methyl group of the morphine molecule by certain other alkyl groups, notably allyl or cyclopropylmethyl,[13] produced 'morphine antagonists'; that is, compounds capable of blocking the effects of morphine and related agents. Conversely, a 'morphine agonist' is a compound which produces the same physiological effects as morphine. Morphine antagonists are of considerable importance because of their ability to block or reverse the effects of opiates and other morphine agonists. Thus compounds such as nalorphine (13) or naloxone (14) can be employed as antidotes to opiate-induced narcosis or to accidental overdoses of morphine agonists.

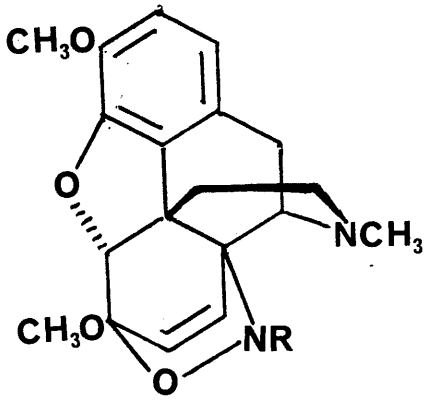
Arising from these results came a number of compounds such as buprenorphine (15a)[14] and diprenorphine (15b) which included structural features associated with both agonist and antagonist activity. Such compounds show mixed agonist-antagonist activity; that is, at low doses they behave as morphine agonists, while at higher doses, or if administered following treatment with an agonist, they act as antagonists. These compounds have considerable potential in clinical use; since a mixed agonist-antagonist acts as its own antidote, the risk



(15)

a. R=CH_3

b. R=*t*-Bu



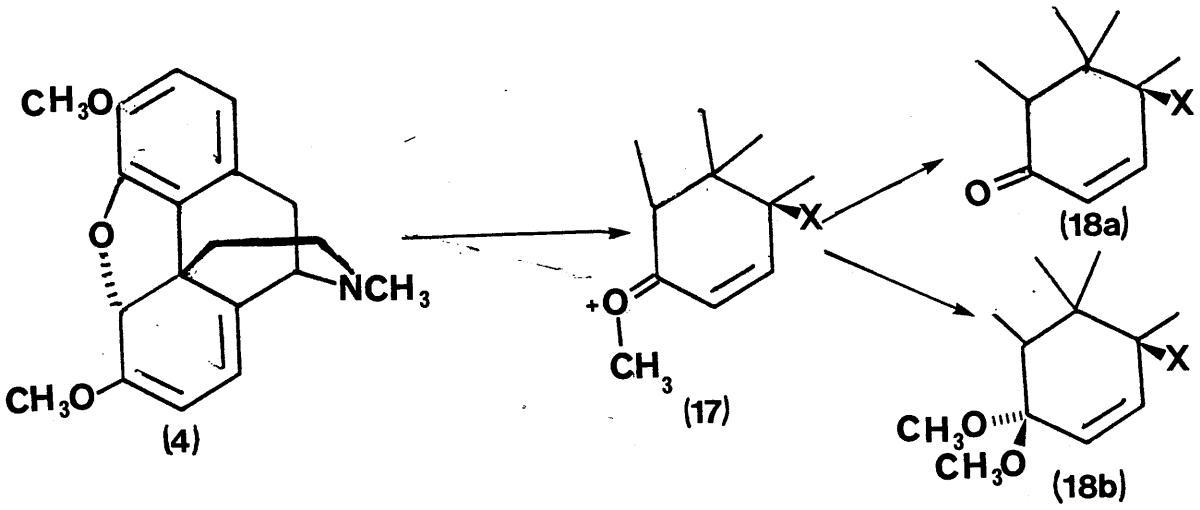
(16)

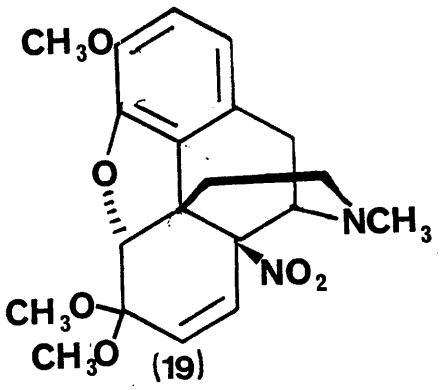
of overdose is greatly reduced and there is much less chance of drug dependence developing. Buprenorphine, for example, shows very low dependence liability. In addition, it is possible to select particular structural features, on the basis of known structure-activity relationships, so that the relative levels of agonist and antagonist activity can be controlled. Thus diprenorphine (15b) is a relatively weak analgesic but a highly potent antagonist, and behaves essentially as a pure κ-agonist. It is used as an antidote to etorphine (10a) and related compounds in veterinary applications.[15]

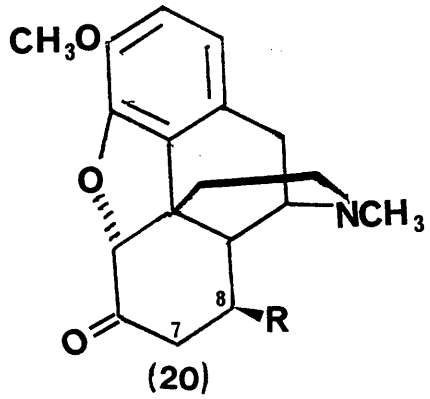
A great many alkaloids with useful pharmaceutical properties have been produced in recent years; for many of these compounds, thebaine has served as an essential synthetic precursor. As a consequence of its methoxydiene system, thebaine undergoes two major classes of reaction which lead either directly to biologically active alkaloids or to intermediates which can be readily converted into highly active compounds;

(1) Diels-Alder type additions

Addition of substituted alkenes to thebaine is the first step in synthesis of compounds such as etorphine (10a), buprenorphine (15a) and diprenorphine (15b) via the ketone (8) as described above. A similar approach has been used in one synthesis of 14 β-acylamino-codeinones,[11] in which C-nitrosocarbonyl compounds react with thebaine to give cyclo-adducts (16), (R=acyl) which are then readily converted into the desired codeinone derivatives.


CH3O
O
NCH3
CH3O
(4)
+O
CH3
(17)
X
O
(18a)
X
CH3O
CH3O
(18b)


CH3O
O
NCH3
NO2
CH3O
CH3O
(19)

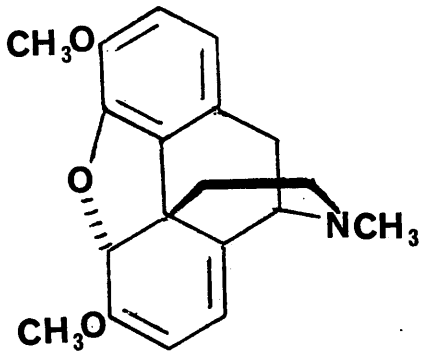

CH3O
O
NCH3
8
7
R
O
(20)

The reaction of thebaine with nitroso-arenes leads to very similar adducts[16] (16; R = aromatic group).

(2) Attack by electrophilic reagents

Usually, electrophiles attack thebaine at the electron-rich 14-position, giving an intermediate methoxonium species (17) which may then undergo hydrolysis to a codeinone derivative (18a) or be trapped by reaction with, for example, methanol to give the codeinone in protected form as its dimethyl acetal (18b). This route is used in synthesis of 14 β-hydroxycodeinones, involving peracids as the electrophilic reagents.[17] It is also employed in the nitration of thebaine with tetranitromethane in methanol,[18] giving 14-nitrocodeinone dimethyl acetal (19) which has been used as an intermediate in the synthesis of 14 β-acylaminocodeinones. Halogens have also been introduced at C-14 by this method, giving 14 β-bromo-and chloro-codeinones.[19] Also in this category are a number of free-radical reactions, such as nitration of thebaine by dinitrogen tetroxide to give 14 β-nitrocodeinone.[20] Again, the entering species is an electrophile, although of a radical rather than ionic nature.

Finally, thebaine can be converted to codeinone in high yield by treatment with hydrogen bromide.[21] In addition to providing an additional source of both codeine and morphine, this reaction has been used as a starting point in other syntheses. For example, the 8 β-alkyldihydrocodeinones (20) have been synthesised from codeinone by 1,4-addition



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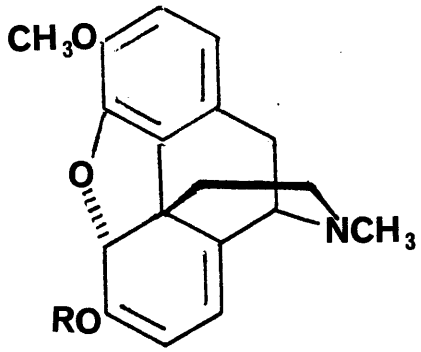


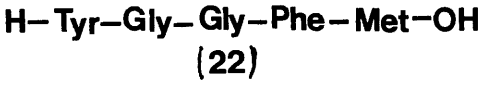
(21)

of lithium dialkylcuprates,[22] and treatment of codeinone with various alcohols under acid catalysis provides one route to the codeinone enol ethers (21).[23]

Thus, the reactions of thebaine (4), based on the properties of its methoxydiene ring C, form the basis of synthetic routes to many highly active opiate agonists and antagonists. Indeed, the utility of thebaine is such that methods for its synthesis from both codeine and morphine have been developed in order to ensure an adequate supply should the quantities of thebaine available from opium prove inadequate.[24] This once neglected compound is now an invaluable synthetic precursor for alkaloids of high biological activity, and will probably continue to provide a starting point for the synthesis of novel opiate alkaloids for many years to come.

2. Alkaloids, Neuropeptides and the Opiate Receptor

Much effort has been devoted to determining the mode of action of opiate alkaloids on the central nervous system. It is known that opiates bind to receptor sites on the membranes of neuronal cells in the brain,[13] usually only one of a pair of enantiomers exhibits strong binding. Such receptors are also found in other tissues, including some in the gut; the presence of these receptors accounts for the nausea or constipation sometimes caused by morphine agonists. The activity of an opiate agonist depends on its ability to bind at these receptors; the stronger the binding, the greater the potency. Further,the potency o



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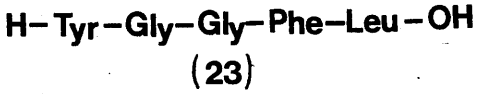

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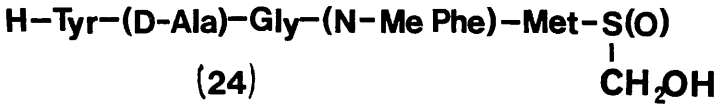


(24)

an opiate depends on its ability to penetrate the neuronal cell membrane, and thus on its solubility in lipids.[25] An additional factor which may influence the activity of opiates is the presence of certain metal ions; morphine, and agonists such as etorphine, bind to the receptor sites more strongly in the presence of divalent cations such as Ca^{2+}, while Na^{+} ions reduce the binding of opiate agonists and increase the affinity of antagonists.[26]

The presence of receptors, in the brain and elsewhere, capable of binding opiate alkaloids implied the existence of endogenous compounds capable of acting as the normal substrates for these receptors. Hughes and Kosterlitz, in 1975, isolated a peptide fraction from pig brain homogenates which had opiate activity; this turned out to be composed of two pentapeptides of structures (22) and (23)[27] which were named enkephalins. These were isolated in the ratio, methionine enkephalin (22) to leucine enkephalin (23), 3:1. Like morphine, the effects of enkephalins are reversed by opiate antagonists, and they appear to bind competitively at the same receptor sites as do opiates.

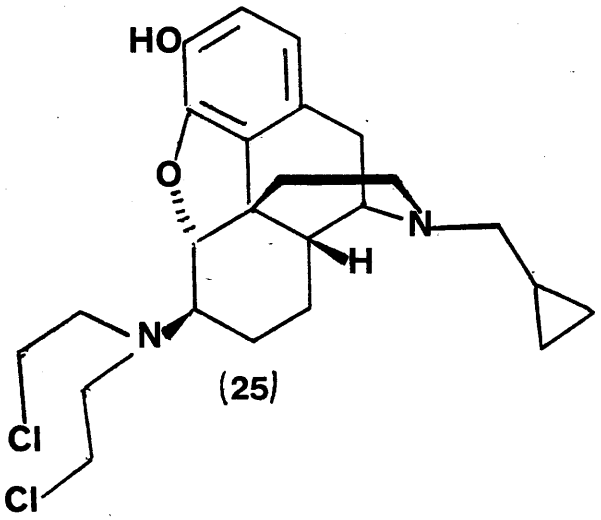
Recent studies have shown that the relative activities of opiates and methionine enkephalin appear to differ in differing tissues. Thus in guinea pig ileum tissue preparations, normorphine and Met-enkephalin display comparable agonist activity, whereas in mouse vas deferens tissue normorphine is some thirty times more potent than Met-enkephalin. Use of tritium-labelled derivatives at very low doses revealed that two distinct types of binding site existed in rat brain; one of these bound opiates

preferentially, while the other displayed preference for enkephalins.[28] In the rat brain, the two types of receptor are present in roughly equal amounts; in other tissues the opiate-selective sites may be present in small amounts or not at all, while enkephalin-selective sites are always present.

The natural enkephalins appear to act as endogenous opiate equivalents. They are destroyed rapidly in body fluids and do not penetrate the blood-brain barrier. However, a number of synthetic analogues such as (24) have been synthesised which combine high opioid activity with stability towards peptidase enzymes. The synthetic enkephalin (24) has approximately 1000 times the analgesic activity of morphine, and about 30,000 times that of Met-enkephalin (23).[29] The presence of an unnatural D-amino acid gives greater stability towards peptidases; indeed this compound is orally active.

Methionine-enkephalin has the same structure as the first five residues of a larger neuropeptide, β-endorphin. β-Endorphin, a polypeptide of 31 amino-acid residues, also displays opiate activity and appears to bind equally well to both types of brain opiate receptor.[28] However, there is no evidence to indicate that β-endorphin is a biosynthetic precursor of Met-enkephalin; indeed enkephalins and β-endorphin are localised in different areas of the brain.[30] The search for enekphalin precursors continues, as does research into the chemistry and biochemistry of neuropeptides.

The structure of the opiate receptors in nervous tissue has not yet been established, and attempts to isolate them have so far failed, since the receptors are very delicate and break down if attempts are made to separate them from the cell membranes.[31] However, some structural features may be deduced, on the basis of known structure-activity relationships in opiate alkaloids. Thus the high potency of phenolic derivatives such as morphine, compared to their 3-methyl ethers (e.g. codeine) implies an anionic site, presumably near a flat, perhaps lipophilic region to accommodate the aromatic ring A. There must also be a lipophilic region at some distance from the anionic site to accommodate the large hydrophobic residues of compounds such as (10b). Further, the 6,14-bridged compounds, such as (10), remain active analgesics; it must therefore be assumed that this bridge is directed away from the receptor, and that the opiate receptor includes a cleft or cavity to accommodate the two carbons of the nitrogen-containing bridge. These are the basic features of the Lewis, Bentley and Cowan model;[32] the lipophilic site is presumably in the vicinity of C-7 and C-8 of the morphine nucleus. A number of plausible configurations exist for the enkephalins which would fit this receptor model. However, there is no evidence to suggest that binding of opiates and enkephalins at the two types of receptor site already discussed (vide supra) involves identical interactions; indeed it is not clear whether all opiate derivatives bind in the same manner at the receptor site. It may well be that the opiate receptor is



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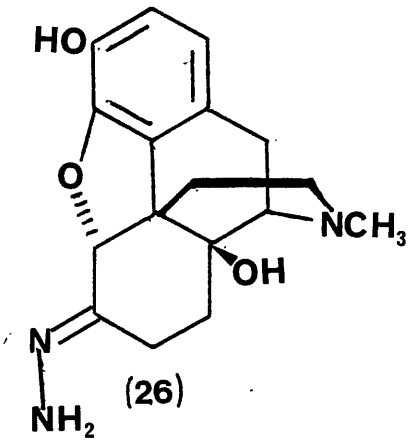
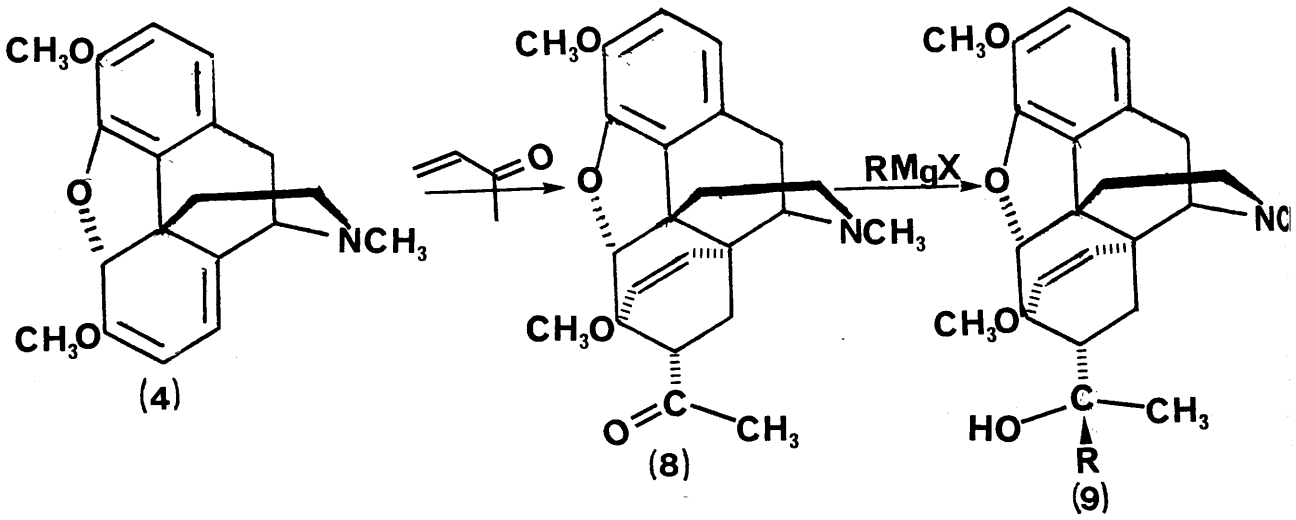


(26)

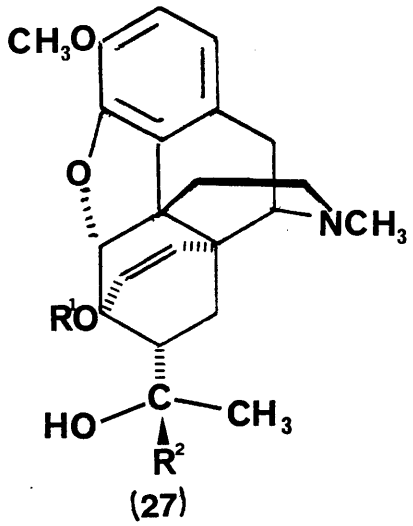
flexible, within certain limits, and can accommodate a range of substrates with comparable affinities.

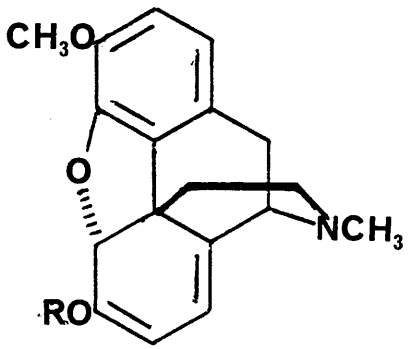
At time of writing, even the nature of the opiate receptor is still unknown. One recent model[33] involves a composite receptor composed partly of a protein (which binds enkephalins preferentially) and partly of an acidic lipid (the preferential binding site for alkaloids). This model assumes that the sites are close enough for β-endorphin to associate with both at once. It accounts for a number of features of opiate binding, such as the reversible inhibition of binding of morphine by phospholipase enzymes, but fails to account for the observation that certain tissues contain only the enkephalin receptor.

A possible means for isolating opiate receptors is suggested by the recent synthesis of ultralong-duration opiate antagonists such as chlornaltrexamine (25)[34] and naloxazone (26).[35] These appear to act by alkylation of the receptor sites, and can prevent the binding of opiates at these sites for 72 hours or more. Perhaps the separation of a brain homogenate by affinity chromatography, on a column carrying these or similar compounds immobilised on the stationary phase, could provide a means of isolating the 'pure' opiate receptor. Until then, the structure of this important receptor remains a matter for speculation.



Scheme1





a.R=Et
b.R=*n*-Pr
c.R=*i*-Pr
d.R=*n*-Bu
e.R=CH_2OMe

DISCUSSION

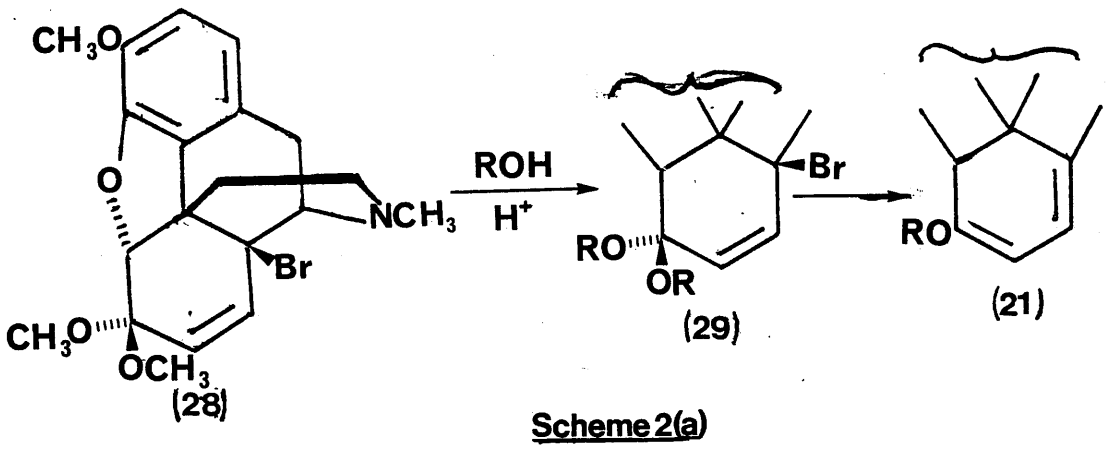
I. SYNTHESIS OF 6-ALKOXY-6-DESMETHOXY-19-ALKYLTHEVINOLS

1) Homologues of thebaine: the codeinone enol ethers

It has been known for many years that thebaine (4) can be converted into tertiary alcohols of general structure (9) by the simple procedure of Scheme 1.[67] Many of these '19-alkylthevinols' are potent analgesics with activities up to several hundred times that of morphine. The chemistry and structure-activity relationships of these compounds have been investigated in some detail; the effects of varying substitution on C-19, on nitrogen and on the aromatic ring have been studied. As yet, however, no data are available regarding the effect of changes in the 6-alkoxy substituent on analgesic activity. Since this substituent may possibly occupy the same region on the opiate receptor site as does the C-terminal amino acid residue of the enkephalin peptides (see Introduction), a small change in the length of the 6-alkoxy substituent might well have a profound effect on opiate activity.

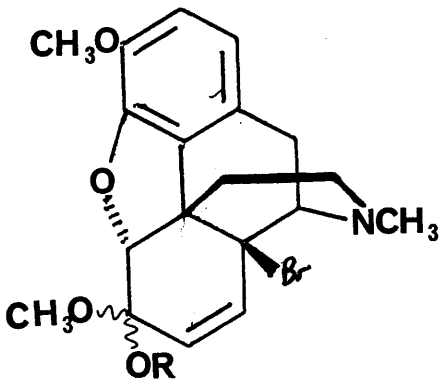
Accordingly, synthesis of the codeinone enol ethers (21) from thebaine was projected, as an essential step in the synthesis of the 6-alkoxy-6-desmethoxy-19(R)-alkylthevinols (27).

A preparation of the enol ethers (21) from codeinone is available,[23] and several (21a - e) have been produced. The method, however, suffers from a number of drawbacks, namely



(28) (29) (21)

Scheme 2(a)



(30)

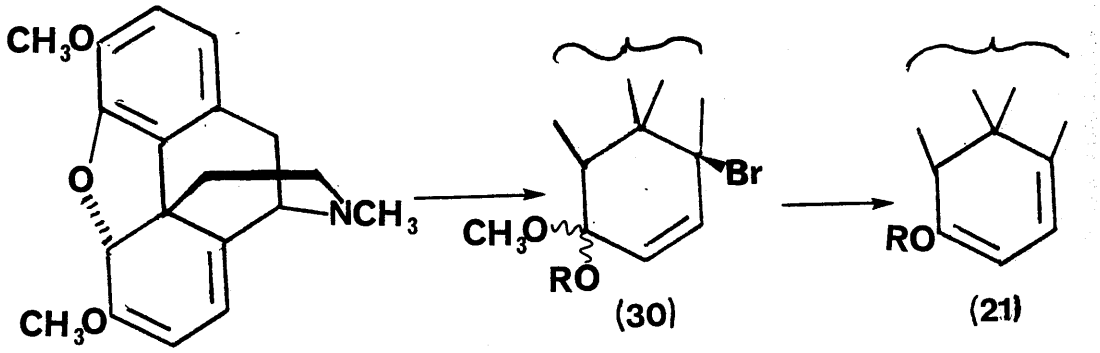
a) Although the preparation is simple (direct enol ether formation under acid catalysis, in the presence of the appropriate alcohol) the subsequent workup is extremely lengthy, involving several chromatography steps.

b) Yields are low; invariably less than 50%.

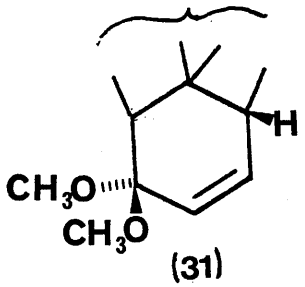
c) The yield of codeinone enol ether is highly sensitive to the nature of the R group.

Accordingly, an alternative route to these compounds was sought. A promising line of enquiry was suggested by the description of two methods whereby 14-bromocodeinone dimethyl acetal (28) could be reduced to thebaine (4).[36] Both the reagents investigated, sodium dihydrobis (2-methoxyethoxy) aluminate ('Vitride') and chromium (II) sulphate, gave high yields of thebaine. The acetal (28) itself was readily accessible by bromination of thebaine in methanol.[37] It was hoped that exchange of the 6,6-dimethoxy groups of this acetal for other alkoxy groups might be feasible; if so, reduction by one of the above methods could be used to give the desired enol ethers (21) via the dialkyl acetals (29) (Scheme 2a).

Another attractive possibility was that of reduction of the mixed acetals (30), resulting from bromination of thebaine in higher alcohols. The success of this method was dependent upon the correct stereochemistry in both bromination

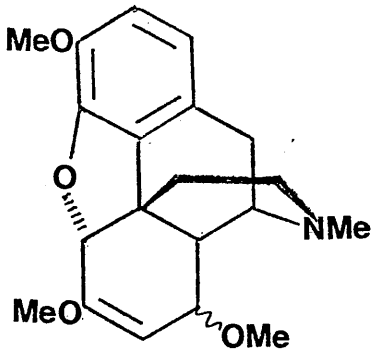


Scheme 2(b)

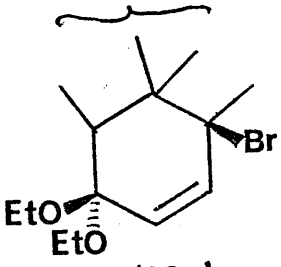


and reduction. However, Rapoport and coworkers have described highly stereoselective routes to thebaine, by elimination of methanol from codeinone dimethyl acetal (31).[38] By selection of the correct reaction conditions, one or other of the stereochemically distinct methoxy groups could be eliminated. There was, of course, no guarantee that reduction of 14-bromocodeinone acetals would display similar stereoselectivity to that shown in the simple 1,4-elimination employed by Rapoport but, if the correct stereochemistry could be obtained, this method would provide a simple synthesis of the desired enol ethers (Scheme 2b). The required bromoacetal (28) was prepared from thebaine in good yield by treatment with N-bromosuccinimide in methanol. Reduction of this acetal was carried out by both literature methods, giving good yields of thebaine, although it was noted that chromium (II) sulphate gave lower yields than did sodium dihydrobis (2-methoxyethoxy) aluminate ('Vitride'); this is contrary to the reports of earlier workers.[36] At this stage, the utility of a third reagent, n-butyl-lithium, was investigated following a report of its use in reduction of (28) to thebaine.[39] This reagent also gave satisfactory results.

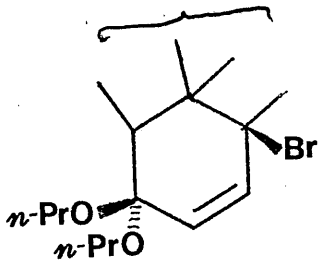
Acetal exchange to give the dialkyl acetals (29a,b) proceeded smoothly, if slowly, at room temperature under mildly acidic conditions, and high yields of the desired acetals were obtained. Although hydrolysis to 14-bromocodeinc proved troublesome at first, this was readily overcome by



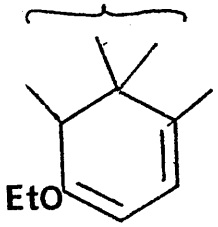
(32)



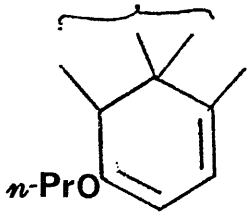
(29a)



(29b)



(21a)



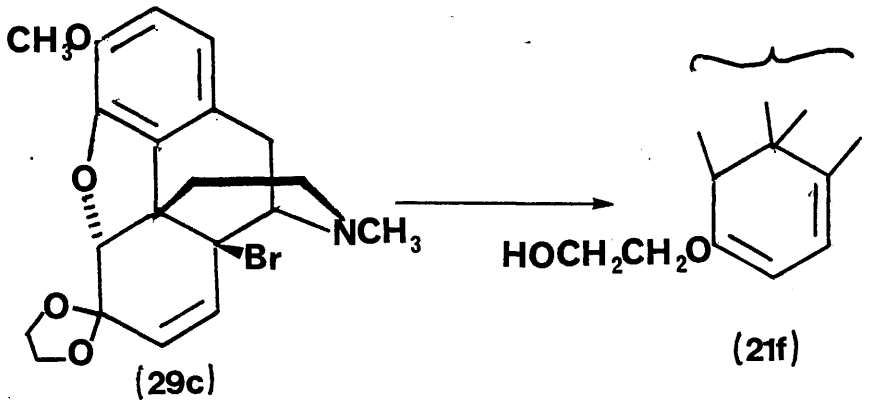
(21b)

careful drying of solvents and the incorporation of 2 - 3 equivalents of triethyl orthoformate as an in situ water trap.

14-Bromocodeinone diethyl acetal (29a) was also made directly from 14-bromocodeinone, although somewhat harsher conditions were required. By contrast, codeinone itself does not readily form acetals; thus Rapoport obtained only 8,14-dihydro-8-methoxythebaine (32) in an attempted synthesis of (31) directly from codeinone.[40]

Spectroscopically, these dialkyl acetals (29) are very similar to the parent dimethyl acetal (28) and show only such differences as might be expected for the replacement of methoxy by other alkoxy groups. It is noteworthy that the non-equivalence of the 6-methoxy groups observed in the ^{1}H n.m.r. spectrum of (28) also appears in the O-methylene groups of (29); indeed, in (29a) the methyl groups of the ethoxy groups are also distinct in the n.m.r. spectrum.

Reduction of the acetals (29a,b) was carried out by each of the three methods investigated, and proved entirely successful; the codeinone enol ethers (21a,b) were isolated in moderate to good yields. Of the reagents employed, chromium (II) sulphate gave the lowest yields; n-butyl-lithium, although giving high yields on occasion, showed rather poor reproducibility. This, together with difficulties obtained in isolating crystalline products, tended to outweigh the greater speed of reaction obtained with this reagent.



(29c) (21f)

For these reasons, the complex hydride, sodium dihydrobis-(2-methoxyethoxy)aluminate ('Vitride') was employed as the reagent of choice for reduction of the dialkyl acetals, as it gave high and reproducible yields of crystalline products.

The melting points of the codeinone and ethers (21a,b) were in good agreement with those given in earlier studies,[23] and their infrared and ^{1}H n.m.r. spectra were very like those of thebaine, the only differences observed being those which arose from the presence of a higher alkoxy group on C-6. Overall yields of these compounds were consistently in the range 50 - 55%, based on thebaine; this compares very favourably with the quoted yields of 22% for (21a) and 45% for (21b), from codeinone. Although the route of Scheme 2(a) is lengthier than that already employed by Seki, it appears to lead to higher yields and is less sensitive to the nature of the R group.

Attention at this stage was directed towards synthesis of the cyclic acetal (29c). It was hoped that this could be reduced, with concomitant opening of the acetal ring, to give the novel enol ether (21f), which is not accessible by Seki's method.

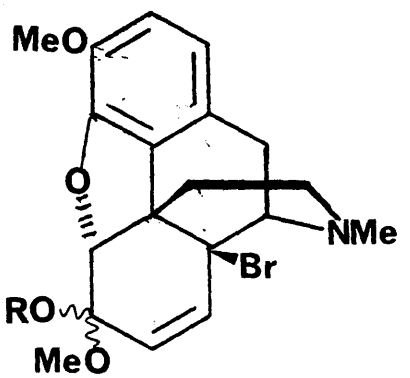
Conversion of dimethyl acetal (28) to the cyclic acetal (29c) was accomplished in good yield by treatment with hydrogen chloride in dry ethylene glycol. The rate of reaction appeared much higher than for the dialkyl acetals (29a,b), the reaction being complete in 3 - 4 hours at room temperature. Reduction of (29c) was carried out successfully using 'Vitride' as

reducing agent, and a high yield of (21f) was obtained. The other reducing agents gave unsatisfactory results with this system and no enol ether was isolated.

The novel enol ether (21f) is of particular interest as an intermediate in the synthesis of compounds of the 'thevinol' type (9;27) with a polar group at a site remote from the tertiary alcohol function. In addition, it provided a means whereby both polar (e.g. -CHO, $-CO_2H$) and nonpolar (e.g. methyl or benzyl ether) functions could be introduced on a flexible side chain.

The identity of (21f) was confirmed by both analytical and spectroscopic data; particularly the similarity of its u.v. spectrum to that of thebaine, and marked similarities in the olefinic regions of their n.m.r. spectra, confirmed the structure of (21f). An unusual feature of the n.m.r. spectrum of this compound is the near equivalence of the protons of the 2-hydroxyethyl side chain and of the 3-methoxy group; these appear as a seven-proton singlet.

In summary, the method of Scheme 2(a) was applied successfully to the synthesis of the known codeinone enol ethers (21a,b) and of the novel enol ether (21f). The alternative method of enol ether synthesis shown in Scheme 2(b) was next investigated. Bromination of thebaine in ethanol gave the noncrystalline mixed acetal (30a) whose ^1H n.m.r. spectrum showed only one 6-methoxy singlet (δ 3.44). By contrast, the dimethoxy compound (28) displays two well separated singlets (δ 3.44 and δ 3.17).



(30)

a. R = Et

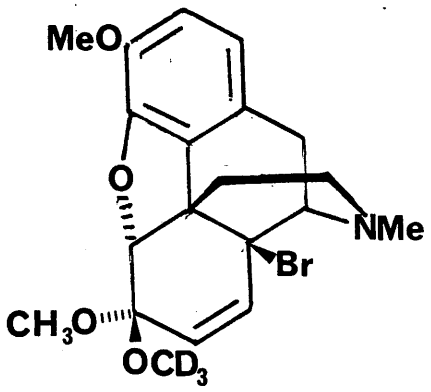
b. R = Et

c. R = CH_2CH_2OH

It was clear that bromination was highly stereoselective. Similarly, bromination of codeinone and ethyl ether (21a) in methanol gave a crystalline compound (30b) whose ^{1}H n.m.r. spectrum displayed only the higher-field methoxy singlet (δ 3.17). The products of these bromination reactions were clearly epimers at C-6, but unambiguous assignments of the geometry at this centre could not be made at this point.

Reduction of the mixed acetal (30a) derived from thebaine was carried out using chromium (II) sulphate and yielded a crystalline product which was in all respects identical with thebaine. No trace of the other possible product, codeinone enol ethyl ether (21a) was detected by n.m.r. spectrocopy. In a further attempt at enol ether synthesis by this route, another mixed acetal, (30c), was obtained by treatment of thebaine with N-bromosuccinimide in ethylene glycol. This acetal, on treatment with chromium (II) sulphate or 'Vitride' following the procedures used in reduction of the dialkyl acetals (29), again afforded thebaine as the sole product of reduction.

These results indicated that both bromination of thebaine and reduction of the resulting acetals proceeded with a high degree of stereoselectivity; however, the overall stereochemistry was such that the alkoxy group introduced on bromination was also the one removed during reduction. Consequently, it was apparent that codeinone enol ethers would not be accessible by this route, and the acetal exchange reaction of Scheme 2(a) was necessary if synthesis of these compounds was to be accomplishe



(33)

2) Stereochemistry of acetal formation and reduction

To establish the degree of stereoselectivity of the bromination of thebaine, and to examine the selectivity of each of the reduction methods employed, it was decided to introduce deuterium labels into the 6-methoxy groups of the acetal (28). This was carried out without difficulty by treatment of thebaine with N-bromosuccinimide in perdeuteriomethanol, and it was apparent from the n.m.r. spectrum of the resulting acetal that the same stereoselectivity shown in other mixed acetals was also displayed here. The n.m.r. spectrum of (33) showed only the 6-methoxy singlet at δ 3.44; the high-field methoxy resonance at δ 3.17 could not be detected. Apart from this, the spectrum of (33) was identical in all respects with that of unlabelled material. From the apparently total absence of the high-field 6-methoxy resonance, it was deduced that the bromination of thebaine exhibits essentially 100% stereospecificity in favour of a single C-6 epimer.

Reduction of the labelled acetal (33) was carried out using each of the reagents already employed in acetal reduction (vide supra). The n.m.r. spectra of the products in each case indicated that the thebaine produced consisted mainly of undeuteriated material.

The mass spectra of the reduction products were examined to determine the degree of loss of label. The results proved to be remarkably uniform; as calculated from the relative intensities of the m/e 314 and 311 peaks, the ratio

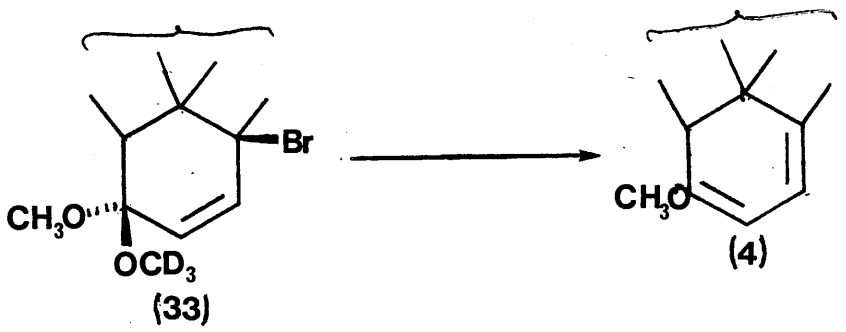


TABLE 1

Reduction of the Labelled Acetal (33) to Thebaine

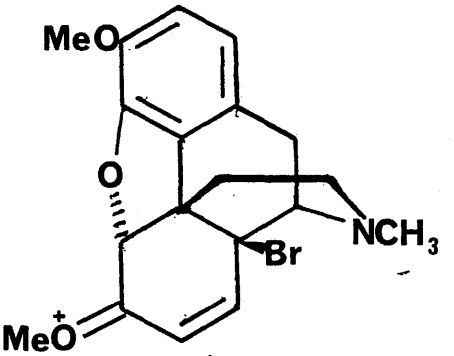
	Cr(II)	'Vitride'	$Bu^n li$	Natural Thebaine
m/e 314: m/e 311	0.11 ± 0.01	0.077 ± 0.005	0.095 ± 0.005	$(8.5 \pm 0.5) \times 10^{-3}$
m/e 299: m/e 296	0.07 ± 0.01	0.06 ± 0.01	0.09 ± 0.01	a
m/e 258: m/e 255	0.11 ± 0.01	0.07 ± 0.01	0.10 ± 0.01	a

Note: a. No peak visible at the higher m/e value.

of trideuteriothebaine to thebaine lay in the range 0.07 - 0.10 (see Table 1). Similar ratios were observed for two major fragment ions.

These results indicate that reduction of the labelled acetal (33) shows high selectivity, at least 90% of the deuterium label being lost. Consequently, it is apparent that both bromination of thebaine and reduction of the resulting acetals show identical stereochemistry. The degree of stereoselectivity in the reduction process is little affected by the reducing agent employed.

That three reagents of such differing nature should exhibit such similar degrees of stereoselectivity is quite remarkable and would seem to suggest some similarity between their mechanisms of reaction. The selectivity shown may well reflect the greater accessibility of one face of ring C, and it is likely that the reducing agent will approach preferentially from the β face of the acetal. Earlier workers[36] have suggested that reduction by 'Vitride' and by chromium (II) involves attachment of the reducing agent at C-7, and this would certainly be easier to accomplish from the β face (i.e. from the same side as the nitrogen bridge) since approach to the convex α face of ring C is likely to be hindered by the π-electron clouds of ring A. This would be particularly applicable in the case of the bulky dihydrobis (2-methoxyethoxy) aluminate ion of 'Vitride'.



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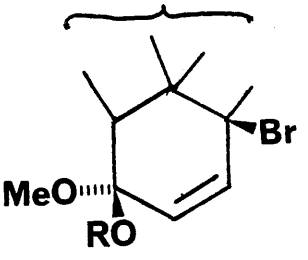
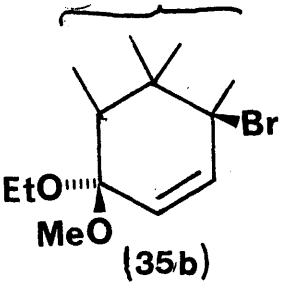


(35a) R=Et

(35c) R=CH_2CH_2OH

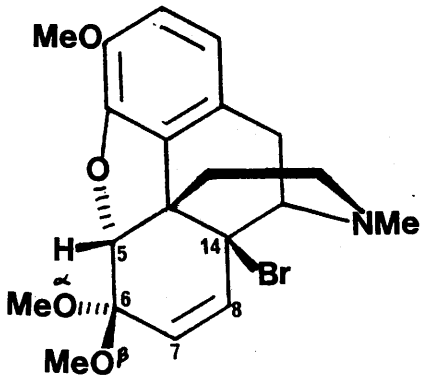


(35b)

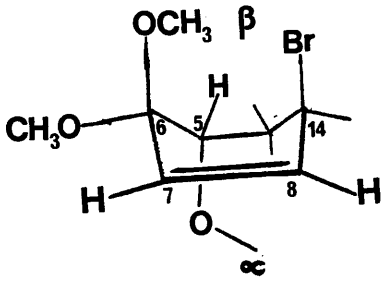
On the same steric arguments, it seems likely that the labelled methoxy group in (33) is in fact the 6 β-methoxy group. It would seem reasonable to assume that the intermediate methoxonium ion (34), arising from attack of electrophilic bromine at C-14 of thebaine, would be attacked preferentially by an alcohol from the less hindered β face. Thus, the entering alkoxy group will be incorporated in the 6 β-position with high selectivity, giving structure (35a) for the mixed acetals derived from thebaine and structure (35b) for the acetal derived from bromination of codeinone enol ethyl ether in methanol.

The results of this study illustrate the very high stereoselectivity involved in the formation of 14-bromo-codeinone acetals. On the basis of the configuration of thebaine, it appears very likely that the stereochemistry of acetal formation is syn, with both the bromine and the entering alkoxy group approaching from the less hindered β face of the diene.

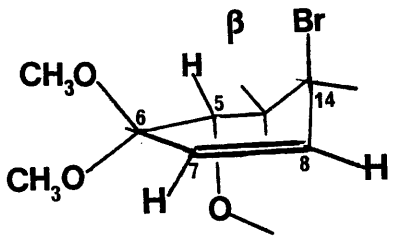
Similarly, the reduction of the labelled acetal (33), shows a high degree of stereoselectivity, giving at least 90% loss of the deuterium label incorporated in acetal formation. The degree of selectivity is little affected by the choice of reducing agent, and the preferred stereochemistry of reduction is apparently the same as that of acetal formation, namely syn, leading to loss of the 6 β-methoxy group. Although these arguments appear to account for the stereochemistry of acetal


MeO
O
NMe
H
5
14
Br
α
MeO
6
8
MeO
β
7

(28)


OCH3
β
Br
H
CH3O
6
5
14
H
7
8
H
O
α

I


β
Br
CH3O
H
5
6
14
CH3O
7
8
H
H
O
α

II

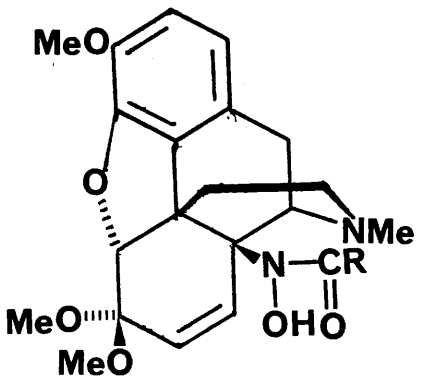
formation, confirmation that they were indeed an accurate explanation depended on an unambiguous assignment of the methoxy resonances in the n.m.r. spectrum of (28). The above line of reasoning supposes the high-field resonance at δ 3.17 to be due to the 6β - and the low-field resonance at δ 3.44 to the 6 α -methoxy group. The accuracy of this assignment, however, depends on the conformation adopted by ring C of the acetal, and it was quite possible that, given the correct conformation of ring C, the 6 α -methoxy group might occupy the more shielded environment.

Study of molecular models revealed two possible conformations, namely:

(i) A boat conformation (structure I). Here, the 6 α-methoxy group is quasi-equatorial and is directed away from the π-electron clouds of ring A, which might otherwise have shielded it. The quasi-axial 6 β-methoxy group, although similarly out of the shielding zone of ring A, might still experience shielding from the π-electrons of the olefinic double bond.

In this conformation, H-7 and H-5 are positioned favourably for long-range 'W' coupling.

(ii) A half-chair conformation (structure II). Here, the positions of the methoxy groups are reversed; the 6 α-methoxy is in an axial position, in which it is tucked under ring A and will be shielded by the aromatic π-electrons. The 6 β -methoxy is equatorial



(36)

and could not be shielded, either by the aromatic ring or by the olefinic double bond.

In this conformation, the relative positions of H-5 and H-7 appear to be unfavourable for long-range coupling.

Thus, the two possible conformations lead to exactly opposite results for the assignment of the methoxy groups based on chemical shift. However, the ^{1}H n.m.r. spectrum of (28) displays a small (J ca 1 Hz) coupling between H-5 and H-7. This was confirmed by a decoupling experiment and is strong evidence in favour of conformation I.

Earlier work by Rapoport et al[38,40] tends to support this conclusion. Study of the ^{1}H n.m.r. spectrum of codeinone dimethyl acetal (31) led to the conclusion that ring C adopts a boat conformation, in which the quasi-equatorial 6 α-methoxy group gives rise to the low-field methoxy resonance. A similar assignment of the methoxy resonances has been arrived at in the acetals (36); it was found that the precise position of the high-field 6-methoxy resonance depended on the nature of R, whereas the low-field resonance was essentially unaffected. On this basis, the high-field resonance was assigned to the 6 β-methoxy group, and the low-field resonance to the 6 α.[11] This, however, revealed little regarding the conformation of ring C; it was still possible that interaction between a bulky 14 β-substituent and the axial methoxy group might make the boat form energetically unfavourable.

Further spectroscopic evidence in favour of one or other of the possible conformations was therefore sought by means of nuclear Overhauser experiments. Models indicated that in the boat conformation of ring C both methoxy groups could occupy positions close to either H-5 or H-7, given free rotation. By contrast, the axial position of the 6 α - methoxy group in the half-chair conformation means that it will be directed away from H-5, and so could not show any nuclear Overhauser enhancement with this proton. Both methoxy groups might still be close enough to H-7, and the 6 β - methoxy group close enough to H-5, for enhancement to occur.

Given that free rotation of the methoxy groups was possible, then one might expect to see enhancement of the H-5 and H-7 signals when irradiation was carried out at either methoxy resonance, if ring C adopts a boat conformation. If, however, ring C is a half-chair, irradiation at the 6 α -methoxy resonance should lead only to enhancement of the H-7 signal, while irradiation of the 6 β -methoxy resonance should again give enhancement of H-7 and possibly of H-5 as well.

Nuclear Overhauser enhancement studies were carried out and the effect of irradiation at the methoxy resonances on the integration heights of the H-5, H-7 and H-8 resonances was observed. Enhancement was determined by comparison of integration heights for these resonances with those of a control spectrum in which irradiation was carried out far from the methoxy resonances.

Irradiation at the high-field methoxy resonance (δ 3.17) led to an enhancement of 12.4% in the H-7 resonance, while the H-5 resonance was not affected. A small enhancement of 3.4% was observed in the H-8 resonance; this latter result was probably not significant as it was within the likely range of experimental error.

Irradiation at δ 3.44, on the low-field methoxy resonance, left the olefinic protons unaffected; however, there was an enhancement of 5.1% in the H-5 resonance.

These results are inconclusive. The lack of enhancement of H-5 on irradiation at δ 3.17 seems to favour the assignment of this resonance to the 6 α-methoxy in a half-chair conformation (structure II). However, the results of irradiation at δ 3.44 tend to support the opposite assignment - that of 6α-methoxy in boat conformation I, since the 6 β-methoxy group in conformation II would lie almost in the plane of the double bond and would tend to remain close to H-7. Thus, if the 6 β-methoxy group was responsible for the δ 3.44 signal irradiation at this position would almost certainly lead to enhancement of the H-7 resonance.

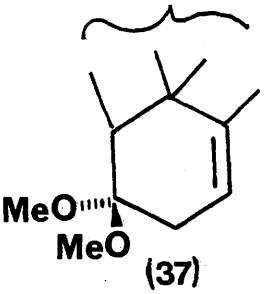
To summarise, then, it has been found that bromination of thebaine gives one of the possible mixed acetals with almost complete stereospecificity. The shape of the thebaine molecule suggests that syn-stereochemistry is preferred, with the bromine and entering alkoxy group approaching from the less hindered β-face of the diene system to give the 6 α-methoxy-6 β-alkoxy epimer(35a). These conclusions have been confirmed by deuterium labelling.

The observed coupling between H-5 and H-7 indicates that ring C of the acetal (28) adopts a boat conformation in solution, as is already known to be the case in codeinone dimethyl acetal.[38] However, nuclear Overhauser experiments to confirm this conformation have proved inconclusive.

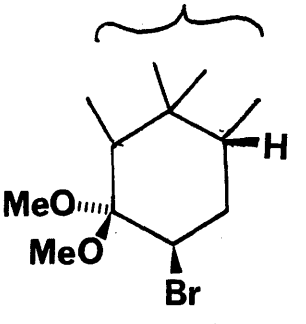
3) Tri-n-butyltin hydride reduction

Earlier workers had postulated a free-radical intermediate in the reduction of dimethyl acetal (28) by chromium (II) sulphate. The mechanism as advanced, however, seemed unlikely, involving as it did unassisted homolysis of the carbon-bromine bond as the first step of reaction. Nevertheless, the possibility of a free-radical intermediate remained, and it was decided to attempt reduction using a reagent known to react by a free-radical mechanism.

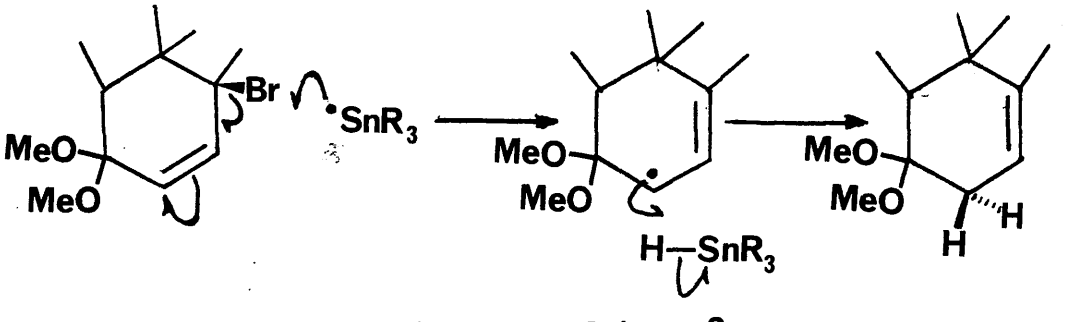
The reagent chosen was tri-n-butyltin hydride, which is known to reduce alkyl bromides to alkanes via alkyl radicals.[41] Some initial difficulties were encountered in removal of the tin-containing byproducts, but success was achieved by the method of Borge and Roberts.[42] A large excess of hydride was employed and complete consumption of starting material was apparent by t.l.c. However, the product when isolated was, quite clearly, not thebaine; it was noncrystalline and its ^{1}H n.m.r. spectrum differed radically from that of thebaine. In particular, only one resonance (a double doublet corresponding to one proton) was visible in the olefinic region and both 6-methoxy groups were



(37)



(38)



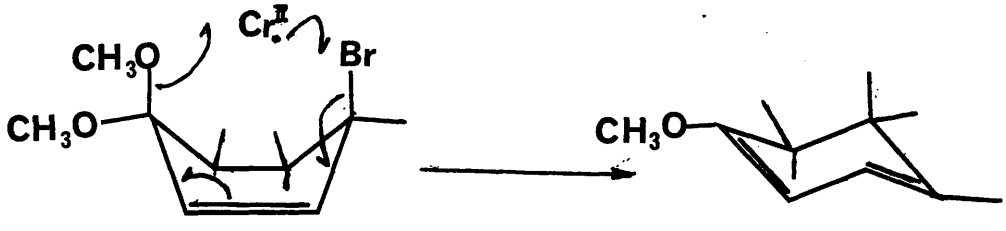
Scheme 3

apparently still present, although one signal had shifted upfield to δ 2.93.

The presence of only a single olefinic proton was strongly suggestive of a neopine-like system, and a brief inspection of the literature revealed that the ^{1}H n.m.r. spectrum of the isolated material was identical in all respects to that of neopinone dimethyl acetal (37). This compound has been reported[43] as a product of the catalytic hydrogenation of bromoacetal (28).

Reduction of the labelled bromoacetal (33) gave a product whose ^{1}H n.m.r. spectrum displayed only the high-field methoxy signal at δ 2.93. Given the stereochemistry of bromination (vide supra) this resonance must be due to the unlabelled 6 α -methoxy group, indicating that this group is being shielded by the π -electrons of ring A. It seems unlikely that such a degree of shielding could be accounted for by the π -electrons of the double bond. Shielding by the aromatic ring would imply in turn a half-chair conformation for ring C of the neopinone acetal (37) in contrast to the boat conformation preferred in codeinone acetals (28) and (31). A similar degree of shielding is exhibited in the 7 β -bromo species (38), in which ring C adopts a chair conformation with the axial 6 α -methoxy appearing at δ 3.09.[38]

Quite clearly, then, 'pure' free-radical reduction of (28) gave an entirely different result from that obtained employing chromium (II) sulphate. The reaction probably proceeds as shown in Scheme 3.

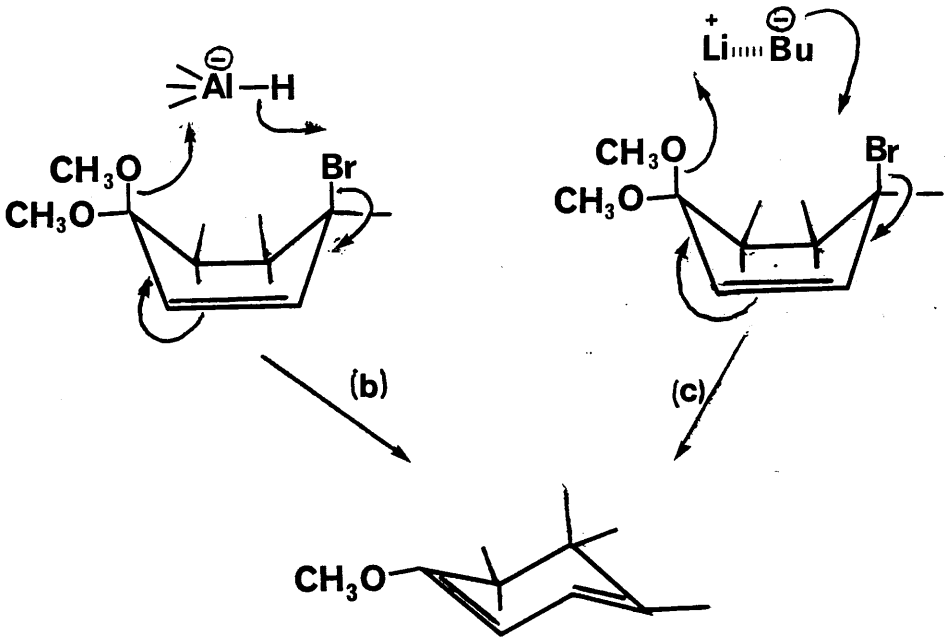


Scheme 4(a)

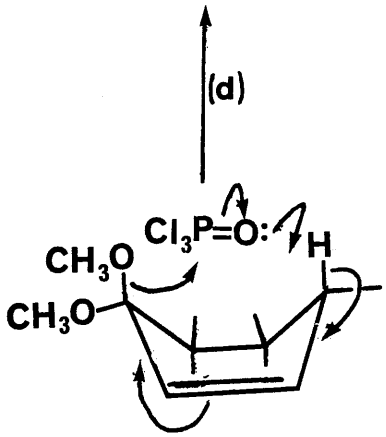
As a further test, it was decided to attempt interception of the presumed radical intermediate involved in chromium (II) sulphate reduction. It was already known that the related reagent, chromium (II) acetate, reacted with alkyl halides in the presence of a thiol to give products consistent with trapping of an intermediate alkyl radical.[44] However, when (28) was reduced with chromium (II) sulphate in the presence of several equivalents of 1-hexanethiol, thebaine was the sole product. No trace could be detected of either neopinone dimethyl acetal or codeinone dimethyl acetal, the expected products of radical trapping.

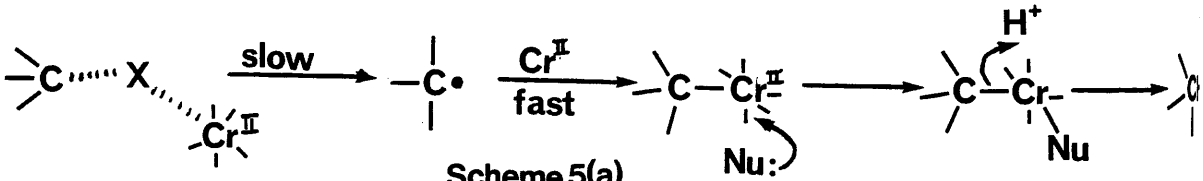
It is apparent from the above results that the presumed radical intermediate in chromium (II) sulphate reduction cannot be long-lived, since it evidently undergoes conversion to some non-radical form far more rapidly than it abstracts hydrogen from a thiol. Indeed, the results of tri-n-butyltin hydride reduction cast doubt on the presence of such an intermediate as a distinct species, given the different products obtained. It is therefore suggested that, while reduction by chromium (II) sulphate involves one-electron transfer, the radical intermediate does not, in fact, exist as a separate entity, but is co-ordinated at all times to a chromium (II) or (III) species.

The mechanism of Scheme 4(a) is proposed for reduction by chromium (II) sulphate. This mechanism accounts for the observed stereochemistry of reduction; the greater ease of approach to the β face of ring C and the favourable orbital overlap between the axial bonds at C-6 and C-14 and the π-orbitals of the double bond

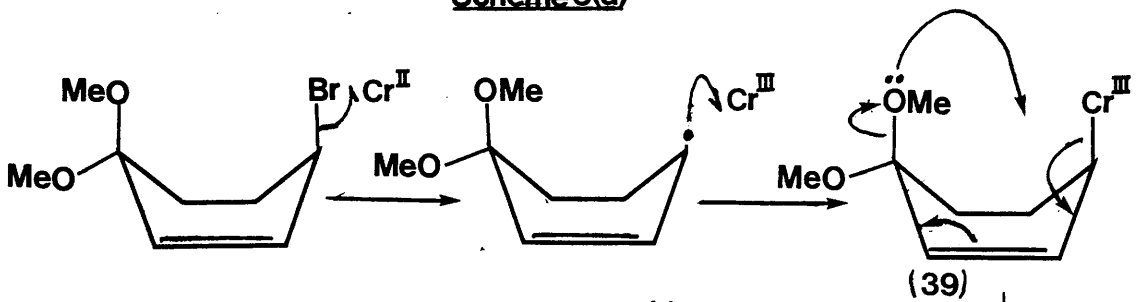


Scheme 4

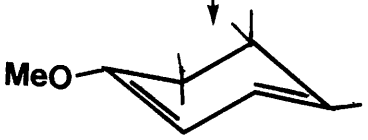




Scheme 5(a)



Scheme 5(b)



would lead to highly selective loss of the 6 β-methoxy group.

It is tempting to invoke similar mechanisms for reduction by 'Vitride' or n-butyl lithium (Scheme 4(b) and (c)). Such similarities account for the observed similarity in stereoselectivity of reduction (vide supra). In support of this, Rapoport describes a virtually identical mechanism in the syn-elimination of methanol from codeinone dimethyl acetal by $POCl_3$ (Scheme 4(d)).

The accepted mechanism of chromium (II) reduction of alkyl halides was described by Castro and Kray,[45] and involves initial formation of a carbon radical by ligand exchange with the halide (Scheme 5a). This intermediate is then trapped by a second chromium (II) ion giving an organo-chromium intermediate. Such intermediates have been detected during reduction of benzyl halides,[46] and it is assumed that trapping of the radical is rapid compared to its formation. However, "it remains open whether the radical is entirely free as shown or loosely affiliated with the metal ion".[45] Thus the bromo-chromium species formed by bromine transfer may be involved in the trapping step, leading to eventual liberation of an unstable chromium (II) species which would then react with chromium (II) to give the green chromium (III) species (Scheme 5b).

Such a mechanism has the advantage that it accounts for the failure of attempted trapping of the radical intermediate by a thiol (vide supra). If the chromium species involved in

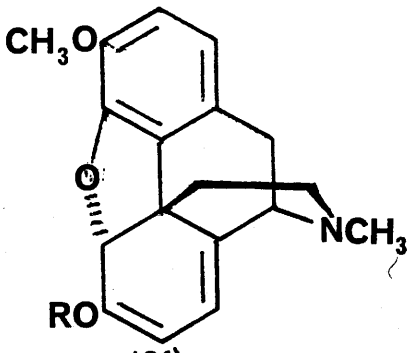
radical trapping is the bromochromium (III) ion, then the trapping step would be virtually instantaneous since the radical centre and chromium (III) species would remain in close proximity after radical formation.

By this reasoning, the radical intermediate formed in reduction of (28) by chromium (II) has only a transient existence and, as postulated earlier (vide supra) is coordinated to a chromium ion - in this mechanism, a chromium (III) ion. This is not inconsistent with the observed stereochemistry of reduction, as the 6 β -methoxy group in the organochromium intermediate (39) is close enough (2.5Å) for oxygen-chromium bond formation. This, in turn, would result in elimination of a methoxychromium species which, under the acidic conditions of reaction, would rapidly decompose. The bromochromium (III) ion is also known to be unstable under the conditions of reaction.

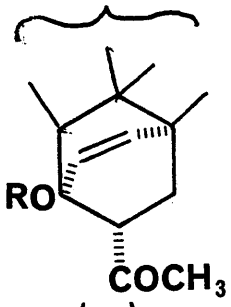
4) Diels-Alder and Grignard reactions: 6-alkoxy-6-desmethoxy-19-alkylthevinols

The synthesis of the codeinone enol ethers (21) was accomplished as described in Section 1 (vide supra) and conversion of these compounds to the corresponding 'thevinol' homologues was next attempted, following the method of Bentley and coworkers.[6,7].

The enol ethers (21) were converted into their Diels-Alder adducts (40) without difficulty in refluxing methyl vinyl ketone. The product isolated in each case appeared to be the



(21)

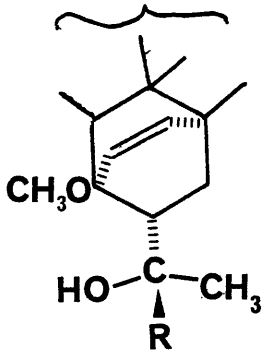


(40)

a. R = Et

b. R = n-Pr

c. R = CH_2CH_2OH

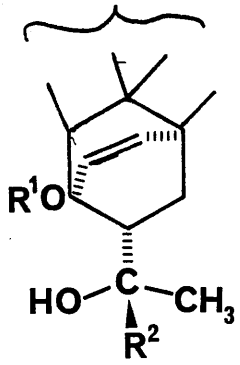


(9)

a. R = CH_3

a. R = n-Pr

b. R = CH_2Ph



(27)

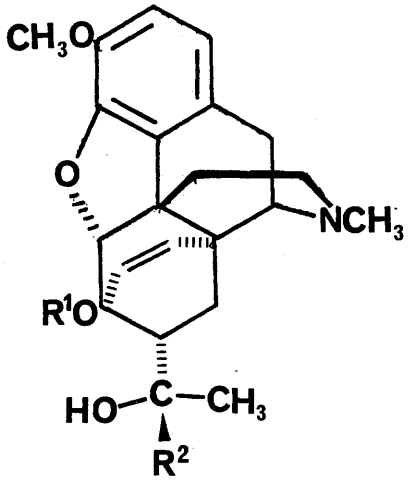
7 α-acetyl isomer; no trace could be detected either spectroscopically or by t.l.c., of the 7 β -epimer reported by Bentley as a minor product (ca. 1%) of Diels-Alder reaction between thebaine and methyl vinyl ketone. The ^{1}H n.m.r. spectra of the novel adducts (40) appeared virtually identical with that of the parent ketone (8) as described by Fulmor et al,[47] apart from the differences to be expected from the presence of higher 6-alkoxy substituents. However, one noteworthy feature was the magnetic non-equivalence of the O-methylene protons in these compounds; the methylene resonance in all cases appears as a complex multiplet. The novel adducts (40) were fully characterised by spectrocopic methods and gave correct elemental analyses; (40c) analysed as a hemihydrate.

Grignard reactions of the parent ketone (8) in diethyl ether were successfully carried out leading to the known tertiary alcohols (9). Spectroscopic and melting point data were in accord with the literature values.[7,47]. However, attempted reaction of the novel ketones (40) under identical conditions led to unsatisfactory results. At best, only poor yields of the tertiary alcohol (27a) were obtained by reaction of (40a) with n-propylmagnesium bromide, and chromatography on silica was required to give the tertiary alcohol in pure form. The ketones (40b,c) failed to yield any tertiary alcohol under the same conditions.

A variety of reaction conditions were employed in an attempt to circumvent this problem. Use of tetrahydrofuran as solvent failed to improve results, as did employment of alkyl lithium reagents in diethyl ether. In the former case, intractable mixtures resulted; in the latter, only unreacted ketones were recovered. An attempt was made to react the ketone (40b) with n-propyl lithium in the presence of N,N,N^1,N^1-tetramethylethylenediamine, in the hope that co-ordination of lithium by this chelating agent would increase the reactivity of the organolithium reagent. The method has been employed successfully in simpler systems,[48] but in this case it proved ineffective and only unreacted starting material was recovered.

The problem appeared to be due to increased steric hindrance in the vicinity of the ketone group, arising from the bulkier 6-alkoxy substituent. Accordingly, a method was sought which gave improved yields in Grignard reactions of hindered ketones and a search of recent literature revealed the work of Cannone and coworkers,[49] in which the reaction is carried out in benzene containing a small amount of ether (usually 1 mole ether per mole of Grignard reagent). The method was adopted with some modification, more ether being used (5 - 10% by volume) to allow for evaporation of ether at the elevated temperatures employed.

The method was applied to the ketones (40a,b) and moderate yields (ca. 50%) of the crystalline tertiary alcohols (27a,b) were obtained. The 2-hydroxyethyl derivative (40c)



(27) a. R^1=Et, R^2=*n*-Pr

b. R^1=R^2=*n*-Pr

c. R^1=CH_2CH_2OH, R^2=CH_3

gave an intractable mixture in reaction with n-propylmagnesium bromide, but reaction with methylmagnesium bromide gave the tertiary alcohol (27c) in good yield.

The novel tertiary alcohols (27a,b) displayed ^{1}H n.m.r. and infrared spectra with very close similarities to those of the corresponding 'thevinols' (9a,b). The ^{1}H n.m.r. spectra differed only in those features which might be expected given the differing 6-alkoxy substituents. The O-methylene protons in (27a,b) again gave a complex multiplet. This effect is also observed in the parent ketones (40)(vide supra); this is consistent with the postulated 'crowding' invoked earlier to explain the results of Grignard reaction with these ketones. The infrared spectra of the novel tertiary alcohols (39a,b) displayed the concentration-invariant hydroxyl absorption at 3500 cm^{-1} observed in the parent 'thevinols' (9) due to intramolecular hydrogen bonding between the hydroxyl group and the oxygen of the 6-alkoxy group. This represents strong circumstantial evidence for the 19(R)-configuration in (27a and 27b). Further, reaction of thevinone (8) with n-propyl-magnesium bromide, under identical conditions, gave the known compound, 7α - 1 -[(R)-hydroxy-1-methylbutyl]-6,14-endo-ethenotetrahydrothebaine (19-propylthevinol; (9a)); this compound was identical in all respects with material prepared as described by earlier workers.[7] It seems reasonable to assume that the same stereoselectivity in favour of the

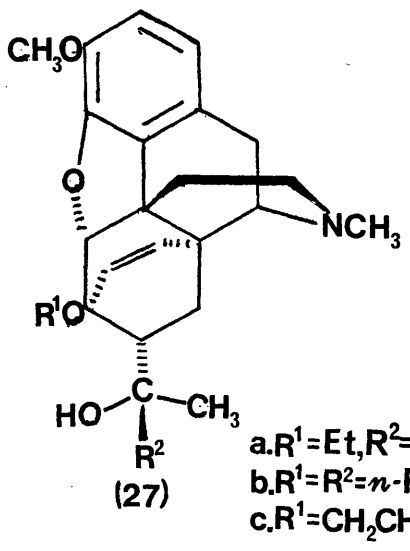


TABLE 2

Potencies of the Tertiary Alcohols (27)[a]

Compound	ED_{50} (mg/kg)[b]	Potency(Morphine=1)
(9a)	0.066	4.2[c]
(27a)	0.17	1.65
(27b)	0.23	1.2
(27c)	0.060	4.7
Morphine	0.28	1

Notes:
a. Determined by inhibition of phenylbenzoquinone-induced writhing in mice.
b. ED_{50} is the dose required to induce analgesia in 50% of test animals; the lower ED_{50}, the greater the analgesic potency.
c. Known tertiary alcohol included for comparison purposes. See also ref.7.

19-(R)-isomer applies in Grignard reactions of the ketones (40a,b).

The tertiary alcohol (27c) displayed a hydroxyl absorption at 3520 cm^{-1}, presumably due to the tertiary hydroxyl group, and a somewhat weaker absorption at 3640 cm^{-1}, apparently due to the primary alcohol of the 6-(2-hydroxyethoxy) side chain. Both of these absorption frequencies were independent of concentration.

The new tertiary alcohols (27), together with the known compound 19-propylthevinol (9a), have been tested for opiate activity by the 'mouse writhing' method. Inhibition of phenylbenzoquinone-induced writhing in mice was observed after subcutaneous injection of the test compounds. 19-propylthevinol, already known to be a potent analgesic, and morphine were included for comparison purposes. Results are shown in Table 2.

The novel compounds (27a,b) show significant opiate agonist activity, being somewhat more active than morphine in this test. However, they are slightly less potent than the parent 19-propylthevinol; apparently the increased size of the 6-alkoxy substituent has a detrimental effect on agonist activity.

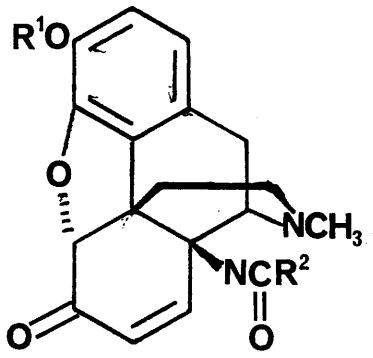
By contrast, the hydroxyethyl compound (27c) exhibits agonist activity comparable with that of 19-propylthevinol. Further, (27c) is considerably more active than the corresponding 19-methylthevinol (9b), which has only a fraction of the activity of its 19-propyl homologue. It has been observed by Bentley and others that high agonist activity in the thevinol

series is associated with a substituent whose length is equivalent to a 3 - 5 carbon chain; the high activity of (27c) is therefore unusual and must arise from the presence of the polar substituent in the 6-position. This supports the idea (vide supra) that the 6-alkoxy substituent might occupy the same region on the opiate receptor as does the C-terminal amino acid residue of enkephalin peptides. The presence of a polar group in this position in the thevinol analogues appears to have the same effect on agonist activity as the presence of polar groups in certain synthetic enkephalin analogues.[29]

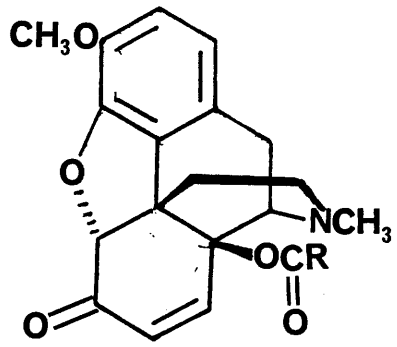
Thus, the codeinone enol ethers (21a,b) have been converted, without difficulty, into their Diels-Alder adducts with methyl vinyl ketone. The resulting methyl ketones (40) proved unreactive towards Grignard reagents under normal conditions, but reaction in benzene containing 5 - 10% ether by volume gave satisfactory yields of tertiary alcohols (27). The stereochemistry of reaction is apparently identical with that observed in the 'parent' series derived from (8), giving only the 19(R)-isomers. All the new compounds have significant opiate agonist activity, the hydroxyethyl derivative (27c) being particularly active.

Introduction of a primary alcohol group in (27c) leaves scope for further modification. Thus a lipophilic group, such as a benzyl ether, may be attached at this position. Alternatively, oxidation of the primary alcohol could be used to give aldehyde or carboxylic acid groups at a site relatively

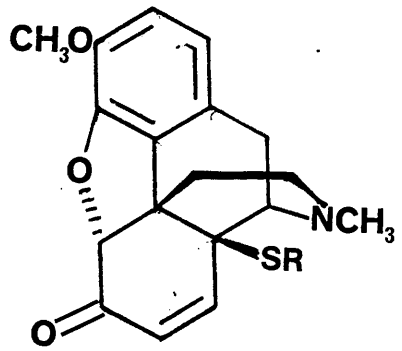
remote from the tertiary alcohol function. Given the high potency which seems associated with a polar group at this position, this latter option may be the more likely to give potent analgesics. Regrettably, delays in the testing of the tertiary alcohols (27) have left insufficient time for any detailed examination of these possibilities.



(12) a.R^1=CH_3
b.R^1=H



(41)



(42)

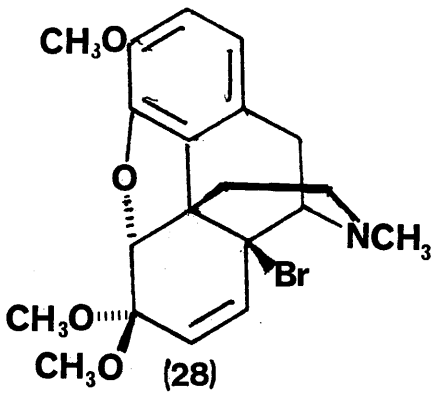
II. REACTIONS OF THEBAINE DERIVATIVES WITH SULPHUR REAGENTS

1) Approaches to 14β-alkylthiocodeinones

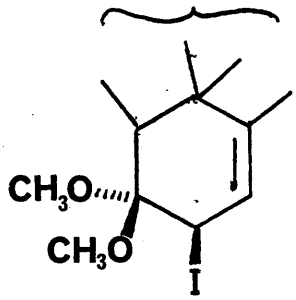
It is already known that the presence of a lipophilic group attached to a heteroatom at C-14 of the morphinan skeleton leads to high opiate agonist activity. Thus, 14-acylaminocodeinone and -morphinone derivatives[12] (12) and 14-acyloxymorphinones[50](41) have agonist activities up to several thousand times that of morphine. The highest activities are observed where R^2 is an alkyl group of 4-6 carbons, or a 2-phenylethyl group.

A method for introduction of a sulphur-containing functional group at C-14 would have considerable potential as a route to 14-alkylthiocodeinones (42). In these compounds, the 14β-substituent might be chosen to be of comparable length to those in the corresponding 14-acylaminocodeinones (12), many of which are of high potency; comparable agonist activity might be expected from 14-alkylthio compounds. In addition, the partial π-bond character of the amide C-N bond in 14-acylamino compounds makes the attachment at C-14 relatively rigid; the greater polarisability and flexibility of the thioether linkage may allow a better fit at the receptor site. Further, the greater lipophilicity of 14-alkylthio derivatives might well confer improved medicinal properties.

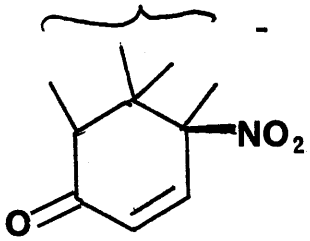
The diene system of thebaine has been subjected to modification by a variety of electrophilic reagents. In particular,


CH3O
O
NCH3
Br
CH3O
CH3O

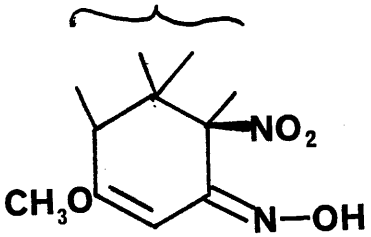
(28)


CH3O
CH3O
I

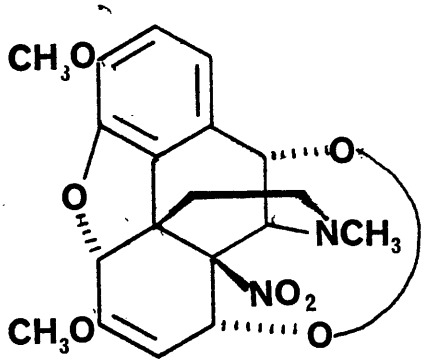
(43)


NO2
O

(44)


NO2
CH3O
N—OH

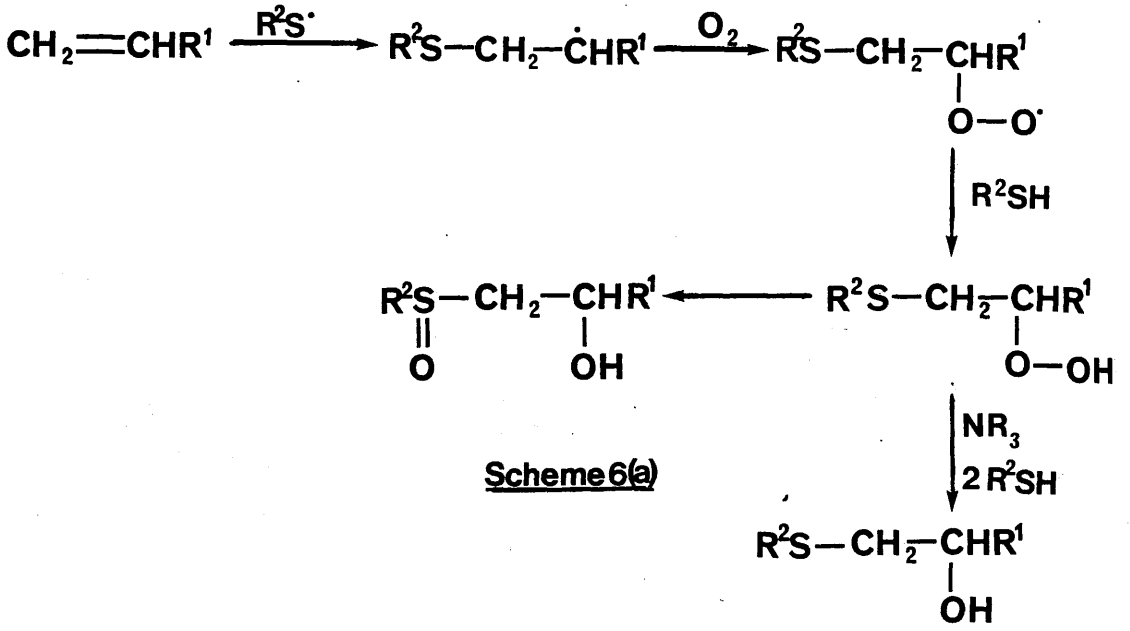
(45)


CH3O
O
O
NCH3
NO2
CH3O
O

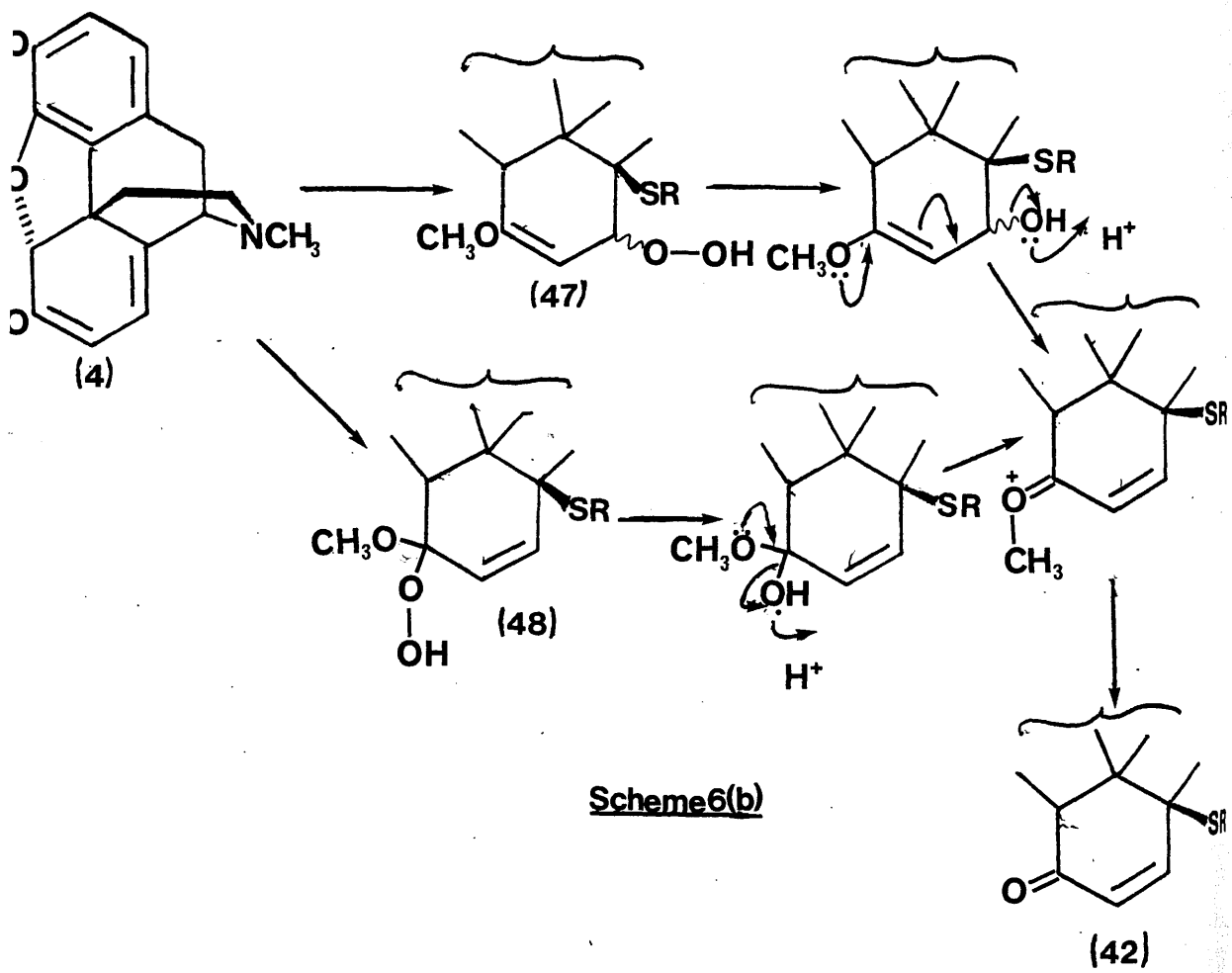
(46)

electrophilic addition has been employed as a means of synthesising 14β-substituted codeinone derivatives, such as the bromo-acetal (28) whose reactions have already been discussed. The majority of electrophiles add in this manner, although iodination of thebaine in methanol proceeds by 1,2-addition giving 7β-iodoneopinone dimethyl acetal[51] (43). At the outset, nothing was known of the reactivity of thebaine with sulphur electrophiles; however, it seemed likely that attack at C-14, in the manner of other electrophiles, might well occur. Moreover, a number of free-radical reagents have also been found to attack at position 14. Thus, treatment of thebaine with dinitrogen tetroxide[20] leads to 14-nitrocodeinone (44) while with dinitrogen trioxide the oxime (45) is formed in low yield.[52] Both of these reactions presumably involve nitro radicals. In addition, the nitration of thebaine by tetranitromethane in benzene appears to proceed via a radical intermediate which then incorporates a molecule of oxygen to give the unusual peroxide (46) as the major product.[18] Again, nothing was known of the reactivity of thebaine towards sulphur radicals.

Despite the lack of information regarding the reactivity of thebaine towards sulphur reagents, a number of reactions of such reagents with simple olefins have been documented and attempts were made to duplicate these with thebaine. Both free-radical and ionic eletrophilic sulphur species are known to react with olefins, and examples of both classes of reaction have been investigated.



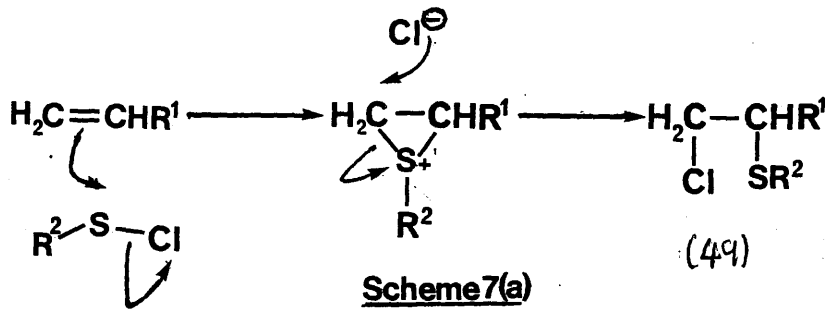
Scheme6(a)



Scheme6(b)

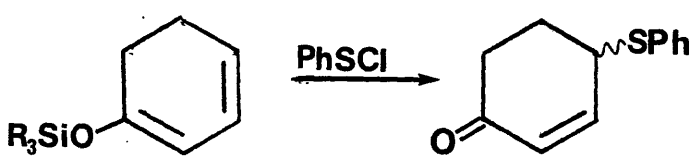
The first reaction to be attempted was a variation of the thiol-olefin co-oxidation ('TOCO') reaction first investigated by Kharasch and coworkers.[53] This reaction involves addition of a thiyl radical to an olefin in the presence of molecular oxygen, as shown in Scheme 6 (a). The intermediate hydroperoxide then disproportionates to give an α-hydroxysulphoxide. However, the hydroperoxide may also be reduced,by reaction with a further two moles of thiol under amine catalysis, to give an α-hydroxysulphide.[54] This latter reaction offered a possible access to 14-alkylthiocodeinones *via* the sequence of Scheme 6(b) although this depended on obtaining the correct orientation of reaction, with addition of sulphur at C-14 to give, e.g. (47). 1,4-Addition to the conjugated diene system of thebaine, leading to a species such as (48), was also feasible; both 1,2 and 1,4-addition products have been reported in thiol-olefin co-oxidation of conjugated dienes.[54] More exotic products, such as 14-alkylthio analogues of the bridged peroxide (46), might also be accessible by this method.

Thebaine failed to react with 1-hexanethiol and oxygen in benzene over a range of reaction temperatures from 0° to 60°. Attempted reaction in the presence of free-radical initiators, using *t*-butyl hydroperoxide in the presence of ferrous sulphate[53] at low temperatures and azo-*bis*-isobutyronitrile ('AIBN') at higher temperatures, failed to give any conversion of thebaine. No reaction could be detected even when thebaine was treated with three equivalents of 1-hexanethiol under an oxygen



(49)

Scheme 7(a)



Scheme 7(b)

atmosphere, at 60° and with AIBN as initiator. It had been hoped that thebaine itself would prove effective as the amine catalyst for reduction of any hydroperoxide intermediate such as (47), however, no reaction whatever could be detected.

When thiophenol was employed instead of 1-hexanethiol, results again proved entirely negative, the only products isolated being unreacted thebaine and diphenyl disulphide. Again, neither use of elevated temperatures nor of radical initiators led to any detectable reaction.

The possibility of addition by reagents of greater ionic character was next considered. Given the reactivity of thebaine towards electrophiles, this seemed to hold out some chance of success, and might lead directly to alkylthiocodeinones.

The electrophiles chosen were sulphenyl chlorides, which were known to react readily with olefins, giving α-chloro-sulphides. The reaction with simple olefins is believed to proceed *via* an episulphonium species, as shown in Scheme 7(a). Nucleophilic attack by chloride ion then opens the three-membered ring to give products of general structure (49),[55] with Markownikoff addition products being preferred.

Sulphenyl chlorides generally add 1,2 to dienes, again with a preference for the Markownikoff addition products.[56] However, it has been shown that benzenesulphenyl chloride adds almost exclusively 1,4 to *O*-silylated dienolates, giving γ-sulphenylated enones (Scheme 7(b)),[57] and it seemed likely that an analogous mechanism would be preferred in addition to the methoxy-diene system of thebaine.

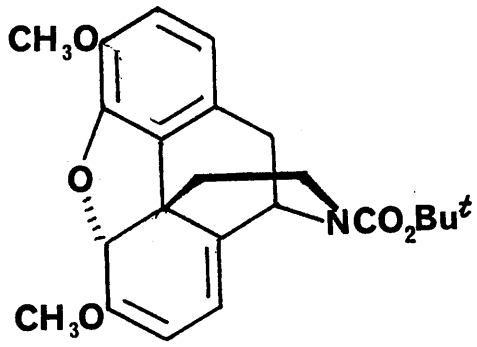
Although sulphenyl chlorides are unstable, particularly towards moisture,[58] this was not a serious practical problem. It was intended that the sulphenyl chlorides be generated as required for reaction and used immediately without being isolated. A convenient small-scale preparation was available, involving treatment of the appropriate thiol with N-chlorosuccinimide in an inert solvent, usually benzene.[59] This had the additional advantage that it did not lead to formation of hydrogen chloride (the byproduct of reaction, succinimide, precipitates out during generation of the sulphenyl chloride and can be readily removed by filtration or decanting the reaction mixture) and avoided the risk of overchlorination; alkane-sulphenyl chlorides can react with chlorine to give α-chlorosulphenyl chlorides,[60] while aromatic sulphenyl chlorides are converted to arylsulphur trichlorides.[61] Further, no special precautions were required in carrying out this reaction; generation of the sulphenyl chlorides proceeded without complication in 40 - 60 minutes at room temperature.

The initial results of reaction between sulphenyl chlorides and thebaine were disappointing. Addition of phenylmethane-sulphenyl chloride in benzene to a solution of thebaine in benzene resulted in the formation of a precipitate which proved to be thebaine hydrochloride, while the supernatant liquid, on evaporation, yielded dibenzyl disulphide. Similarly, treatment of thebaine with benzenesulphenyl or 1-hexanesulphenyl chloride in benzene led to the precipitation of thebaine hydrochloride, and the appropriate disulphides were recovered from the super-

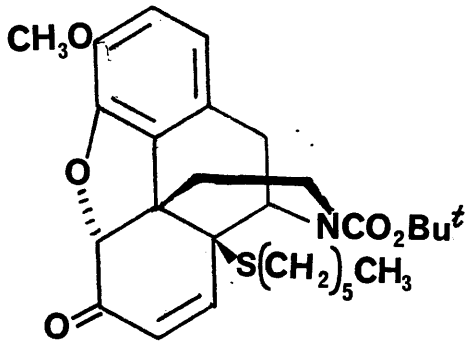
natant solution. After treatment with aqueous alkali thebaine was recovered in 85 - 90% yield.

The procedure was repeated using methylene chloride as solvent. It was hoped that thebaine hydrochloride would remain in solution and might be more likely to undergo reaction. However, treatment of thebaine with 1-hexanesulphenyl chloride under these conditions yielded, on evaporation of solvent, a mixture containing thebaine hydrochloride and dihexyl disulphide. When the reaction mixture was shaken with dilute aqueous alkali, evaporation of the organic phase yielded 96% recovery of thebaine and, once more, some dihexyl disulphide. An interpretation of these reactions will be given later; it was apparent that the basic character of the alkaloid was the cause of the lack of sulphenylated products.

Reaction of thebaine hydrochloride with 1-hexanesulphenyl chloride was next attempted. This likewise proved entirely unsuccessful and no reaction could be detected. Thus, it appeared that the presence of a fully basic nitrogen was undesirable, due to the decomposition of the sulphenyl chloride which resulted, while a full positive charge on nitrogen was equally detrimental. This latter observation may be explained by electron withdrawal from the preferred site of attack at C-14, due to the inductive effect of the positively charged nitrogen and perhaps by hindrance from the ammonium proton to attack at C-14 by the sulphenyl chloride. It is known that thebaine hydrochloride is less reactive towards electrophiles than the free base.[62] An attempt to improve the reactivity of this system using Lewis acid catalysis



(50)

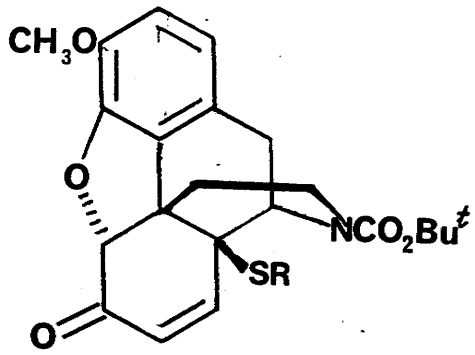


(51a)

by tin (IV) chloride also failed.

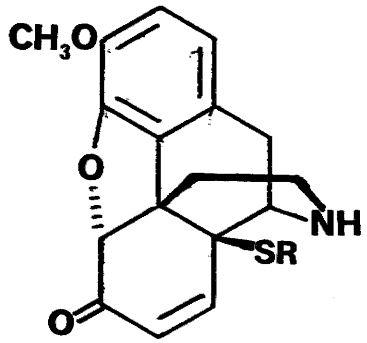
It was decided to attempt reaction of a sulphenyl chloride with an N-protected northebaine derivative, in the hope of finding a compromise between the unfavourable extremes of fully basic nitrogen and full positive charge. The protecting group selected was t-butoxycarbonyl ('t-BOC') which could be easily attacked under mild conditions and was easily removed by acid. N-t-BOC-Northebaine (50) was obtained in good yield by treatment of northebaine with di-t-butyl dicarbonate and potassium carbonate in aqueous t-butanol, following an established procedure.[63]

1-Hexanesulphenyl chloride reacted smoothly with N-t-BOC-northebaine in benzene. The reaction was apparently complete, as judged by analytical t.l.c. after a few hours. The reaction mixture was then shaken with aqueous sodium carbonate, to destroy residual sulphenyl chloride and prevent loss of the N-protecting group. A noncrystalline product was isolated from the organic phase, having a ^{1}H n.m.r. spectrum consistent with 14β-hexylthio-N-t-BOC-norcodeinone (51a). In particular, the spectrum showed perturbed doublets at δ 6.47 and 6.03 (J 10Hz) typical of the olefinic proton resonances in a codeinone system; a complex resonance around δ 1.5, integrating for eight protons, corresponded to the four methylene groups of the aliphatic side chain, and the terminal methyl group resonance appeared as a distorted triplet (J 6 Hz) at δ 0.84. The S-methylene protons appeared as a complex multiplet centred at δ 2.60, and the protons of the N-protecting group were represented by a nine-proton singlet at δ 1.48.



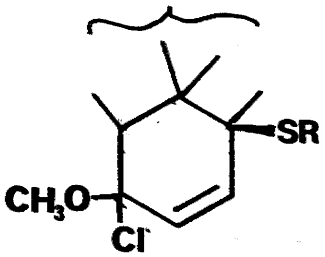
(51)

a. R=C_6H_{13}
b. R=Ph
c. R=CH_2Ph
d. R=$(CH_2)_2Ph$
e. R=$(CH_2)_3Ph$



(52)

a. R=C_6H_{13}
b. R=Ph
c. R=CH_2Ph
d. R=$(CH_2)_2Ph$
e. R=$(CH_2)_3Ph$

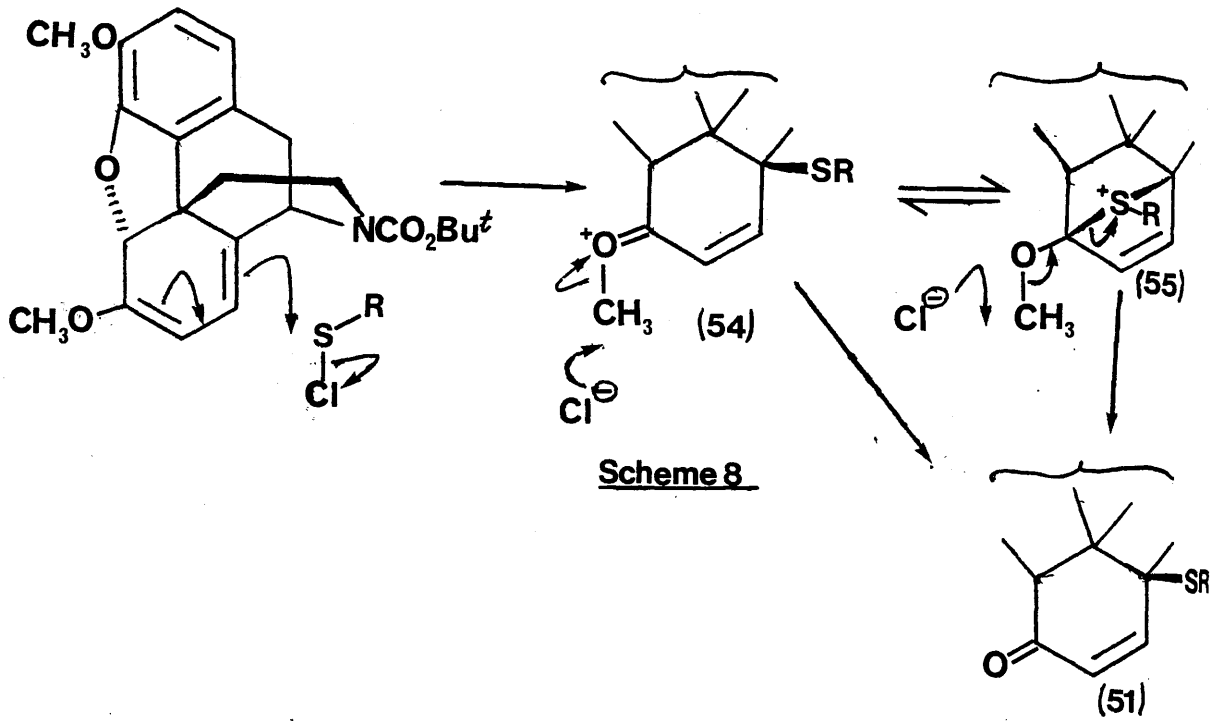


(53)

A small amount of crystalline material was also isolated from the reaction mixture. The ^{1}H n.m.r. spectrum of this material was similar in many respects to that of (51a) but lacked the nine-proton singlet due to the t-butoxycarbonyl group, indicating that the N-protecting group had been lost. Treatment of (51a) with ethereal hydrogen chloride led to the isolation of a crystalline product whose melting point was unchanged on mixing with the original crystalline material. Infrared data indicated that this compound was the hydrochloride salt of the nor base (52a) and this was subsequently confirmed by elemental analysis.

Repetition of this reaction under identical conditions, using other sulphenyl chlorides, gave N-protected 14β-alkylthiocodeinones (51). These compounds are noncrystalline, except for the 14β-phenylthio compound (51b) which has been isolated and characterised in crystalline form. In general, these compounds were not isolated but instead deprotected by addition of ethereal hydrogen chloride to the reaction mixtures. The alkylthionorcodeinones (52) were then isolated as their crystalline hydrochlorides; the free nor bases, like the N-protected compounds (51) are noncrystalline. Yields of crystalline material were typically in the range 60 - 70%, based on N-t-BOC-northebaine.

The formation of codeinone derivatives in this reaction seems consistent with 1,4-addition of the sulphenyl chloride leading to a chloroacetal intermediate such as (53). Such a compound might be expected to be highly susceptible to hydrolysis, either by trace amounts of water in the reaction mixture (generating hydrogen



Scheme 8

TABLE 3

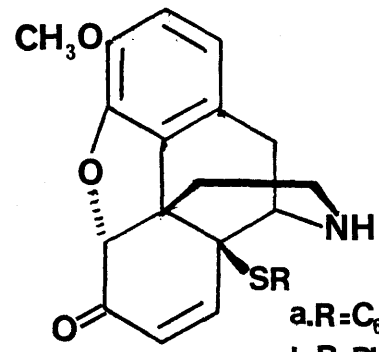
The ^{1}H n.m.r. Spectra of the Norcodeinones (52)

	δ (p.p.m.)			
	H-5	H-7	H-8	H-9
R				
n-C_6H_{13} (52a)	4.70	6.13	6.66	4.30
Ph (52b)	4.27	6.01	6.33	4.42
CH_2Ph (52c)	4.63	6.20	6.73	4.49
CH_2CH_2Ph (52d)	4.72	6.10	6.70	4.30a
$(CH_2)_3Ph$ (52e)	4.63	6.10	6.52	4.20a

Note: a. Broad resonance; precise position uncertain.

chloride *in situ*, which would account for the small amount of deprotected material isolated in the formation of (51a) during alkaline workup. However, this presumed intermediate was not trapped by methanol. Thus, addition of benzenesulphenyl chloride in benzene to N-t-BOC-northebaine in methanol led only to the isolation of the enone (51b). No acetal formation could be detected even when the reaction was carried out using dried and redistilled solvents and in the presence of triethyl orthoformate, which had been used successfully as an *in situ* water trap in the formation of 14-bromocodeinone acetals (29) (*vide supra*). There is, therefore, a strong possibility that the reaction proceeds as shown in Scheme 8, with initial formation of a methoxonium species (54), which then undergoes nucleophilic attack by chloride anion on the methyl group of this intermediate. Another possibility is the formation of a bridged episulphonium species (55) which might well be present in equilibrium with (54). This latter route also accounts for the failure of attempts at acetal formation, since methanol could not enter at the 6β-position in (55), which is occupied by sulphur. Study of molecular models indicate that the molecular geometry in (54) is not unfavourable towards the formation of an episulphonium ion. The results of attempts to form acetals directly from alkylthionorcodeinones are discussed later (*vide infra*).

Spectroscopically, the hydrochlorides of the norcodeinones (52) showed those features to be expected in compounds of this structure. Their infrared spectra were virtually identical in many respects, showing the broad absorption around 2600 - 2700 cm^{-1}



(52)

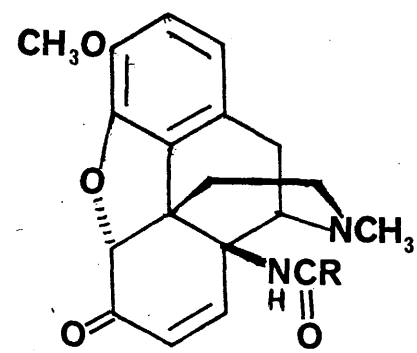
a.R=C_6H_{13}
b.R=Ph
c.R=CH_2Ph
d.R=$(CH_2)_2Ph$
e.R=$(CH_2)_3Ph$

TABLE 4

Potencies of the Alkylthionorcodeinones (52)[a]

Compound	Potency (Normorphine = 1)
(52a)	0.4
(52b)	0.16
(52c)	1.3
(52d)	24.0
(52e)	8.0

Note: a. Determined in mouse vas deferens tissue preparation.

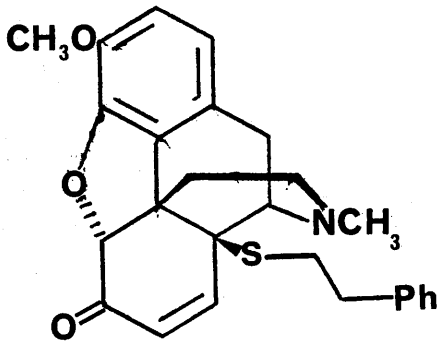


(12)

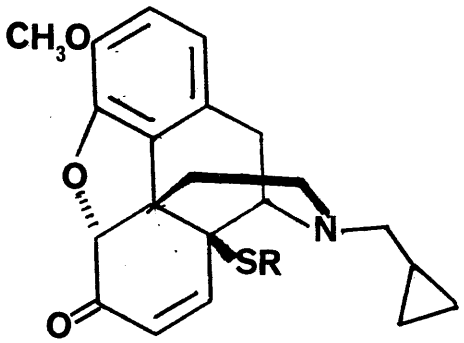
and sharper absorption, normally at 1560 cm^{-1}, typical of amine hydrochlorides, as well as the αβ-unsaturated ketone band at 1685 or 1690 cm^{-1}. The ^{1}H n.m.r. spectra showed a certain amount of variation over and above that expected from the differing 14β-substituents; the positions of the olefinic, H-5 and H-9 resonances varied according to the nature of the alkylthio-group (cf. Table 3). However, there was no obvious pattern of variation. Another feature of these spectra was the nonequivalence of the NH protons of the ammonium salt; thus in the benzylthio compound (52c) these resonances were separated by almost 2 p.p.m.

The proton n.m.r. spectrum of the N-t-BOC derivative (51b) was complex and showed marked temperature dependence. The details of this spectrum are discussed separately (vide infra).

The norcodeinone hydrochlorides (52 a - e) were tested for opiate agonist activity in mouse vas deferens tissue preparations with normorphine as the reference compound. Results are shown in Table 4. As expected, agonist activity varied with the length of the 14β-substituent, with the maximum activity being observed for 14β-(2-phenyethyl)thionorcodeinone (52d). A similar activity profile is observed in the 14β-acyl-amino series (12) where the maximum activity is again associated with a 2-phenylethyl substituent.[11] However, in this latter series, the peak in activity is much more pronounced.



(56)



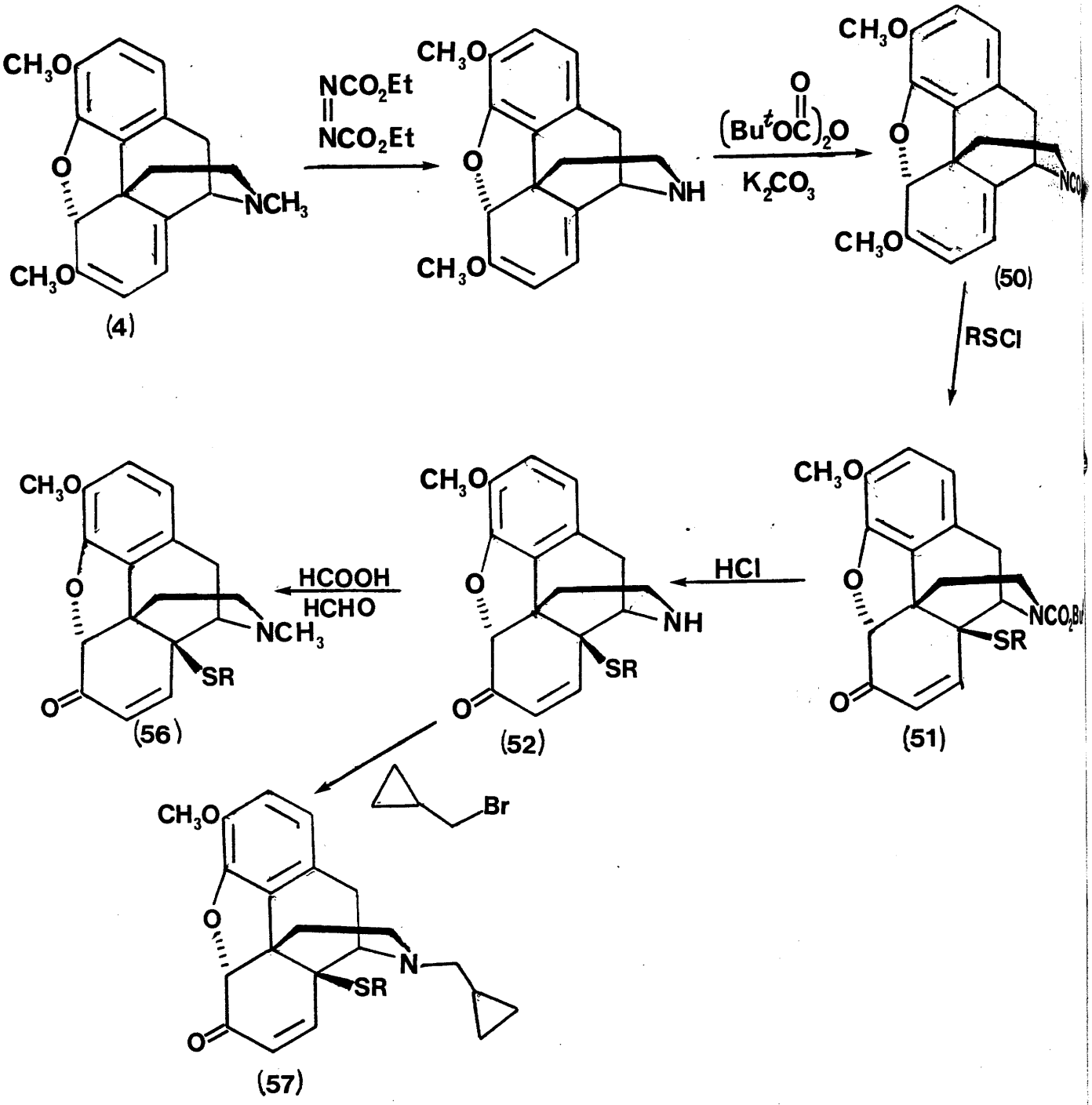
(57) a.R=CH_2CH_2Ph
b.R=Ph

N-Methylation of the most active of the nor bases (52d) was next attempted, to complete the synthesis of a 14β-alkylthiocodeinone. This was especially desirable since N-norcodeinones and -morphinones are usually inactive in whole animals.

Methylation of (52d) was carried out successfully by a modified literature method, by treatment with formaldehyde and aqueous formic acid buffered to pH 4 with sodium formate. 14β(2-Phenylethyl)thiocodeinone (56) was obtained in 70% yield from the free nor base (52d); this represents a yield of 50% from N-t-BOC-northebaine, and of nearly 20% based on thebaine.

The ^{1}H n.m.r. spectrum of (56) displayed the expected features, with the olefinic protons giving an AB quartet (J 10 Hz) at δ 6.47 and 6.11, and H-5 a singlet at δ 4.55. No coupling could be observed between H-5 and H-7. The N-methyl group gave a singlet at δ 2.40. The infrared spectrum of (56) showed the characteristic absorption band at 1678 cm^{-1} due to the presence of an αβ-unsaturated ketone.

The nor base (52d) was converted to the N-cyclopropylmethyl derivative (57a) by treatment with cyclopropylmethyl bromide and potassium carbonate in refluxing acetone, in the presence of sodium iodide as catalyst. Use of sodium iodide generates the more reactive cyclopropylmethyl iodide from the alkyl bromide, giving enhanced rate of reaction. The base (57a) was isolated as a gum in 71% yield based on the nor base (52d). However, (57a) could not be obtained in crystalline form. A similar procedure


CH3O
O
NCH3
CH3O
(4)
NCO2Et
NCO2Et
NH
(Bu^tOC)2O
K2CO3
(50)
RSCl
HCl
HCOOH
HCHO
SR
NCO2Br
(56)
(52)
(51)
Br
N
(57)

Scheme 9

was applied in the synthesis of (57b) from 14β-phenylthionor-codeinone (52b). Given the low agonist activity of (52b), it was thought likely that (57b) would behave essentially as a pure antagonist, while (57a) would show mixed agonist-antagonist activity. (57b) was obtained as an amorphous, resinous solid in 68% yield from the nor base (52b). Although apparently pure by t.l.c., this compound, like (57a) was noncrystalline.

Thus, the addition of sulphenyl chlorides to N-t-BOC-northebaine represents a practicable approach to the synthesis of the target 14β-alkylthiocodeinones. The norcodeinone derivatives (52) have been shown to be opiate agonists of moderate to high potencies; the most potent of these, the phenylethyl derivative (52d) has been converted in good yield to (56a) which has been submitted for pharmacological testing. The same approach has been employed in the synthesis of the N-cyclopropylmethyl derivatives (57a,b).

14β-(2-Phenylethyl)thiocodeinone (56a) displayed some 70 times the analgesic activity of normorphine in mouse vas deferens tissue preparation. When tested in mice by inhibition of phenylbenzoquinone-induced writhing, this compound displayed a potency approximately six times that of morphine (ED_{50} 0.044mg/kg as against 0.28mg/kg for morphine). Thus, methylation of (52d) leads to both increased activity in vitro and to activity in the whole animal.

Yields in this process are 15 - 20% based on thebaine. This is due primarily to the low yield in conversion of thebaine to nor-thebaine as an essential first step. The overall procedure is summarised in Scheme 9.

2) The proton n.m.r. spectrum of 14-phenylthio-N-t-BOC-norcodeinone (51b)

This compound (51b) is the only example of its class to be obtained in crystalline form. Given its structure, this compound might have been expected to have a fairly simple n.m.r. spectrum, compared to other N-protected derivatives with more complex 14β-substituents. However, the n.m.r. spectrum of (51b) proved to be unexpectedly complex; many resonances displayed a far more intricate fine structure than might have been expected. Thus, the H-8 resonance, instead of being a perturbed doublet, appeared to consist of at least four lines. Moreover, the only signal which could reasonably be assigned to H-5 was a widely separated doublet centred at δ 4.28, and that attributed to H-9 comprised two broad signals at δ 4.98 and 4.75.

Such large separations could not be accounted for by spin-spin coupling, or by any reasonable alternative structure for (51b). A probable explanation was indicated by molecular models, which showed that there was a high degree of steric crowding between the aromatic ring of the phenylthio-group and the bulky t-BOC group attached to nitrogen; sufficient, in fact, to lead to restricted rotation about the carbon-sulphur bonds of the 14β-phenylthio-group. It was possible, therefore, that several protons in the vicinity, notably H-8, H-9, the t-butyl protons and perhaps H-5, might be held in two different environments, with the degree of shielding experienced depending on the orientation of the phenylthio-group. By this reasoning, the spectrum observed at 20^{o} is an equilibrium mixture of two or more rotamers.

To confirm this, and to study the effect of increased rates of rotation about the C-S bonds, a variable-temperature n.m.r. study was embarked upon. The 90 MHz n.m.r. spectrum of (50b) was observed over a temperature range of 0 - 60°, with the following results:

(i) At 0°, the H-8 resonance appeared as two separate doublets, at δ 6.50 and 6.39, in an approximate ratio of 2:3. With increasing temperature, these signals moved slightly upfield and began to overlap, until at 60° they coalesced into a perturbed doublet of the type normally observed in 14β-substituted codeinone derivatives, centred at δ 6.35 and coupled to H-7 with J 10 Hz.

(ii) The resonance assigned to H-9 appeared, at 0°, as two triplets (J 4 Hz) at δ 4.99 and 4.76. Decoupling studies indicated that this coupling is to two protons appearing near δ 2.93, presumably the benzylic H-10α and H-10β. With increasing temperature, these resonances broadened and moved closer together until at 60° they merged into a single broad ($W_{\frac{1}{2}}$ 20 Hz) signal at δ 4.88.

(iii) The H-5 signals at δ 4.36 and 4.19 broadened and merged with increasing temperature, again giving a single broad signal at δ 4.31 ($W_{\frac{1}{2}}$ 9 Hz) at 60°.

(iv) At low temperatures, the t-butyl group gave a doublet at δ 1.55 and 1.51, the two lines being of approximately equal intensity. At 20°, two lines were still visible

although the separation between them had decreased from 35 Hz to about 2 Hz. These signals finally merge at 35° to give a slightly broadened singlet at δ 1.53.

These results confirm that restricted rotation, presumably about the C-S bonds of the phenylthio group in (51b) leads to the existence of rotameric forms of this compound which are distinguishable by n.m.r. Rotamers of the N-t-BOC group are distinguishable in this compound, which is not the case in the other N-protected compounds (51).

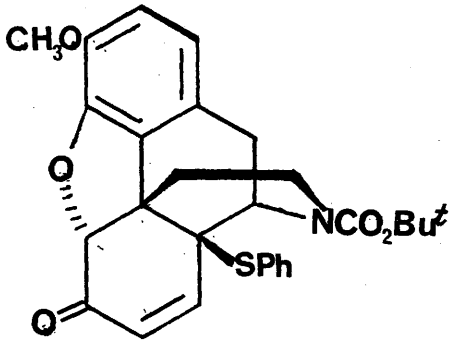
The rate constant for rotation at the coalescence temperature, i.e. the temperature at which signals from rotamers merge into a single broad signal, may be determined from:

$$k_c = \frac{\pi \Delta\nu_{max}}{\sqrt{2}} \qquad (1)^{64}$$

where k_c is the rate constant at coalescence and $\Delta\nu_{max}$ the maximum difference in chemical shift between the signals for individual rotamers. Given k_c, then $\Delta G^{\ddagger}$, the free energy of activation for interconversion at the coalescence temperature may be determined from the Eyring equation:

$$k_c = \left(\frac{KkT_c}{h}\right) e^{-\Delta G^{\ddagger}/RT_c} \qquad (2)^{65}$$

where T_c is the coalescence temperature, R the gas constant, k Boltzmann's constant and h Planck's constant. K is another constant, known as the transmission constant, which represents the fraction of molecules reaching the transition state which go on to products; for most rotational interconversions K may be taken as unity.



(51b)

TABLE 5

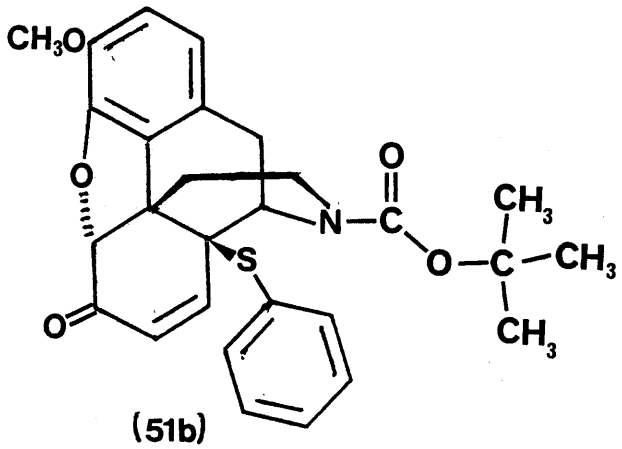
Energy Barriers, $\Delta G^{\ddagger}$, to Rotation in (51b)

Resonance	$\Delta\nu_{max}$(Hz)	$k_c(s^{-1})$	T_c(K)	$\Delta G^{\ddagger}$(kcal mol^{-1})
H-8	10 ± 0.5	22.0 ± 1.0	313 ± 5	16.3 ± 0.3
H-9	20 ± 1	44 ± 2.2	328 ± 5	16.7 ± 0.4
$C(CH_3)_3$	4 ± 0.5	8.9 ± 1.1	308 ± 5	16.6 ± 0.3

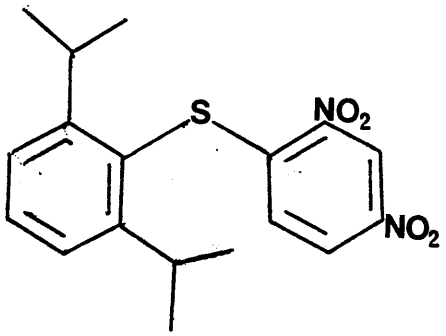
For the N-t-BOC group, $\Delta\nu_{max}$ (at 0°) is 4 ± 0.5 Hz. The coalescence temperature for this group is 35°, i.e. 308 K. Since a full study of the n.m.r. spectrum around this temperature was not carried out, an error of ± 5 K has been assumed in T_c. The observed $\Delta\nu_{max}$ gives $k_c = (8.9 \pm 1.1)s^{-1}$ for the t-BOC group. Inserting these values into equation (2) gives a value for $\Delta G^{\ddagger}$ of 69.9 ± 1.2 k J mol^{-1} (16.6 ± 0.3 kcal mol^{-1}) for interconversion between the rotamers of the t-BOC group.

If it is assumed that the differing chemical shifts of other protons, notably H-8 and H-9, arise from the existence of two rotamers of the phenylthio group, the variable-temperature n.m.r. spectrum of (51b) may also be used to provide values of $\Delta G^{\ddagger}$ for rotation of this group. Thus, the behaviour of the H-9 resonance gives a value of 328 ± 5 K for T_c; $\Delta\nu_{max}$ is 20 ± 1 Hz. Substitution of these values in equations (1) and (2) gives $\Delta G^{\ddagger}$ = 16.7 ± 0.4 kcal mol^{-1}. Similarly, $\Delta\nu_{max}$ for H-8 is 10 ± 0.5 Hz and T_c 313 ± 5 K, giving $\Delta G^{\ddagger}$ = 16.3 ± 0.3 kcal mol^{-1} (see Table 5).

Given the approximations made in these calculations, the similarity in $\Delta G^{\ddagger}$ as determined from the behaviour of these resonances is quite striking. It is tempting to suppose that the interconversion being observed is the same in each case: namely, between two rotameric forms of the 14-phenylthio group, although this does not account for the difference observed in the value of k_c for each pair of signals. It is noteworthy that no evidence could be found for restricted rotation either of the N-t-BOC group or of the alkylthio group in any of the other N-protected compounds (51).

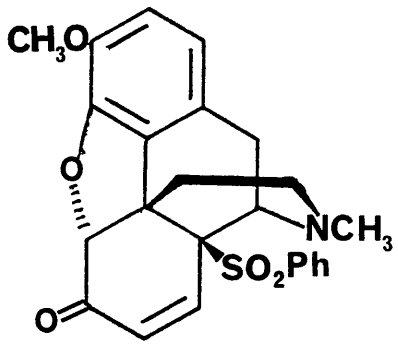


(51b)



(58)

Relatively little information is available on the energetics of restricted rotation in thioethers. Kessler and coworkers[66] have arrived at a value of 15.0 kcal mol^{-1} for $\Delta G^{\ddagger}$ in the simple sulphide (58). The significantly higher value of $\Delta G^{\ddagger}$ in (51b) is attributable to the congestion around C-14, notably due to the proximity of the nitrogen bridge and the bulky N-t-BOC group.



(59)

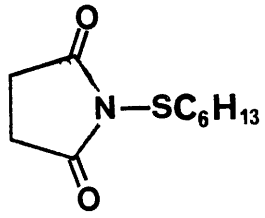
3) Treatment of thebaine with other sulphur reagents

Two further attempts have been made to introduce sulphur-containing functional groups at the 14-position of thebaine using reagents which, it was hoped, would prove stable towards the free base.

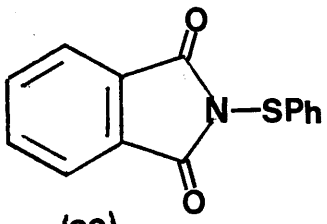
In the first of these, reaction of thebaine with benzene-sulphonyl chloride was attempted, under catalysis by copper (I) chloride. Examples are known of 1,4-addition by sulphonyl chlorides to simple conjugated dienes,[67] and it was hoped that such a reaction with the diene system would lead to the enone-sulphone (59). However, no reaction could be detected even after prolonged refluxing in acetonitrile, and thebaine, in 90% yield, was recovered from the reaction mixture. N-t-BOC-northebaine, similarly, appeared unreactive under these conditions and no product could be detected.

It is possible that these results simply reflect the greater bulk of the sulphonyl group; thus, approach of the sulphonyl chloride to C-14 would be more difficult, for steric reasons, than for a divalent sulphur reagent such as a sulphenyl chloride. Further, it is conceivable that a 'soft' electrophile, such as RSCl, will react more rapidly with a diene than a 'hard' electrophile such as a sulphonyl chloride.

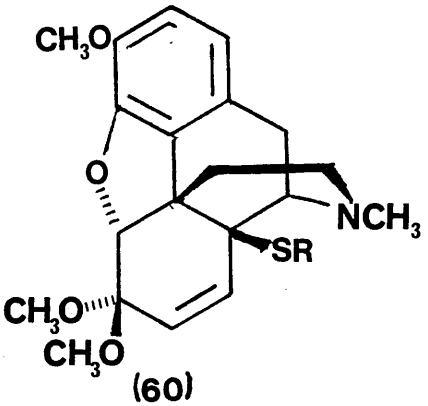
The second attempt involved the use of alkyl sulphenimides. These compounds are readily accessible via the corresponding sulphenyl chlorides[58] and, although there was no record of their use as sulphenylating agents, it was possible that they would



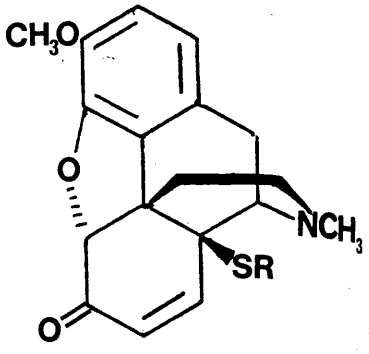
(61)



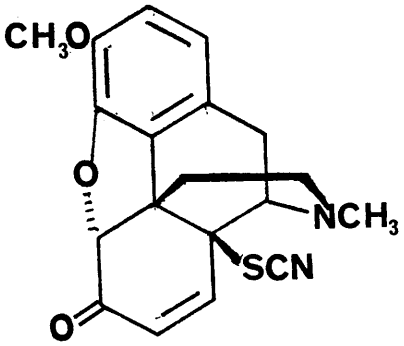
(62)



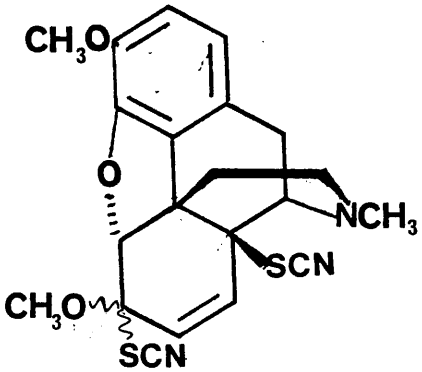
(60)



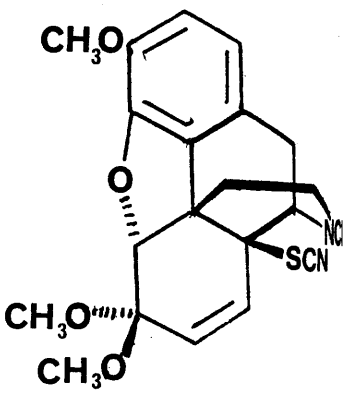
(42)



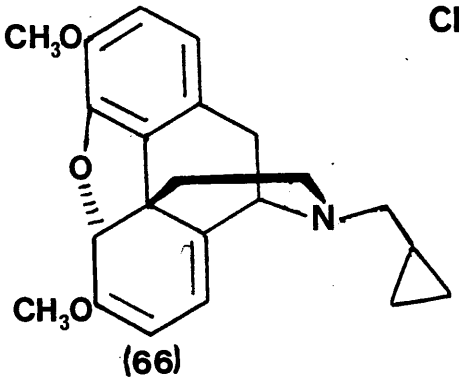
(63)



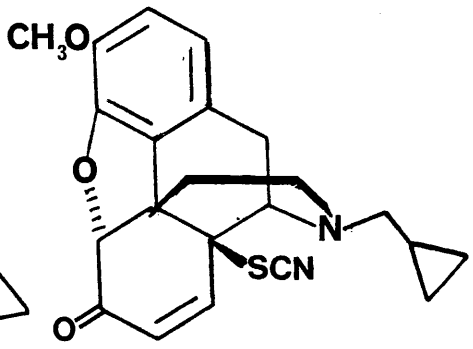
(64)



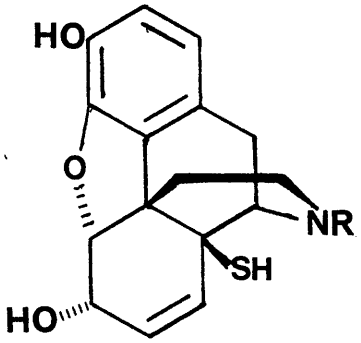
(65)



(66)



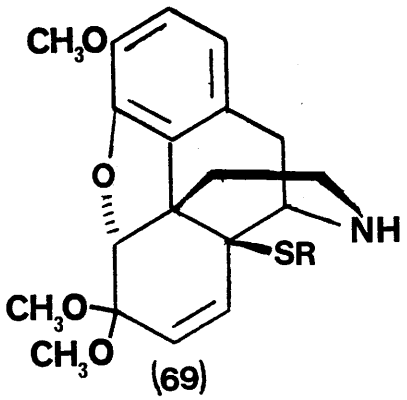
(67)



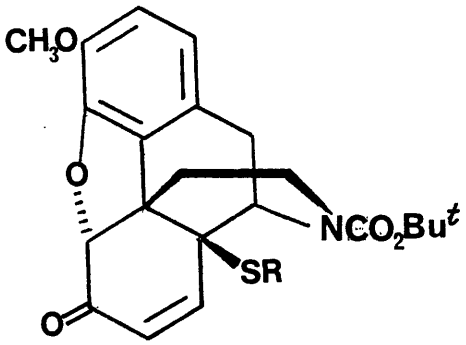
(68) a.R= CH_3
b.R= CH_2-cyclopropyl

react with thebaine in the same way as N-bromosuccinimide, giving 14β-alkylthiocodeinones (42) or their dimethyl acetals (60). However, neither N-hexylthiophthalimide (61) nor N-phenylthiosuccinimide (62) reacted with thebaine in methanol, and only unreacted thebaine was recovered even when prolonged heating under reflux was employed.

Since the commencement of this work on sulphur reagents, a single example of addition of a sulphur reagent to the diene system of thebaine has been reported in the literature. It has been found that thiocyanogen reacts with thebaine giving 14β-thiocyanatocodeinone (63).[69] The reaction apparently proceeds by 1,4-addition of thiocyanogen, presumably by a free-radical mechanism analogous to that involved in the nitration of thebaine by dinitrogen tetroxide.[20] The intermediate (64) thus produced was hydrolysed under mildly alkaline conditions to give (63) and was converted, by treatment with methanol, into the dimethyl acetal (65). Thiocyanogen has also been found to add to N-cyclopropylmethyl northebaine (66) giving the corresponding enone (67). The yields of these reactions are, however, rather low [22% for (63); 9% for (67)] and the analgesic activity of the products is unknown; they have been used primarily as intermediates in the synthesis of 14-mercaptomorphine (68a) and its N-cyclopropylmethyl analogue (68b).



(69)



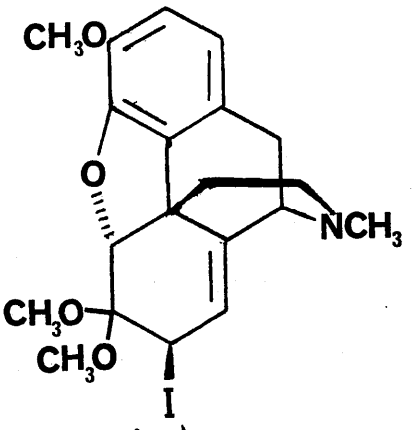
(51)

4) Attempts at the synthesis of 14β-alkylthionorcodeinone acetals

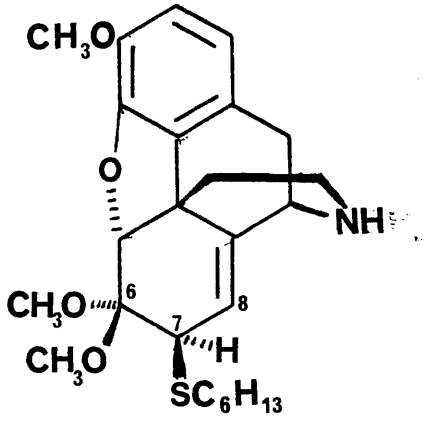
As mentioned earlier (vide supra) treatment of N-t-BOC-northebaine with sulphenyl chlorides in the presence of methanol led only to the codeinone derivatives (51); the dimethyl acetals (69) of these compounds could not be detected. It was decided to attempt direct formation of these acetals from the enones (51, 52) by a procedure analogous to that used in formation of 14-bromocodeinone dimethyl acetal (29a) from 14-bromocodeinone (vide supra).

14β-Hexylthio-N-t-BOC-norcodeinone (51a) was made from N-t-BOC-northebaine as previously described. The N-protected enone, when isolated, was dissolved in dry methylene chloride and treated with dry methanolic hydrogen chloride (approximately 1 M in HCl) in the presence of several equivalents of triethyl orthoformate. After 16 hours at room temperature, the reaction mixture was basified and extracted giving a single non-crystalline product.

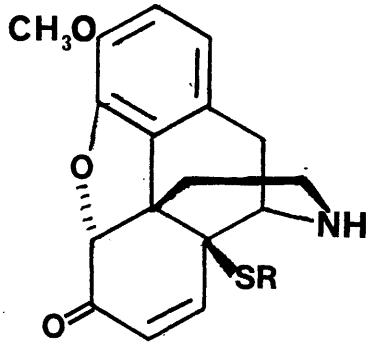
The ^{1}H n.m.r. spectrum of this material showed only one olefinic proton resonance, a doublet (J 7 Hz) at δ 5.56. Three methoxy resonances were observed, one at δ 3.81 being due to the aromatic 3-methoxy group and the others at δ 3.51 and 2.91, due to the methoxy groups of a 6-acetal function. The hexylthio-group was still present, as was clear from the many signals visible around δ 1.5, although the nine-proton singlet due to the N-protecting group had disappeared, as expected, given the acidic conditions of reaction.


CH3O
O
NCH3
CH3O
CH3O
I

(43)


CH3O
O
NH
CH3O
6
7
8
CH3O
H
SC6H13

(70a)


CH3O
O
NH
SR
O

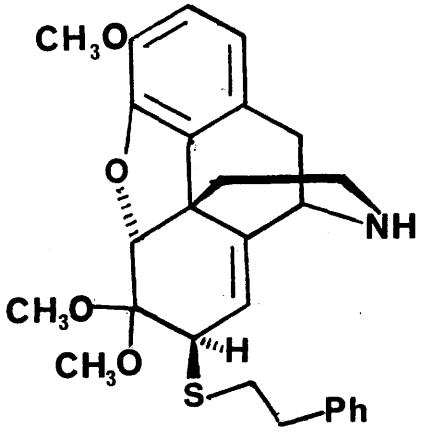
(52)

These features were strongly indicative of a neopinone derivative. Indeed, the ^{1}H n.m.r. spectrum of the isolated material bore many similarities to that of 7β-iodoneopinone dimethyl acetal (43) in which the acetal methoxy groups appear at δ 3.49 and 2.94, and the olefinic proton on C-8 as a doublet (J 6.3 Hz) at δ 5.73. In particular, the magnitude of the coupling constant in this product establishes the presence of a substituent in the 7β-configuration.[68]

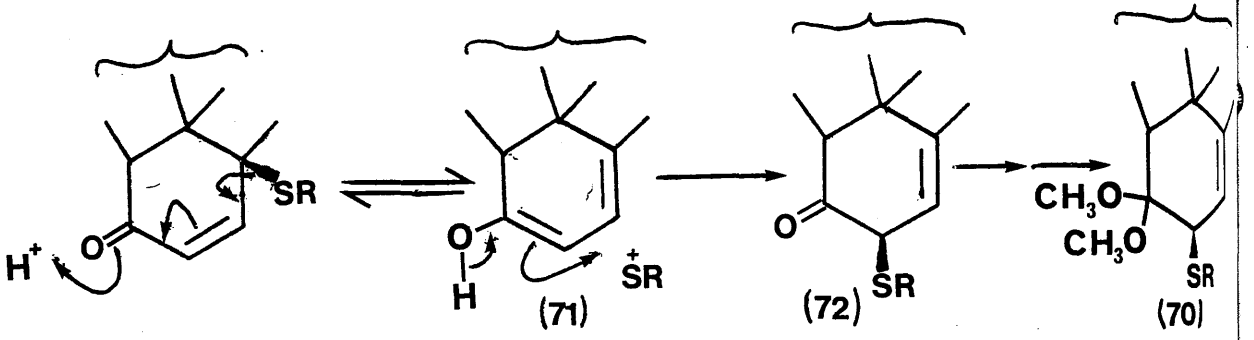
On the basis of the ^{1}H n.m.r. data, therefore, the product of the attempted acetalisation of (51a) was 7β-hexylthionorneopinone dimethyl acetal (70a). This material was converted into its hydrochloride by treatment with ethereal hydrogen chloride; the hydrochloride of this nor base, like those of the norcodeinones (52) was crystalline. The yield of crystalline material was, however, rather low (30%).

This unexpected migration of the alkylthio-group proved to be very difficult to reproduce. Thus, in a similar experiment, the nor base (52a) showed no sign of reaction and was recovered unchanged from the reaction mixture. A subsequent attempt to duplicate the migration process using the N-protected compound (51a) led only to the isolation of the deprotected enone (52a), and no trace could be detected of the desired norcodeinone acetal (70a).

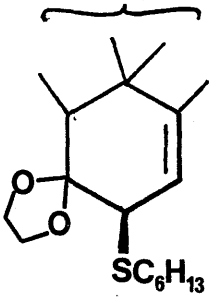
Attempts at acetal formation were made under the same conditions with other N-protected norcodeinones. The phenylthio-compound



(70d)



Scheme 10

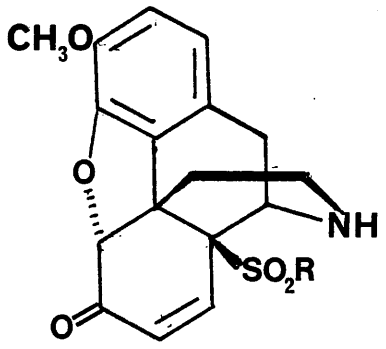


(73)

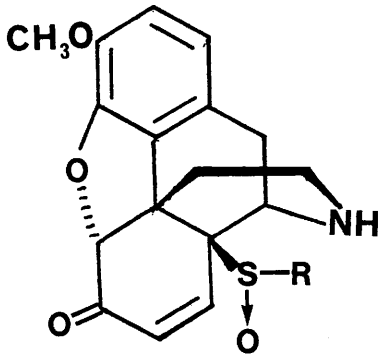
(51b) showed no sign of acetal formation, and the only material recovered was the deprotected enone (52b). The benzyl and 3-phenylpropyl derivatives (51 c,e) also underwent deprotection to the corresponding norcodeinones (52 c,e) although traces of enopinone acetals could be detected in the ^{1}H n.m.r. spectra of the total reaction products. Only the 2-phenylethyl derivative (50d) showed any great degree of acetal formation, giving a mixture of the norneopinone acetal (70d) and the norcodeinone (52d) in a 70:30 ratio. The ^{1}H n.m.r. spectrum of (70d) was very similar to that of the 7β-hexylthio acetal (70a); however, neither (70d) nor its hydrochloride could be obtained in crystalline form.

The yield of the rearrangement products (70 a,d) was low, even when these compounds were isolable. In no case could the expected products, the norcodeinone acetals (69) be detected.

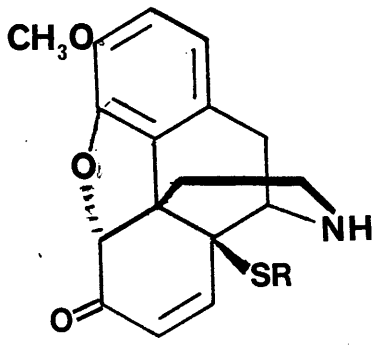
The rearrangement of (52a) to the neopinone acetal (70a) is thought to proceed by the mechanism of Scheme 10. Protonation of the nitrogen apparently prevents migration, presumably because the withdrawal of electrons from C-14 by the positively charged nitrogen prevents dissociation to the postulated intermediate (71). Thus, the alkylthio migration depends on the rate of deprotection of nitrogen being slower than the rate of formation of (71). Acetal formation, by this hypothesis, takes place after the migration of sulphur, since the saturated ketone (72) will form an acetal more readily than the enone (52). It is also conceivable that protonation of nitrogen may suppress the necessary protonation of the enone. This mechanism is, however, speculative.



(74) a.R = Ph
b.R = $(CH_2)_3$Ph



(75)



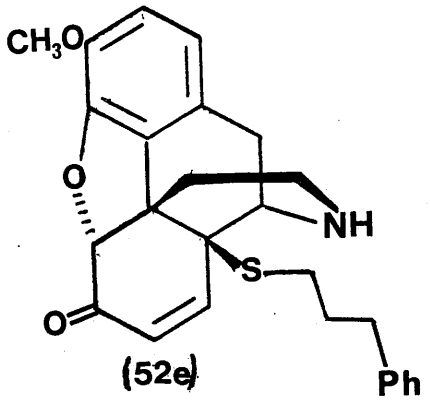
(52)

Treatment of (51a) with glycolic hydrogen chloride in the presence of triethyl orthoformate yielded a noncrystalline product, which again showed only a single olefinic proton in its ^{1}H n.m.r. spectrum, and which was apparently the neopinone acetal (73). The hydrochloride of this compound was also non-crystalline.

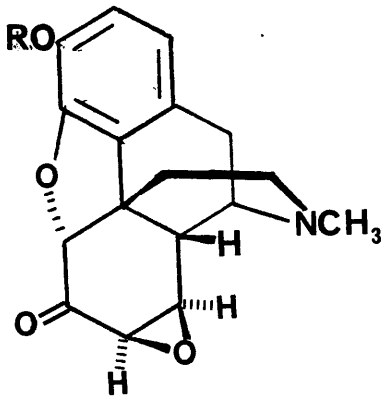
In summary, then, direct acetal formation from the 14β-alkylthionorcodeinones (51) has failed to give the desired acetals (69). The sole products, when reaction of the carbonyl group could be detected at all, were the neopinone derivatives (70), which were isolated in low yield.

5) Oxidation of alkylthiocodeinones: 14β-alkylsulphonylnorcodeinone derivatives

With the completion of synthesis of the norcodeinone derivatives (52), attention was next directed towards the production of the derived sulphones (74). The effect of a more strongly electron-withdrawing group at C-14 on analgesic activity appeared worthy of investigation, and it was hoped that comparison of the analgesic activities of the thioethers (52) and sulphones (74) would prove fruitful. Synthesis of the corresponding sulphoxides (75) was not attempted at this stage, since the likely stereochemistry of sulphoxide formation was unpredictable and it seemed probable that a mixture of stereoisomers at sulphur would be produced.



(52e)

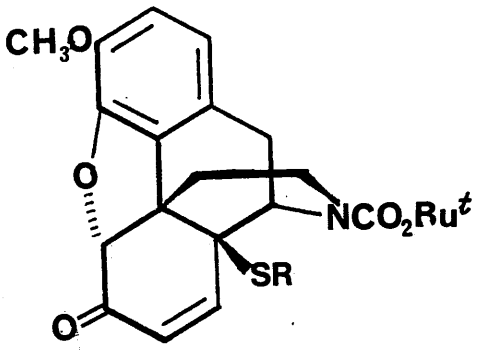


(76)

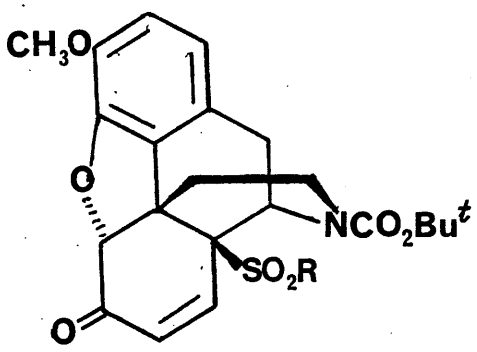
As described earlier (vide supra) attempts at direct formation of 14β-alkylsulphonylcodeinone derivatives by addition of sulphonyl chlorides to thebaine and N-t-BOC-northebaine proved unsuccessful. It was therefore necessary to approach the sulphones (74) by oxidation of the alkylthionorcodeinones (52). The chosen reagent for this purpose was m-chloroperbenzoic acid (MCPBA) which was known to oxidise simple thioethers to sulphoxides and thence to sulphones.[70] This reagent was soluble in most organic solvents and had the additional advantage that it would not react easily with the olefinic double bonds of enones. By contrast, both codeinone and morphinone react with hydrogen peroxide (a reagent also used in the oxidation of sulphur compounds) to give the 7β,8β-epoxides(76).[71]

There was a possibility of reaction at the alkaloid nitrogen, giving N-oxides. It seemed likely, however, that the virtually zero electron density on the protonated nitrogen of the hydrochlorides of (52) would make this site inert towards the electrophilic peracid. Accordingly, the first attempt at sulphone synthesis was made on the hydrochloride of 14β-(3-phenylpropyl) thionorcodeinone (52e).

Treatment of the hydrochloride of (52e) with two equivalents of MCPBA led to the isolation of a gummy residue which proved, on examination by t.l.c., to be a mixture of several compounds. The ^{1}H n.m.r. spectrum of this residue showed many signals, none of which was consistent with a codeinone-type system. This reaction was not further investigated.



(51) b.R = Ph
c.R = CH_2Ph
d.R = $(CH_2)_2Ph$
e.R = $(CH_2)_3Ph$



(77) a.R = Ph
b.R = CH_2Ph

Reaction of an N-protected compound with MCPBA was next attempted. The crystalline phenylthio derivative (51b) was treated with two equivalents of MCPBA in methylene chloride. A precipitate formed, whose melting point was identical with that of m-chlorobenzoic acid. Reaction appeared complete, with a single product visible on analytical t.l.c., after 6 hours at room temperature. The reaction mixture was worked up by shaking with aqueous sodium carbonate, and yielded a white solid from which the sulphone (77a) was obtained in crystalline form in 60% yield.

The reaction was repeated using other N-t-BOC compounds. In general, as mentioned earlier (vide supra) compounds of structure (51) are noncrystalline, and these compounds were produced from N-t-BOC-northebaine as described in an earlier section and treated with MCPBA without further purification. By this method, 14β-phenylmethylsulphonyl-N-t-BOC-norcodeinone (77b) was obtained in crystalline form in 56% yield from (51c).

Similar treatment of the 3-phenylpropyl derivative (51e) yielded a noncrystalline product, which on deprotection with ethereal hydrogen chloride afforded the crystalline hydrochloride of the nor base (74b) in 43% overall yield. The phenylsulphonyl derivative (77a) when deprotected, gave a noncrystalline hydrochloride. However, the free nor base (74a) liberated from its hydrochloride by chromatography on neutral alumina, was crystalline and was isolated in 49% yield based on (51b). This is the only example found of a crystalline free norcodeinone in the sulphur-containing series; the free nor bases (52) are all noncrystalline.

Regrettably, the most active of the alkylthionorcodeinones, the phenylethyl derivative (52d), has proved intractable towards oxidation by MCPBA. Several attempts at oxidation of this compound have resulted only in the isolation of noncrystalline products which are apparently mixtures.

All the sulphones isolated have given accurate microanalyses, although the benzyl derivative (77b), which crystallised from carbon tetrachloride, analysed for the presence of one mole equivalent of solvent. Spectroscopically, these compounds showed few unexpected features; the resonances, due to olefinic protons, were generally further upfield than in the corresponding thioethers, while the singlet due to H-5 was shifted downfield and appeared in the vicinity of δ 5.2 in all cases. In the benzyl sulphone (77b), the olefinic protons are accidentally equivalent and give rise to a singlet at δ 6.36.

In contrast to the complex ^{1}H n.m.r. spectrum of 14β-phenylthio-N-t-BOC-norcodeinone (51b), the derived sulphone (77a) displays a comparatively simple spectrum. It is conceivable that the sulphone is locked in a single preferred conformation, and that there is no significant flexibility in the attachment of the sulphone group at C-14. This contrasts with (51b) in which the less bulky and more flexible thioether permits restricted rotation.

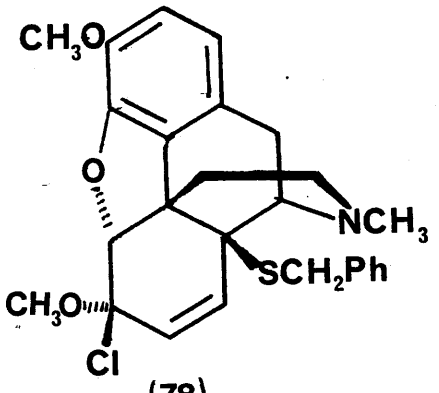
The mass spectra of all the sulphones so far isolated show strong fragment ion peaks due to loss of the complete C-14 substituent; in the case of the nor bases (74) this fragmentation is the preferred process and both (74a) and (74b) display a base peak at m/e 282.

SECTION III. CYCLOADDITIONS OF THEBAINE WITH THIOALDEHYDES

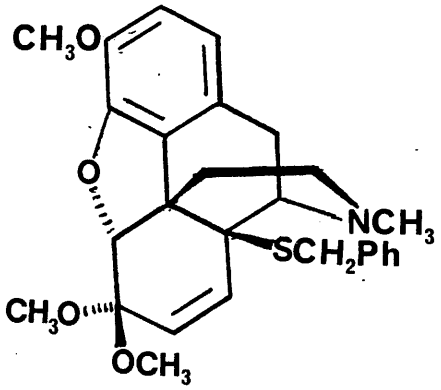
1) Reaction of thebaine with sulphenyl chlorides and triethylamine

As discussed earlier (vide supra) thebaine does not undergo sulphenylation at C-14 when treated with a sulphenyl chloride; in general, the only products isolated under a wide range of conditions were thebaine hydrochloride and the appropriate disulphide. In the search for suitable conditions, an attempt was made to prevent hydrochloride formation, based on the assumption that the presence of a positive charge on nitrogen reduced the reactivity of the diene system towards electrophilic reagents.

A similar problem was encountered in the nitration of thebaine with tetranitromethane, in which it was found that formation of the trinitromethane salt of thebaine greatly reduced yields of the products.[18] In this reaction, improved results were obtained by carrying out reaction in the presence of methanolic ammonia.[72] An identical solution was clearly not practicable in the case of sulphenyl chlorides, which react with ammonia to give primary sulphenamides and hydrogen chloride. However, a tertiary amine which was nevertheless a stronger base than thebaine might be successfully employed, with the by-product of reaction being the hydrochloride of this base rather than thebaine hydrochloride. The base selected was triethylamine, which was volatile enough to be easily removed during workup and whose hydrochloride, if formed, could be removed from the reaction mixture by washing with water.



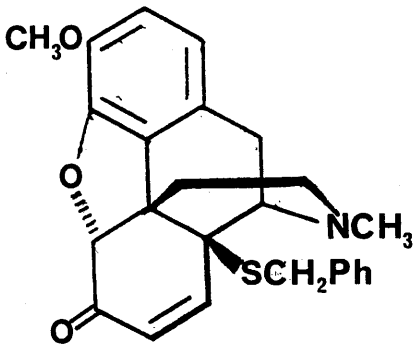
(78)



(79)

In the first attempted reaction, excess phenylmethanesulphenyl chloride in benzene was added to a stirred solution of thebaine in benzene containing triethylamine. Equimolar quantities of triethylamine and the sulphenyl chloride were employed. The reaction mixture became cloudy, but analytical t.l.c. indicated that no reaction had occurred, even after 24 hours at room temperature. When worked up by shaking with aqueous sodium bicarbonate, the reaction mixture yielded a 90% recovery of thebaine.

A further attempt was therefore made, in which the sulphenyl chloride, again in benzene, was added to thebaine and triethylamine in an equal volume of methanol. It was reasoned that sulphenylation of thebaine might be occurring reversibly under the conditions of reaction, and that the presumed intermediate (78) might be trapped by reaction with methanol to give 14-benzylthiocodeinone dimethyl acetal (79). Once again, equimolar quantities of triethylamine and phenylmethanesulphenyl chloride were employed. This time, analytical t.l.c. indicated that partial reaction had taken place within a few minutes of addition of the sulphenyl chloride. Extended reaction times did not appear to increase the yield of the product, which was much less polar than thebaine. The reaction mixture was again worked up with aqueous sodium carbonate, and the residue crystallised from methanol. These crystals proved, by analytical t.l.c., to be a mixture of thebaine (R_f = 0.41 in 9:1 methylene chloride/methanol) and the reaction product (R_f = 0.88). The product was isolated, free of thebaine, after two recrystallisations from ethanol.



(80)

A cursory inspection of the ^1H n.m.r. spectrum of this material indicated that it was neither the expected acetal (79) nor the corresponding enone (80), although there had apparently been reaction with the sulphur reagent. The salient features of the spectrum were as follows:

(i) A five-proton multiplet centred around δ 7.3, assigned to the aromatic protons derived from the sulphenyl chloride.

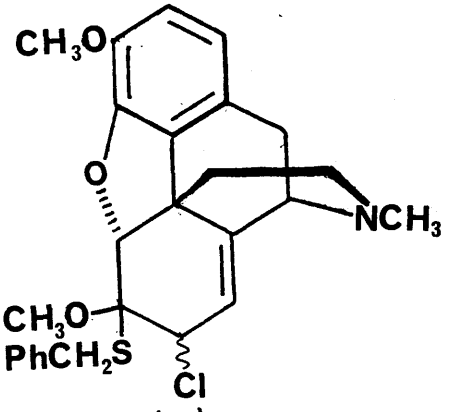
(ii) Two doublets (J 9 Hz) in the olefinic region, at δ 6.31 and 5.20, assigned to H-7 and H-8 respectively.

(iii) Two singlets at δ 5.71 and 5.08. The latter signal showed a small (J 1.5 Hz) coupling to the doublet at δ 6.31, confirmed by decoupling. The δ 5.08 signal was therefore assigned to H-5, and that at δ 6.31 to H-7. The singlet at δ 5.71 could not be easily assigned.

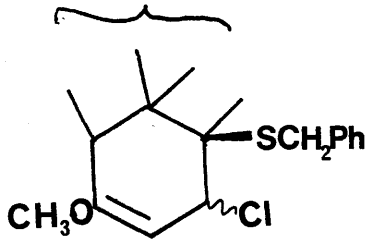
(iv) Two methoxy resonances, at δ 3.80 and 3.68, assigned respectively to the aromatic 3-methoxy group and the 6-methoxy group.

The infrared spectrum of this material displayed no carbonyl or hydroxyl absorption bands. Mass spectrometry revealed a molecular ion at m/e 433, with a strong fragment ion peak of almost equal intensity at m/e 311. Elemental analysis and accurate mass measurement indicated a molecular formula of $C_{26}H_{27}NO_3S$.

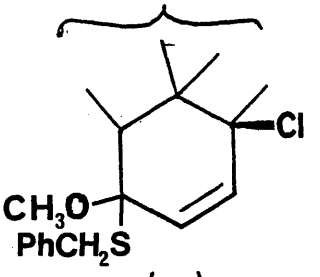
While these features could not be reconciled with 1,4-addition of the sulphenyl chloride, giving either (79) or (80), the most plausible alternative reactions also failed to account for the observed features of these spectra. Thus, 1,2-addition to either


CH3O
O
NCH3
CH3O
PhCH2S
Cl

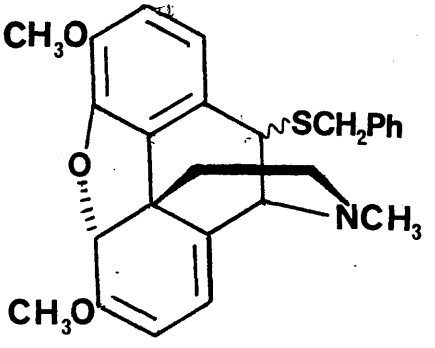
(81)


SCH2Ph
CH3O
Cl

(82)


Cl
CH3O
PhCH2S

(83)


CH3O
SCH2Ph
O
NCH3
CH3O

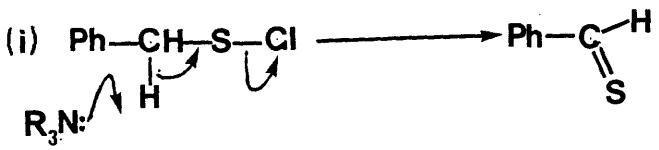
(84)

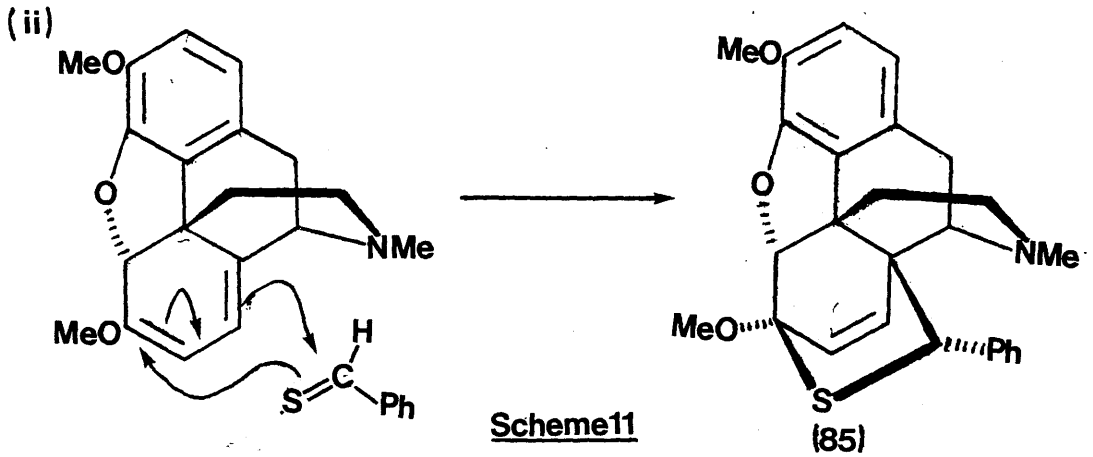
of the double bonds of ring C giving, for example, (81) or (82), could be excluded, as indeed could 1,4-addition in the opposite orientation giving (83). All these reactions led to irreversible incorporation of chlorine, which on the basis of the above analytical data had clearly not occurred. Sulphenylation of ring A could be ruled out since both H-1 and H-2 were still present and gave rise to an AB quartet (δ 6.59 and 6.50, J 8 Hz), while reaction at C-10 giving, for example, (84) seemed unlikely since this position was unreactive towards electrophiles compared to the double bonds of ring C.

The results of mass spectrometry were not, in fact, consistent with the presence of an intact benzylthio-group. Thus, the expected fragment ion at m/e 91, due to the stable tropylium ion and typical of compounds containing a benzyl group, was not observed.

The ^{13}C n.m.r. spectrum of this product indicated a total of twelve aromatic carbon atoms, five of which were shown by off-resonance ^{13}C - ^{1}H decoupling to be without attached hydrogen. Two olefinic carbons, both bearing one proton, were observed at δ 132.46 and 127.10, typical of a $\Delta^{7,8}$ double bond. Remaining resonances indicated three quaternary carbons (δ88.80, 49.01, and 48.44); three methine carbons (δ92.95, 50.11 and 49.01); three methylene carbons (δ45.29, 33.28 and 22.40) and three methyl carbons (δ56.36, 53.20, and 42.77). The chemical shifts and multiplicities of these resonances did not appear consistent with any drastic re-arrangement of the morphinan skeleton.

On the basis of this evidence, it was postulated that the course of reaction was as follows. Phenylmethanesulphenyl chloride reacted first with triethylamine, with elimination of hydrogen

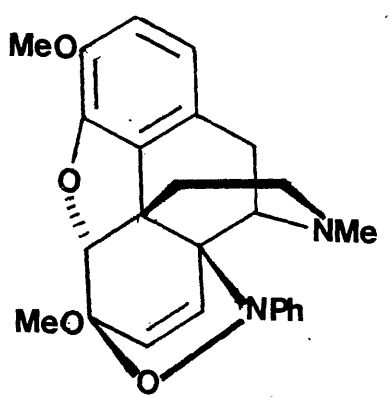




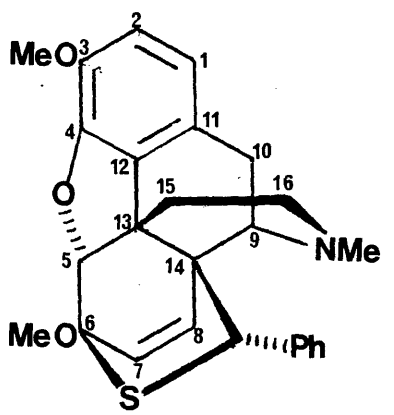
Scheme11

TABLE 6

^{1}H Chemical Shifts of the Adducts (16,R=Ph) and (85)



(16)



(85)

Resonance	δH[a]	δH
H-1	6.55	6.50
H-2	6.58	6.59
H-5	4.75	5.08
H-7	6.25	6.31
H-8	5.36	5.20
3-OMe	3.82	3.82
6-OMe	3.76	3.68
-NMe	2.49	2.33

Note: a. See reference 16.

chloride, to give thiobenzaldehyde. The thioaldehyde then underwent rapid Diels-Alder type cycloaddition with the diene system of thebaine, giving a reaction product which was formulated as (85)(cf. Scheme 11). This structure is very much like that of the adduct (16; R = Ph) of thebaine and nitrosobenzene. Indeed, the ^{1}H n.m.r. spectra of (16; R = Ph) and (85) show many similarities (cf. Table 6).

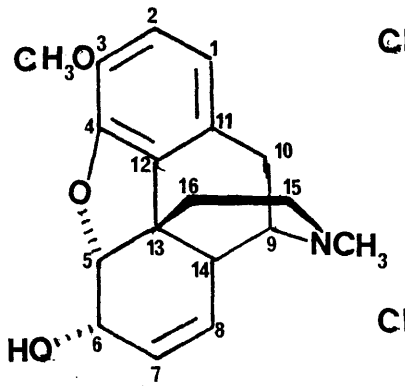
The assignments of ^{13}C resonances for the adduct (85) are listed in Table 7 alongside those of codeine (2) and the 6β,14β-bridged ketone (8). It is noteworthy that the ^{13}C resonances due to C-6 and C-14 in (85) display significant downfield shifts compared to the corresponding resonances in (8). One of the methine carbon resonances (δ 50.1) could not be assigned to a carbon atom in the morphinan skeleton and was therefore assigned to the carbon atom of the epithiomethano bridge. The carbon atoms of the benzene ring attached at this position gave rise to resonances at δ 139.7(s), 130.3(d), 130.1(d, 2c) and 127.6 (d, 2c).

This structure accounts for all the observed spectroscopic features of (85), including the fragmentation pattern observed in its mass spectrum. The principal fragment ion at m/e 311 results from retro-Diels-Alder cleavage of (85), although whether this is due to electron impact or is a purely thermal process is unknown. The fragment ion due to thiobenzaldehyde is also observed, at m/e 122.

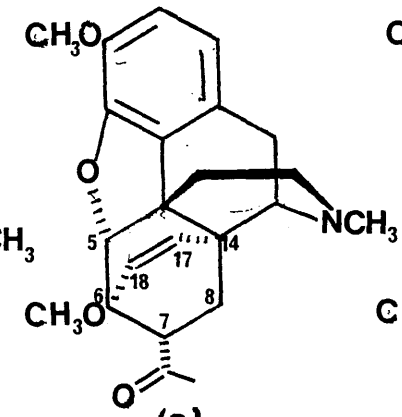
The proton α to sulphur in the 6,14-bridge appears at unusually low field (δ5.71). This may be accounted for, in structure (85), by deshielding due to local magnetic fields arising from the lone

TABLE 7

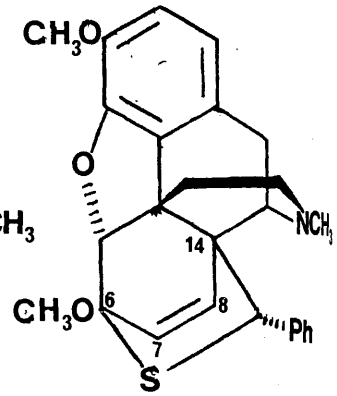
^{13}C Assignments in Codeine (2) and the Adducts (8) and (85)



(2)



(8)



(85)

Resonance	(2) δC[73]	(8) δC[74]	(85) δC
C-1	119.3	119.2	119.0
C-2	112.8	113.4	113.1
C-3	142.0	141.6	142.0
C-4	146.2	147.8	146.8
C-5	91.3	95.0	93.0
C-6	66.4	81.0	88.8
C-7	133.2	135.7a	132.5
C-8	128.1	125.7a	127.6
C-9	58.7	59.8	57.9
C-10	20.4	22.2	22.4
C-11	127.0	128.0	127.1
C-12	130.9	133.8	132.8
C-13	43.0	47.2	49.0b
C-14	40.7	43.0	48.4b
C-15	35.8	33.3	33.3
C-16	46.4	45.2	45.3
NMe	43.0	43.3	42.8
3-OMe	56.2	56.5	56.4
6-OMe	-	53.2	53.2
Others	-	208.7(s),50.5(d), 30.2(q), 29.7(t)	139.7(s),130.3(d), 130.1(d,2c),127.6(d,2c) 50.1(d).

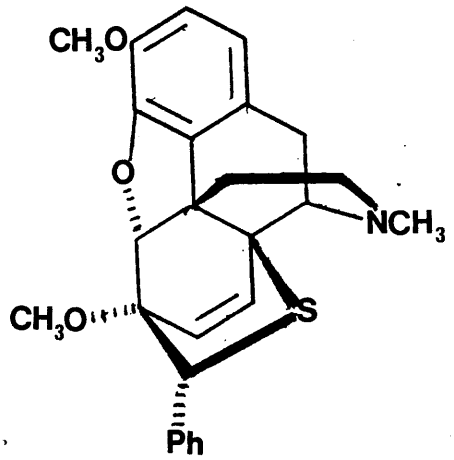
Notes: a. Resonances due to C-17 and C-18 of the endo-etheno bridge.

b. Interchangeable assignments.

pair electrons of nitrogen. The stereochemical implications of this are discussed in the following paragraph.

The stereochemistry of addition is almost certainly that of previously observed Diels-Alder reactions of thebaine, giving a 6β,14β-bridged structure similar to that of the ketone (8) or the nitrosocarbonyl adducts (16). The configuration of the chiral centre in this phenylepithiomethano bridge has not been unambiguously determined. However, molecular models indicate that the phenyl group is likely, on steric grounds, to be on the α face of the bridge; not only is the phenyl group directed away from the nitrogen bridge and so in a less crowded environment than a β-phenyl group, an α-phenyl group is also on the same side as the $\Delta^{7,8}$-double bond, fulfilling the endo-rule for Diels-Alder additions. This gives an absolute (S) configuration at this centre. The presence of only one signal for this methine proton indicates that the (S) isomer is the sole product. In the (R) configuration, the methine proton would be directed away from the nitrogen atom, and would not exhibit the deshielding described above; indeed, an α-proton at this position would probably experience some shielding from the π-electrons of the double bond.

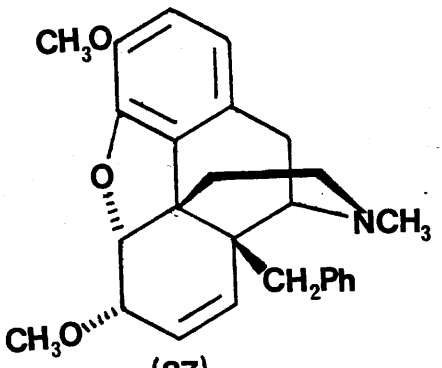
The yield of (85) from this preparation was rather low (42%). Attempts were made to improve this result by, firstly, increasing the mole ratio of sulphenyl chloride and triethylamine to thebaine, thus generating greater quantities of thioaldehyde and, secondly, by increasing further the quantity of triethylamine to increase the rate of thioaldehyde formation.



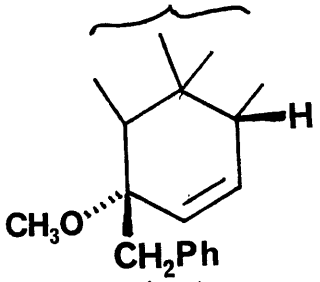
(86)

In the first instance, thebaine reacted with phenylmethanesulphenyl chloride and triethylamine in molar ratios of 1:2.1:2.2, again in 1:1 benzene-methanol, giving (85) in 62% yield; in the second, with the reagents in the ratio 1:2.2:4.5, (85) was obtained in 79% yield based on thebaine. In these latter cases, reaction appeared to be complete within five minutes, as judged from analytical t.l.c., and the adduct (85) was obtained in pure form by crystallisation from ethanol.

While the above results, and particularly the spectroscopic evidence, appeared entirely consistent with (85), it was not possible definitely to exclude the alternative structure (86). With this in mind, attempts were made to remove the sulphur atom from this compound; it was hoped that the two possible structures (85) and (86) could be distinguished on the basis of the structure of the desulphurised material. A number of reagents have been successfully employed in the desulphurisation of thioethers and other sulphur compounds, although the various nickel catalysts of the Raney type are still the best known. It is known that Raney nickel catalysts can hydrogenate olefinic double bonds under some circumstances[75] and so it was decided to attempt desulphurisation initially using other reagents. However, sodium amalgam,[76] aluminium amalgam[77] and lithium aluminium hydride[78] were all entirely ineffective; no trace of reaction could be detected by analytical t.l.c. and the unchanged adduct was obtained in each case with 85 - 90% recovery.



(87)

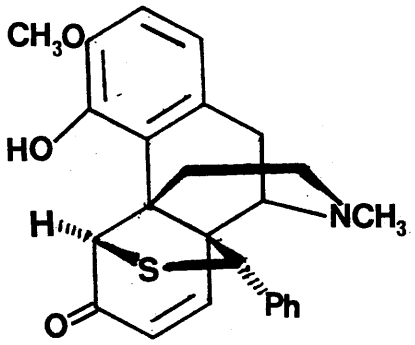


(88)

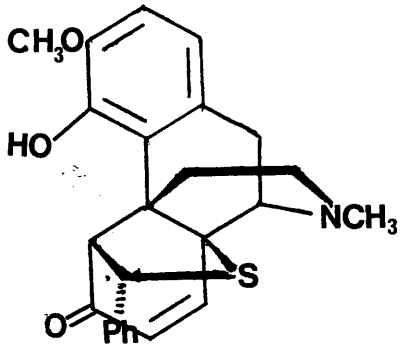
The use of a Raney nickel reagent was next attempted. The reagent selected was that known as 'W-4' Raney nickel, which was chosen for its relative ease of preparation and high catalytic activity.[79] This reagent also failed to give any desulphurisation when employed at room temperature, even when the nickel reagent was employed in large excess.

Treatment of (85) with a large excess of W-4 Raney nickel in refluxing ethanol, under an inert atmosphere, yielded a single crystalline product. However, a cursory examination of the ^{1}H n.m.r. and infrared spectra of the product indicated that it was neither the expected product (87), nor the other possible desulphurisation product (88) derived from (86). Thus, the olefinic region displayed resonances for four protons at δ 6.00 and 5.82 (AB quartet, J 9 Hz; the δ 6.00 resonance displayed a further splitting of ca. 1.5 Hz) assigned to H-7 and H-8 respectively. Also, singlets were observed at δ 5.89 (disappeared on shaking with D_2O) and δ 5.81. Only a single methoxy resonance was visible at δ 3.80, presumably due to the aromatic 3-methoxy group. The H-5 resonance appeared as a close doublet (J ca. 1.5 Hz) at δ 4.72; coupling between H-5 and H-7 was confirmed by a decoupling experiment. No coupling of H-5 or H-8 to any other proton could be observed, and the multiplicity of the H-7 and H-8 resonances could be accounted for entirely by the coupling of H-8 with H-7, and of H-7 with H-5. The absence of both the 6-methoxy group and of any C-6 proton suggested that a codeinone derivative had been formed, although the olefinic proton resonances were closer together than might be expected in an enone.

The presence of an αβ-unsaturated ketone was confirmed by the infrared spectrum of the product, which displayed a strong



(89)



(90)

absorption band at 1675 cm^{-1}. A somewhat weaker absorption band at 3530 cm^{-1}, which was unaffected by changes in concentration, indicated the presence of a hydroxyl group; this was already suggested by the presence of an exchangeable proton signal in the n.m.r. spectrum.

Treatment of the product with ethanolic iron (III) chloride gave an intense deep green colour; this result was consistent with the presence of a phenol. The starting material was inert to iron (III) chloride.

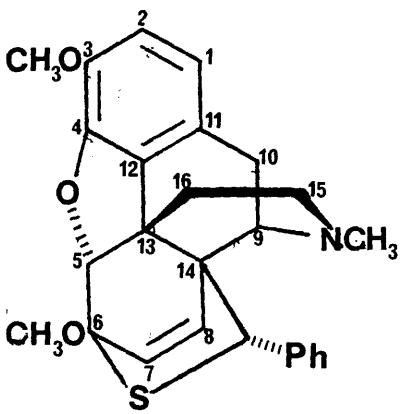
The mass spectrum of the product indicated a molecular weight of 419, and mass measurement indicated a molecular formula of $C_{25}H_{25}NO_3S$. Analytical data indicated that the crystalline material was a hemihydrate.

On the basis of these features, the product of reaction was assigned the 5β,14β-bridged structure (89). This rearrangement may best be explained in terms of reaction of (85) with traces of alkali present in the nickel reagent. Confirmation that rearrangement under alkaline conditions was possible was provided by treatment of (85) with sodium hydroxide in refluxing ethanol. The phenol (89) was isolated from this preparation in 66% yield.

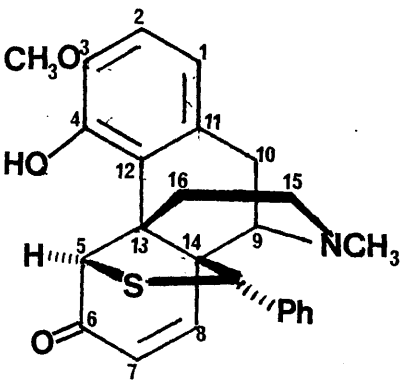
Although unexpected, this rearrangement confirms the identity of the original adduct as (85). The rearrangement product (90), derived from the alternative structure (86) of the adduct, would have a markedly different proton n.m.r. spectrum. In particular, coupling between H-5 and the bridging methine proton would be significant, and H-5 would appear as a doublet of doublets.

TABLE 8

^{13}C Assignments in (85) and the Rearrangement Product (89)



(85)



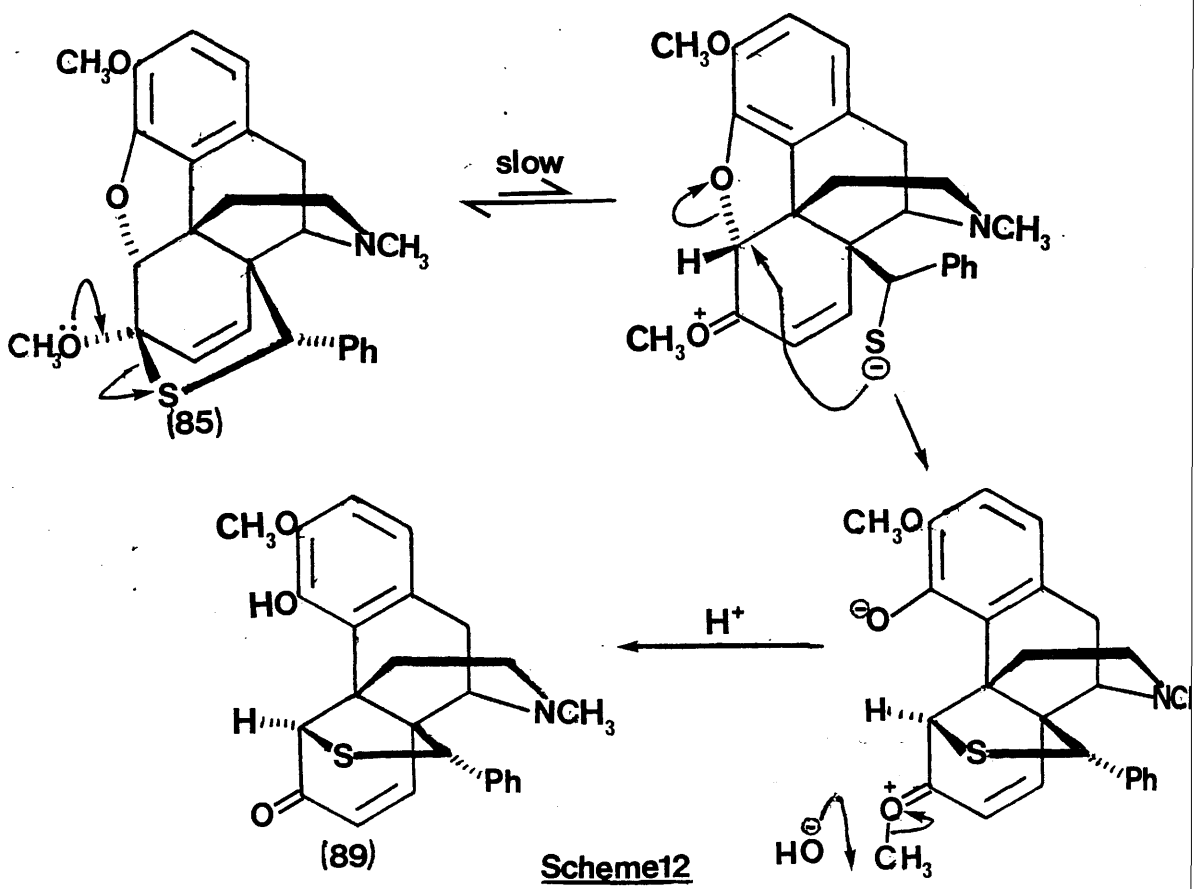
(89)

	(85)	(89)
	δC	δC
C-1	119.0	117.8
C-2	113.1	108.8
C-3	142.0	142.8
C-4	146.8	144.8
C-5	93.0	53.7
C-6	88.8	194.6
C-7	132.5	127.6
C-8	127.6	148.8
C-9	57.9	59.5
C-10	22.4	25.3
C-11	127.1	125.0
C-12	132.8	130.2
C-13	49.0	52.4
C-14	48.4	55.9
C-15	33.3	29.7
C-16	45.3	45.8
NMe	42.8	42.6
3-OMe	56.4	55.9
6-OMe	53.2	-
Others	139.7(s),130.3(d), 130.1(d,2c),127.6(d,2c) 50.1(d)	135.6(s),131.1(d), 130.0(d,2c),128.0(d,2c) 55.0(d)

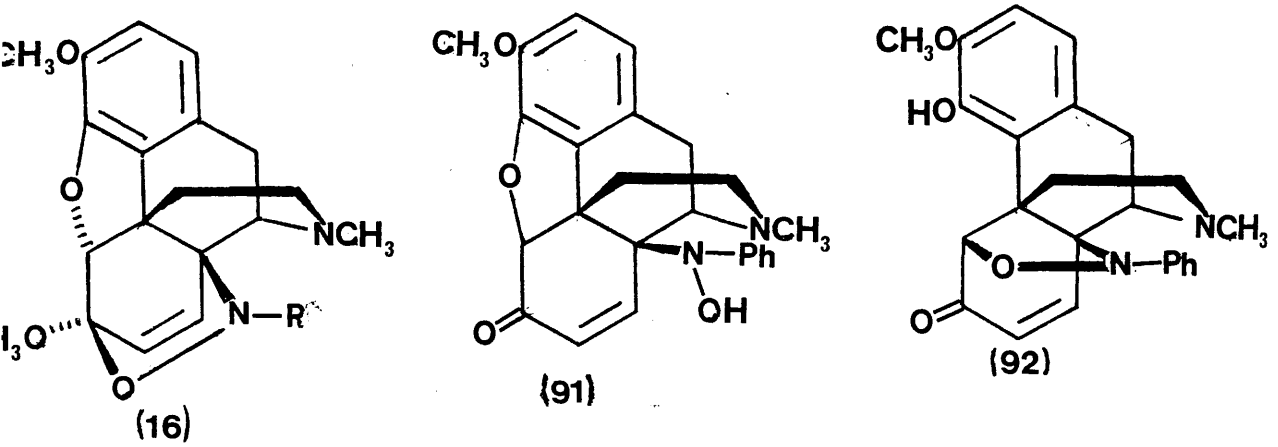
The structure proposed for (89) accounts satisfactorily for all the observed spectroscopic features. The unusually small separation between the H-7 and H-8 resonances may be accounted for by shielding of H-8 by the phenyl group. Normally in codeinone derivatives, the H-8 resonance is much further downfield than that due to H-7, whereas in (89) the H-8 resonance is slightly further upfield. The methine proton of the 5,14-bridge gives rise to the singlet observed at δ 5.81; this is comparable with the chemical shift of the corresponding proton in (85), which appears at δ 5.71. It is assumed that deshielding due to the lone pair electrons of nitrogen influences the chemical shift of this proton in the same way in both (85) and (89). This, in turn, implies that the (S) configuration of the bridging methine in (85) is retained in (89).

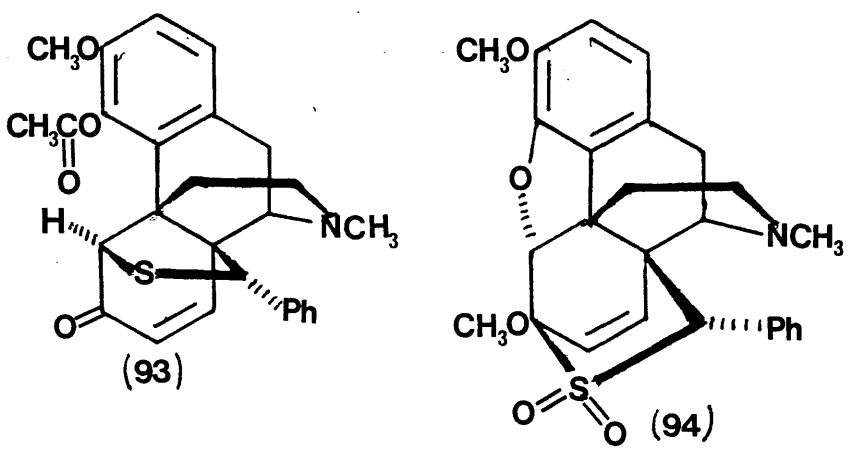
Further confirmation of the structure of (89) was provided by its ^{13}C n.m.r. spectrum. The chemical shifts and assignments for both (85) and (89) are shown in Table 8. Apart from the presence of the carbonyl carbon resonance at δ 194.6, several other changes were apparent. Notably, the resonance due to C-5 had shifted markedly upfield, reflecting the attachment of sulphur rather than oxygen at this position. The C-8 resonance showed a pronounced downfield shift due to deshielding by the carbonyl group. Small shifts in the positions of other resonances associated with carbon atoms in the immediate vicinity of the 5β,14β-bridge probably reflect changes in shielding due to displacement of the phenyl group as the phenylepithiomethano bridge shifts from C-6 to C-5.

The mechanism by which (85) rearranges to (89) under alkaline conditions is conjectural, but may follow the mechanism of Scheme 12.


CH3O
slow
NCH3
Ph
(85)
H+
HO
(89)

Scheme12


NCH3
N—R
N—Ph
OH
HO
(16)
(91)
(92)

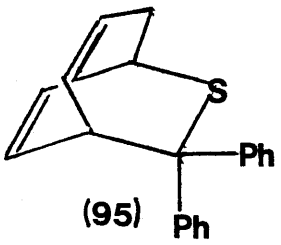

CH3CO
NCH3
Ph
(93)
(94)

Opening of the 6β,14β-bridge, presumably by hydroxide ion, to give a thiolate intermediate may proceed reversibly; however, the 4,5α-oxygen bridge is the best available leaving group and is ideally positioned to undergo nucleophilic displacement by attack of the thiolate ion at C-5. Further, the thiolate ion is likely to be an extremely good nucleophile; thus, the subsequent nucleophilic displacement will probably proceed rapidly and certainly irreversibly.

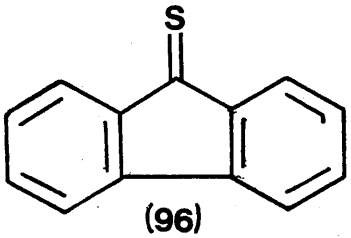
The rearrangement of (85) to (89) finds a significant parallel in rearrangement of the thebaine-nitrosobenzene adduct (16, R = Ph). The 6-acetal function of this compound is readily hydrolysed giving the hydroxylamine (91); treatment of (91) with sodium methoxide then affords the 5,14-bridged phenol (92)[11,16].

The identity of the phenol (89) was further confirmed by its conversion to its 4-O-acetate (93) by treatment with acetic anhydride in dry pyridine. This compound displayed carbonyl absorption bands at 1690 cm^{-1} (enone) and 1770 cm^{-1} (aromatic ester). The mass spectrum of (93) showed major ion peaks at m/e 461 (M^+) and 419 ($M-CH_2CO$). This fragmentation is typical of aromatic esters, and was confirmed by the presence of a metastable ion peak at m/e 381.

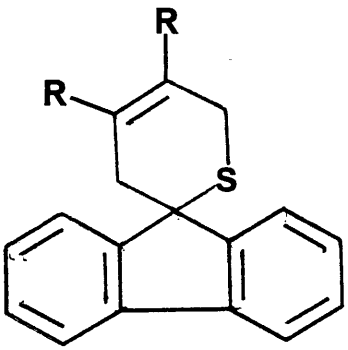
In a further approach to desulphurisation of (85), an attempt was made to oxidise the sulphur bridge giving the sulphone (94). It was hoped that this compound could be more readily desulphurised than could (85). However, treatment of (85) with two equivalents of m-chloroperbenzoic acid led only to the isolation of an amorphous residue which was apparently a mixture of several compounds. It was assumed that this resulted from formation and decomposition of an N-oxide; the investigation was not pursued further.



(95)

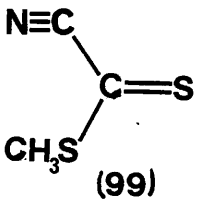


(96)

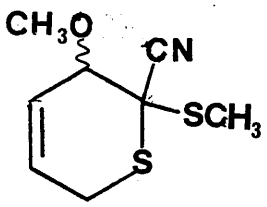


(97)

(98)



(99)



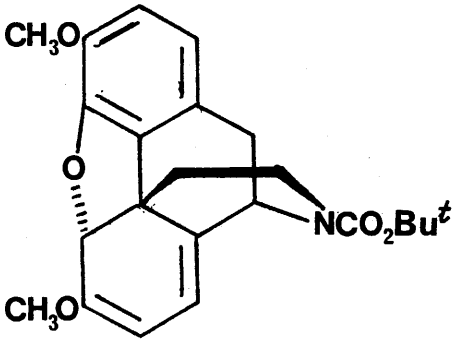
(100)

In summary, then, the reaction of thebaine with phenylmethanesulphenyl chloride and triethylamine in 1:1 benzene-methanol gives a single product which is apparently the Diels-Alder adduct of thebaine and thiobenzaldehyde. Attempts at desulphurisation of this product have proved unsuccessful; however, the adduct undergoes rearrangement under alkaline conditions to a phenolic product identified unambiguously as (89). This, in turn, confirms that the Diels-Alder adduct formed is of structure (85).

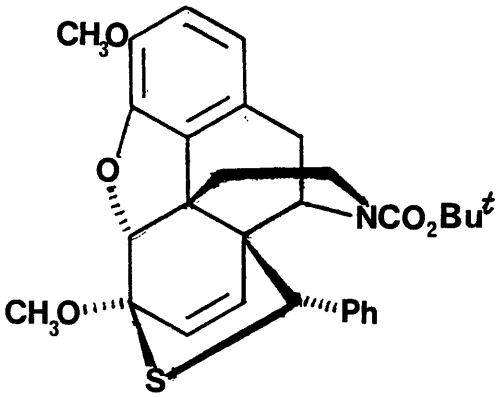
The use of thiocarbonyl compounds - most frequently, thioketones - as dienophiles is already well documented. Thus, thiobenzophenone adds to cycloheptatriene to give a (2 + 4) cycloadduct (95),[80] while thiofluorenone (96) adds to substituted butadienes giving adducts (97)[81]. Thioaldehydes have been less widely applied, since they tend to be unstable. However, it is known that thioformaldehyde, generated in situ undergoes reaction with dienes giving adducts such as (98)(derived from cyclopentadiene).[82]

A single example has been reported of addition of a thiocarbonyl compound to a methoxydiene. Thus, methyl cyanolithioformate (99) adds to 1-methoxybutadiene to give the adduct (100).[83] In this case, the orientation of the dienophile is the opposite to that observed in formation of (85), the sulphur atom becoming attached at the 4-position of the diene. This may be accounted for by electron withdrawal due to the nitrile group making the sulphur more electrophilic and favouring attack at the 4-position by sulphur.

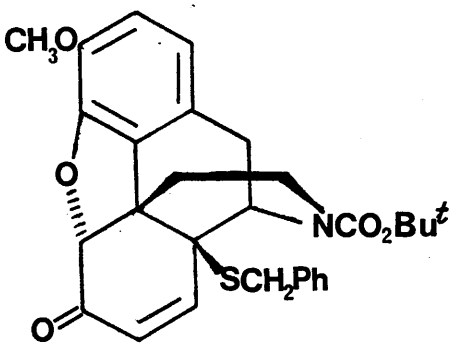
The formation of thiocarbonyl compounds by elimination reactions is not a well-documented process. The only example reported to date is the postulated formation of thioformaldehyde in


CH3O
O
NCO2Bu^t
CH3O

(50)


CH3O
O
NCO2Bu^t
CH3O
Ph
S

(101)


CH3O
O
NCO2Bu^t
SCH2Ph
O

(51c)

reaction of methanesulphenyl chloride with dimethylamine.[84] In this reaction, the major product is, as was expected, the appropriate sulphenamide. However, a number of other products were isolated; namely, dimethyl disulphide, dimethyl trisulphide and bis(dimethylamino) methane. These observations were rationalised in terms of formation of thioformaldehyde, by elimination of hydrogen chloride from the sulphenyl chloride, followed by reaction of the thioaldehyde with dimethylamine according to the following sequence :

$$CH_2S + 2\ Me_2NH \longrightarrow (Me_2N)_2CH_2 + H_2S$$

$$H_2S + MeSCl \longrightarrow MeS\text{-}SH + HCl$$

$$2\ Me\text{-}S\text{-}SH \longrightarrow MeS\text{-}S\text{-}SMe + H_2S$$

$$Me_2S_3 \longrightarrow Me_2S_2 + S.$$

Similar results were observed on treatment of ethanesulphenyl chloride with dimethylamine. Little more is known of this reaction however, and the synthesis of (85) represents the first preparative application of the phenomenon.

A further example of the cycloaddition reaction was provided by treatment of N-t-BOC-northebaine (50) with phenylmethanesulphenyl chloride and triethylamine in a 1:2.2:2.5 mole ratio. The N-protected adduct (101) was obtained in 75% yield using 1:1 benzene-methanol as reaction medium. In this case, the presence of methanol was apparently not essential; the adduct (101) was also formed when the reaction was carried out in benzene only, although the yield was lower (58%). In neither case was sulphenylation at C-14, giving the enone (51c) detectable. The ^1H n.m.r. spectrum of (101) differed in several respects from that of its N-methyl analogue (85). Most notably, the signals due to the S-methine proton and to the 6-methoxy group were shifted upfield, appearing at δ 4.25 and 3.36

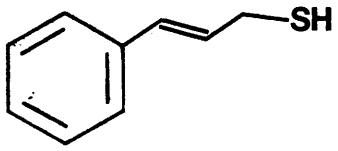
respectively; the corresponding resonances in (85) appear at δ 5.71 and 3.58 . The pronounced upfield shift of the bridge methine resonance reflects the removal of deshielding by the lone pair on nitrogen, encountered in (85). The 6-methoxy resonance now appears at a more normal position for a simple methyl ether. There is no obvious explanation for this upfield shift.

Other resonances, including those due to H-5 (δ 4.63) and the olefinic protons (AB quartet, δ5.95 and 5.80, J 10 Hz) showed pronounced shifts relative to the corresponding signals from (85). The t-BOC group gave rise to a sharp singlet at δ 1.47; either rotation of this group is rapid at 20^{o}, or the group adopts one greatly preferred conformation, as seems to be the case in the sulphone (77a) (vide supra).

The mass spectrum of (101) displays an extremely weak molecular ion at m/e 519. As in (85), the principal fragmentation process appears to be a retro-Diels-Alder cleavage, giving a much stronger peak at m/e 397.

The infrared spectrum of (101) was very similar to that of (85), apart from the presence of an additional very strong band at 1685 cm^{-1} due to the carbonyl function of the N-t-BOC group. (101) gave a satisfactory elemental analysis.

Attempts were next made to reproduce the cycloaddition reaction using other sulphenyl chlorides. As expected, benzenesulphenyl chloride failed to react with thebaine in the presence of triethylamine; elimination to form a thioaldehyde was impossible in this system. Thebaine was recovered in 86% yield from the reaction mixture.



(102)

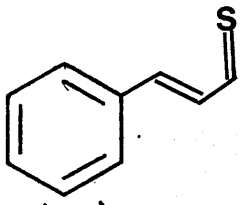
$EtO_2C—CH_2SH$

(103)

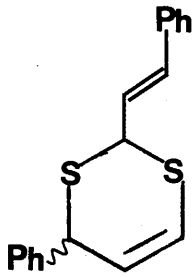
Rather more surprising, perhaps, was the failure of 2-phenylethanesulphenyl chloride and triethylamine to give any reaction with thebaine; the unchanged starting material was recovered in greater than 90% yield. The formation of triethylamine hydrochloride during this reaction suggested that the thioaldehyde had been generated; however, no cycloaddition products could be detected. Conceivably, 2-phenylethanethial, the thioaldehyde produced in this case, might rapidly tautomerise to the corresponding enethiol, which would be essentially inactive as a dienophile. The total absence of cycloaddition products indicated that the thioaldehyde was being removed faster than it was formed, and before it could react with thebaine. In the formation of (85), thiobenzaldehyde when formed could not tautomerise and might, in any event, be more stable due to conjugation of the thiocarbonyl group with the aromatic ring.

For successful cycloaddition it seemed, therefore, necessary to select a thioaldehyde which was non-enolisable and could be generated rapidly from the corresponding sulphenyl chloride. Two thiols were selected for use as starting materials, namely cinnamyl mercaptan (102) and ethyl mercaptoacetate (103). Both of these could be converted to sulphenyl chlorides which contained acidic methylene groups, and which could in turn be expected to undergo elimination of hydrogen chloride to give non-enolisable thioaldehydes.

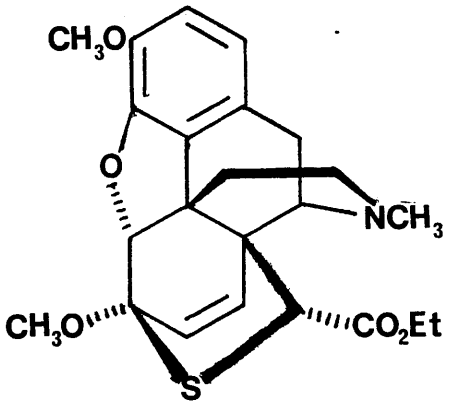
Cinnamyl mercaptan was prepared from the alkyl bromide by treatment with thiourea followed by alkaline hydrolysis, in accordance with a literature method.[85] Conversion to the sulphenyl chloride proceeded smoothly with a 90% recovery of succinimide and,



(104)



(105)



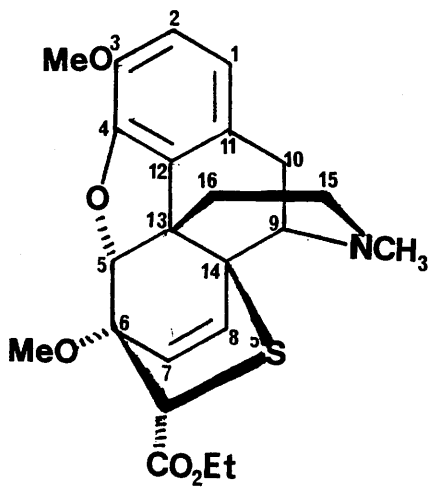
(106)

when the sulphenyl chloride was added to thebaine and triethylamine, triethylamine hydrochloride was formed. However, no cycloaddition could be detected, and an 84% recovery of thebaine was obtained. Repetition of the reaction using a 2:1 mole ratio of sulphenyl chloride and triethylamine to thebaine also failed to give any cycloaddition, and the recovery of thebaine from this reaction was again over 80%.

These results may be explained if it is assumed that the thioaldehyde produced, 3-phenylprop-2-enethial (104) undergoes Diels-Alder addition to itself faster than reaction with thebaine, giving products such as (105), and this would remove the thioaldehyde from the reaction mixture before it could react with thebaine.

Ethyl mercaptoacetate (103), available commercially, was converted into the sulphenyl chloride with N-chlorosuccinimide, and this was added to thebaine and triethylamine in the molar ratio thebaine : sulphenyl chloride : triethylamine 1 : 2.2 : 4.5, in 1:1 benzene–methanol. The reaction conditions selected were those giving best results in the preparation of (85), and the reaction appeared to proceed smoothly to completion after 15 minutes at room temperature. After alkaline workup the product of reaction, first formulated as the adduct (106), was isolated by column chromatography on silica and crystallised from isopropanol in 70% yield based on thebaine.

Examination of the ^{1}H n.m.r. spectrum of the product revealed that it differed in detail from that of the thiobenzaldehyde adduct (85). In particular, the olefinic proton resonances due to H-7 and H-8 had moved markedly closer, appearing as an AB quartet(δ 5.87 and 5.70, J 10 Hz). As before, the H-7 resonance at δ 5.87 was



(107)

further split by coupling to H-5 (J ca. 0.5 Hz). The H-5 resonance showed a pronounced upfield shift to δ 4.38, while the bridging S-methine proton signal was not observed; it appeared to be hidden under the 3-methoxy signal at δ 3.80. The methoxy group of the ester gave a quartet at δ 4.06 and a triplet at δ 1.19 (J 7 Hz).

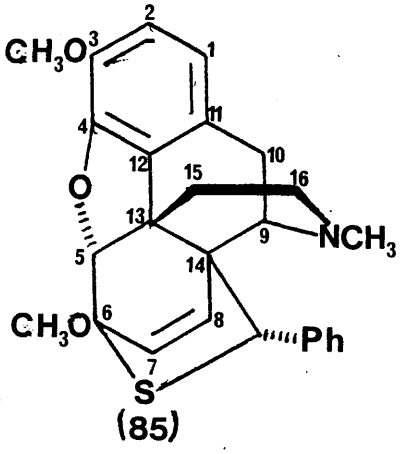
A ^{13}C n.m.r. spectrum of this adduct also showed some differences from that of (85), quite apart from those expected from the presence of a carboethoxy group in place of a phenyl group. Although the differences in chemical shift were generally rather small (see Table 9) the resonance due to C-6 showed an upfield shift of 8 p.p.m. compared to the corresponding resonance in (85), while the C-14 resonance had moved downfield by almost 4 p.p.m. This latter shift was difficult to confirm since the resonances due to C-13 and C-14 cannot be unambiguously assigned.

The infrared spectrum of the adduct displayed a saturated ester carbonyl absorption band at 1740 cm^{-1}. The mass spectrum showed a molecular ion at m/e 429 and, as in (85), a major fragment ion (in this case the base peak) at m/e 311 due to retro-Diels-Alder cleavage. Analytical data were consistent with a molecular formula of $C_{23}H_{27}NO_5S$.

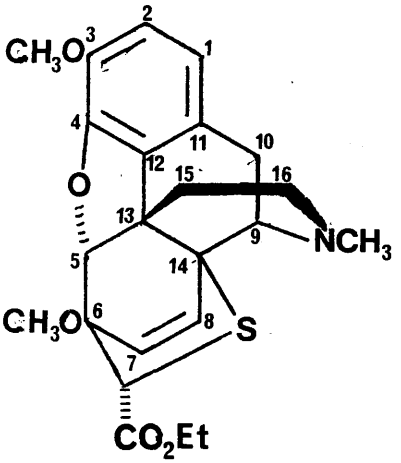
The results of n.m.r. spectroscopy (vide supra) tended to favour the alternative structure (107) for this adduct. Thus the methine proton of the epithiomethano bridge does not display the pronounced deshielding observed in (85); this may indicate that this proton is remote from the lone pair electrons of nitrogen, unlike the corresponding proton in (85). It seems unlikely that the carboethoxy group

TABLE 9

^{13}C Assignments in the Adducts (85) and (107)



(85)



(107)

	(85) δC	(107) δC
C-1	119.0	119.7
C-2	113.1	114.1
C-3	142.0	142.1
C-4	146.8	147.1
C-5	93.0	91.7
C-6	88.8	80.7
C-7	132.5	132.4
C-8	127.6	127.0
C-9	57.9	59.9
C-10	22.4	23.1
C-11	127.1	126.8
C-12	132.8	133.6
C-13	49.0	48.2a
C-14	48.4	52.3a
C-15	33.3	33.3
C-16	45.3	45.7
NMe	42.8	43.3
3-OMe	56.4	56.6
6-OMe	53.2	52.8
Others	139.7(s),130.3(d), 130.1(d,2c),127.6(d,2c) 50.1(d)	169.6(s),61.1(t), 50.8(d),14.0(q)

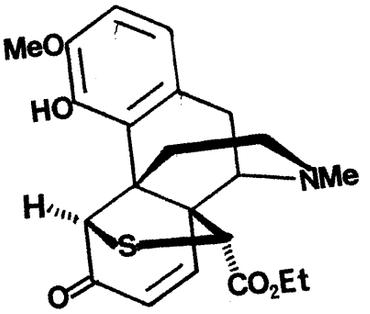
Note: a. Interchangeable assignments.

of (106) would adopt a β-configuration since, as in (85), a bulky substituent at this position would interact unfavourably with the nitrogen bridge. Thus, although a β-substituent may account for the absence of the deshielding effect, it is unlikely on steric grounds. Further, the shifts of the C-6 and C-14 resonances in the ^{13}C n.m.r. spectrum may be best explained in terms of structure (107). Thus, the C-6 resonance appears at a chemical shift virtually identical with that of C-6 in the ketone (8) (cf. Table 9) while the downfield shift observed in the C-14 resonance reflects the attachment of sulphur rather than carbon at this position.

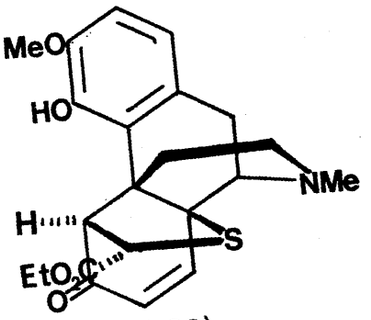
In an attempt to resolve this problem, it was decided to study the effect of base treatment of the adduct. It was hoped that a rearrangement analogous with that of (85) to (89) would occur giving one of the possible phenols (108) or (109). The presence of the ester group meant that water had to be rigorously excluded to prevent hydrolysis

The adduct was treated with sodium ethoxide in dry ethanol under an atmosphere of dry argon. Prolonged reaction at room temperature gave a mixture which could not be characterised. This result is inconclusive and so the orientation of addition of the thioaldehyde in this reaction remains unconfirmed. However, the results of ^{13}C n.m.r. seem to favour the alternative structure (107). Further, this orientation is also observed in addition of methyl cyanodithioformate (99) to 1-methoxybutadiene (vide supra); in this reaction, the thiocarbonyl carbon also carries a strongly electron-withdrawing substituent.

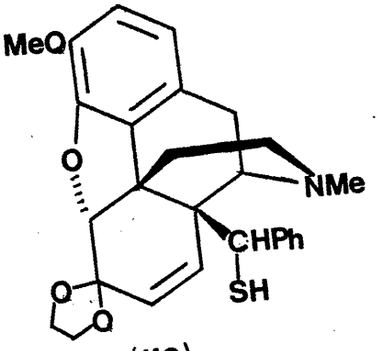
Further reactions of the adducts (85) and (107) have been investigated. In the first instance, (85) was treated with hydrogen chloride in ethylene glycol. It was hoped that this might lead to



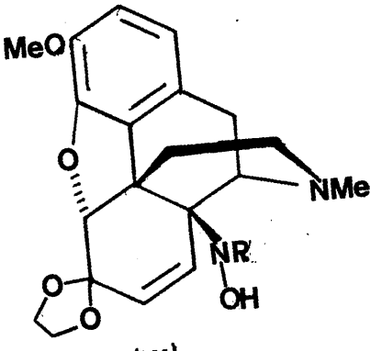
(108)



(109)



(110)

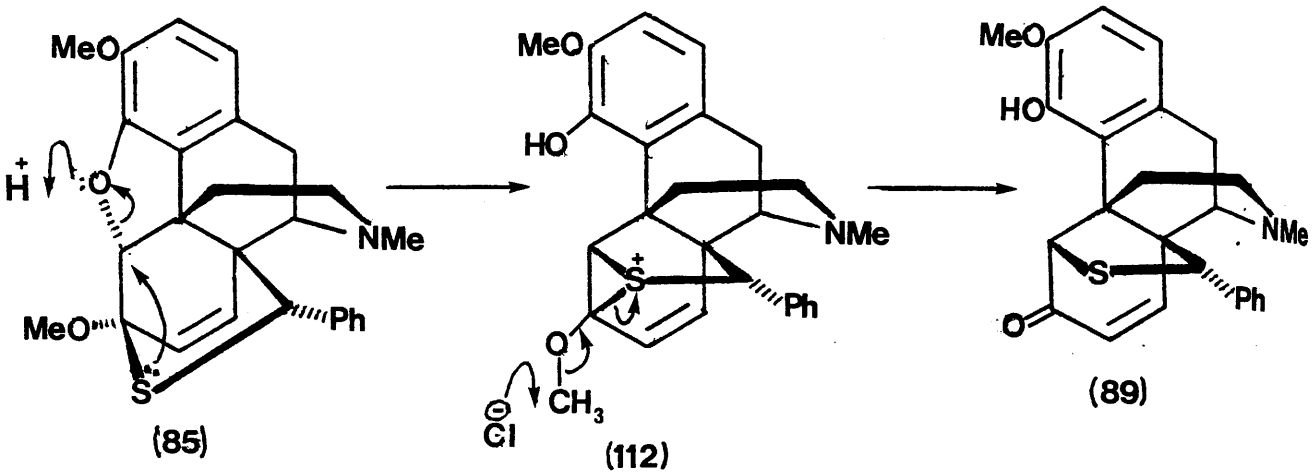


(111)

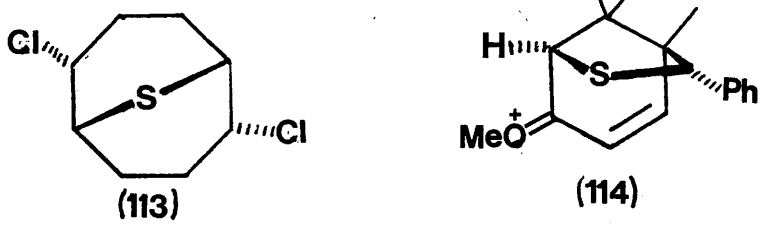
opening of the monothioacetal, followed by formation of the cyclic acetal at C-6 to give the codeinone derivative (110). A similar reaction has been employed in the synthesis of 14-acylaminocodeinones; thus adducts such as (16, R = acyl) were converted to the acetals (111, R = acyl) by treatment with glycolic hydrogen chloride.[11]

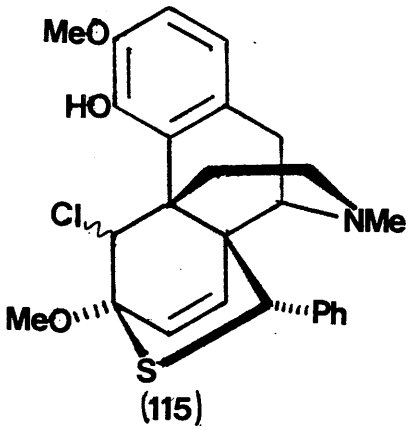
Treatment of (85) with molar glycolic hydrogen chloride, in the presence of triethyl orthoformate as an *in situ* water trap, followed by alkaline workup, led not to the hoped-for product (110) but to the 5β,14β-bridged phenol (89) in 60% yield. No acetal formation was detectable, the enone system of (89) being apparently unreactive under the chosen reaction conditions. Extended reaction time did not affect this result, (89) being the only product isolated even after 48 hours at room temperature. Similarly, (85), when treated with methanolic hydrogen chloride, gave only (89), and repetition of this treatment followed by removal of solvent without workup yielded the hydrochloride of (89) as the sole product. This material was converted to (89) by treatment with aqueous sodium bicarbonate solution.

The hydrochloride of (89) was insoluble in the majority of solvents but its ^{1}H n.m.r. spectrum was eventually obtained in d_6-dimethyl sulphoxide. The ammonium proton was observed as a broad ($W_{\frac{1}{2}}$ 12Hz), D_2O-exchangeable resonance at δ 8.9. The N-methyl resonance appeared as a slightly broadened singlet at δ 2.41. The olefinic protons gave rise to a two-proton singlet at δ 5.99, and the phenolic hydroxyl proton gave a singlet at δ 6.13. No signal was visible which could be assigned to the bridge methine proton. It was assumed that this resonance had shifted markedly upfield, as might be


MeO
H
O
NMe
MeO
Ph
S
(85)
MeO
HO
NMe
S
Ph
O
CH3
Cl
(112)
MeO
HO
NMe
S
Ph
O
(89)

Scheme13

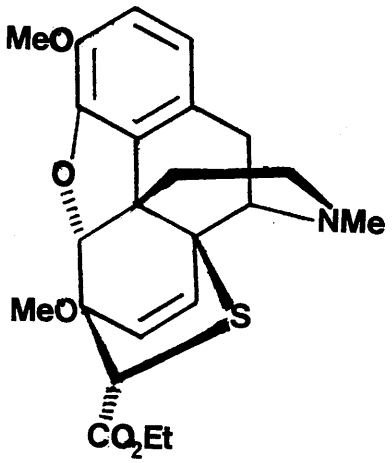

Cl
S
Cl
(113)
H
S
Ph
MeO
(114)


MeO
HO
Cl
NMe
MeO
Ph
S
(115)

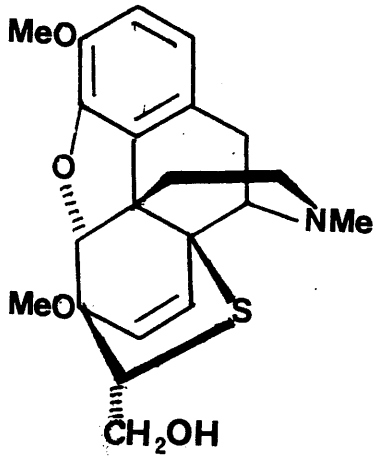
expected if the local magnetic fields due to the lone pair on nitrogen had been removed, and was hidden by other resonances above δ 4.0, such as the very broad signal due to absorbed water.

Rearrangement of (85) to (89) under acidic conditions probably proceeds as shown in Scheme 13. The first step is protonation of the 4,5α-oxygen bridge, followed by sulphur-assisted expulsion of the protonated oxygen to give an episulphonium intermediate (112). The geometry of the molecule is suitable for such a displacement, and episulphonium intermediates are known to be involved in nucleophilic substitution of simpler sulphur-bridged compounds such as (113).[86] It is then postulated that nucleophilic attack by chloride ion or a solvent molecule, brings about opening of the episulphonium intermediate to give (89). This step avoids formation of a methoxonium species such as (114), which might be expected to be trapped as an acetal such as the original target compound (110). No evidence has been found for attack by chloride ion at C-5, giving the 5-chloro derivative (115); perhaps such an attack is precluded on steric grounds.

Reduction of the ester group of the adduct (107) was next investigated. Earlier work on the thiobenzaldehyde adduct (85) indicated that the sulphur bridge of (85) was stable under treatment with lithium aluminium hydride, and it was hoped that the bridge in (107) might show similar stability, allowing reduction of the ester without skeletal rearrangement of the adduct. Further reduction of the ester group to a primary alcohol was an essential preliminary step to the introduction of other functional groups at this position, perhaps by acylation to give substituents of varying length, or perhaps formation of, for example, benzyl or methyl ethers.



(107)

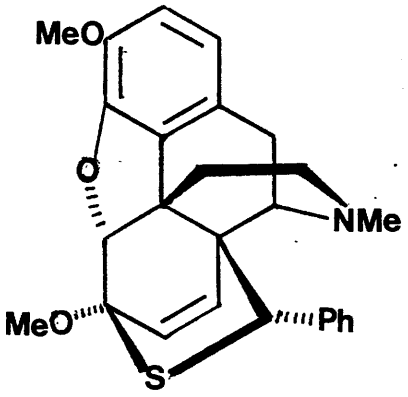


(116)

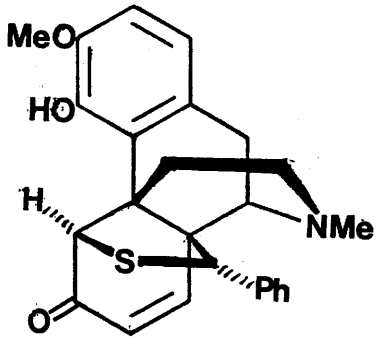
Treatment of (107) with several equivalents of lithium aluminium hydride in dry tetrahydrofuran gave complete reaction within a few minutes. Cautious destruction of the residual hydride followed by extraction gave a single crystalline product, identified as the primary alcohol (116), in 68% yield. Although crystalline, this material proved impossible to recrystallise from a wide variety of solvents; recrystallisation attempts gave an amorphous glass.

The ^{1}H n.m.r. spectrum of (116) showed some features not observed in the other adducts. Thus the olefinic protons were equivalent, giving rise to a two-proton singlet at δ 5.76. The H-5 resonance showed a small downfield shift (δ 4.58 as against δ 4.38) relative to the corresponding resonance in (107). A triplet (J 6Hz) at δ 3.50 was assigned to the methine proton of the 6,14 bridge, and a doublet (J 6Hz) at δ 3.34 to the methylene group of the primary alcohol. The methoxy and N-methyl resonances appeared at the same positions as the corresponding signals in (107). The hydroxyl resonance was not clearly visible; it appears to be superimposed on the complex resonances due to H-10α, H-15 and H-16 around δ 2.60.

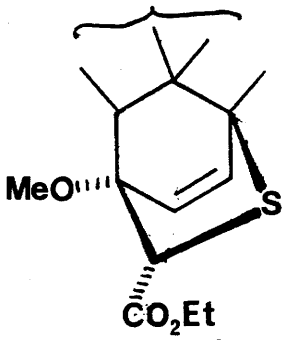
The infrared spectrum of (116) displayed a broad absorption band at 3520 cm^{-1} due to the primary hydroxyl group. Apart from the absence of any carbonyl absorption, the remainder of the spectrum was similar to that of (107). The mass spectrum of (116) displayed a molecular ion peak at m/e 387; the base peak at m/e 311 observed in the adducts (85) and (107) was also observed in this compound. Accurate mass measurement confirmed a molecular formula of $C_{21}H_{25}NO_4S$.



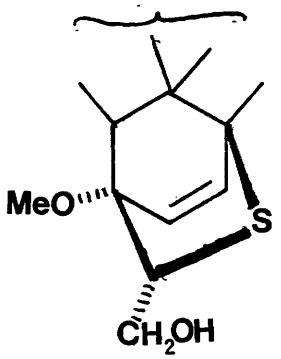
(85)



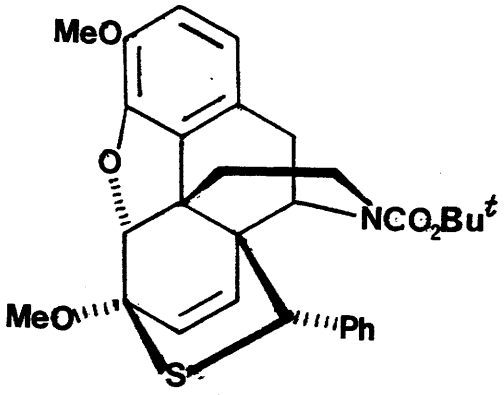
(89)



(107)

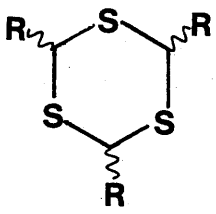


(116)

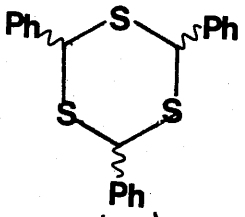


(101)

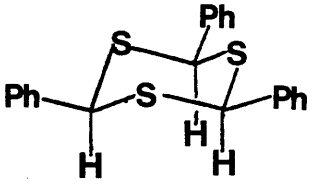
To summarise, then, it has been found that thebaine reacts with certain sulphenyl chlorides in the presence of triethylamine giving products consistent with cycloaddition of thioaldehydes. The adduct (85) of thebaine and thiobenzaldehyde generated from phenylmethanesulphenyl chloride and triethylamine, has been fully characterised. Attempts at desulphurisation have failed; the adduct (85) rearranges with acid or base to give the 5β,14β-bridged phenol (89). Reaction of ethoxycarbonylmethanesulphenyl chloride and triethylamine with thebaine also gives a successful cycloaddition. The mode of addition in this case has not been confirmed by chemical means, although spectroscopic evidence indicates that (107) is the more likely structure. Reduction of (107) with lithium aluminium hydride gives the primary alcohol (116). N-t-BOC-Northebaine has also been converted into the cycloadduct (101) by treatment with phenylmethanesulphenyl chloride and triethylamine giving an N-protected analogue of the adduct (85). The reactions of (101) with acid or base have not been investigated.



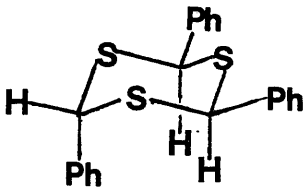
(117)



(118)



(118a)



(118b)

2) Studies of the thebaine-thioaldehyde reaction

With the synthesis of the adducts (85), (101) and (107) completed, a more detailed study of the reaction leading to their formation was embarked upon with three main objectives:

(a) To determine the role, if any, played by methanol in these reactions.

(b) To obtain direct evidence for the formation of thioaldehydes under the conditions of reaction.

(c) To extend the reaction to other dienes.

It was already known that N-t-BOC-northebaine was converted to the adduct (101) when treated with phenylmethanesulphenyl chloride and triethylamine in benzene alone, whereas thebaine proved unreactive under these conditions. This might indicate that a solubility effect was involved. Perhaps thebaine hydrochloride was being formed, in equilibrium with free thebaine and triethylamine, and the poor solubility of the thebaine salt prevented its reaction with thiobenzaldehyde. In the case of N-t-BOC-northebaine, such salt formation was not possible.

Thebaine was treated with phenylmethanesulphenyl chloride and triethylamine in molar ratios of 1:2.2:3.0, approximately those conditions giving the best yields of (85), in three different reaction media, namely:-

(i) benzene containing 2% methanol by volume

(ii) benzene-methanol in 1:2 volume ratio

(iii) benzene-methylene chloride, 1:2 by volume.

In all of these preparations, some reaction was observed and, after alkaline workup, crystalline products were obtained. In (i), the product was shown by proton n.m.r. and analytical t.l.c. to be an approximately equimolar mixture of the adduct (85) and unconverted thebaine. After two recrystallisations from ethanol, (85) was finally obtained in 31% yield.

Preparation (ii), in which the quantity of methanol was increased, gave a product which crystallised from ethanol to give a 55% yield of the adduct (85), while (iii), with no methanol present but with methylene chloride to provide a good solvent for the likely products of reaction, gave the pure adduct in 59% yield. The reaction times were identical (2 hours at room temperature in each case) as were the methods of workup.

On the basis of these results, it would appear that the presence of methanol is not essential in the preparation of (85). However, if methanol is present the relative amount appears to be important; thus, in (i), with only a trace of methanol present, the yield of (85) was low and only partial reaction had occurred. The standard conditions for preparation of (85), with 1:1 benzene-methanol, gave complete reaction and a high (77%) yield of (85) (vide supra), while (ii), in 1:2 benzene-methanol again gave a reduced yield of the adduct. It would seem that the original choice of reaction medium for the synthesis of (85) was fortuitously the best yet discovered.

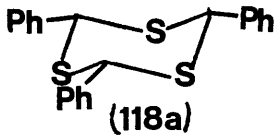
Use of methylene chloride rather than methanol as the co-solvent in this reaction led to complete consumption of thebaine, although a reduced yield of (85) was obtained. This result indicates that the

presence of a co-solvent is important. The results of these preparations seem to imply that the polarity of the reaction medium is important in determining the yield of (85) obtained. With low solvent polarity (e.g. in benzene only) little or no adduct is formed; increase of polarity gives increased yield up to an optimum polarity and thereafter the yield of (85) begins to decrease.

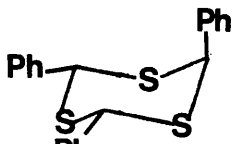
Evidence for the presence of thioaldehydes in these reactions has proved difficult to obtain. It is known that thioaldehydes tend to polymerise, although the cyclic trimers (117) are also found as products of self-condensation of thioaldehydes.[87] In the first instance, it was hoped that the trimer (118) could be isolated from the mother liquors after formation of (85). Failing this, (118) might be isolable after treatment of phenylmethanesulphenyl chloride with triethylamine in the absence of any diene. The preparation and ^{1}H n.m.r. spectra of a number of 1,3,5-trithianes, including the desired compound (118), have already been described and it is known that (118) is formed from thiobenzaldehyde primarily as the all-cis isomer (118a) in which the phenyl groups are all equatorial.[88]

A number of attempts have been made to isolate the trimer (118) from the reaction mixtures leading to (85) by chromatography and by crystallisation from various solvents. However, the only identifiable material isolated by this approach had melting point and ^{1}H n.m.r. spectrum identical with those of dibenzyl disulphide.

Treatment of phenylmethanesulphenyl chloride with triethylamine in benzene yielded, firstly, a precipitate which proved to be triethylamine hydrochloride. Removal of this material, followed by evaporation of the filtrate, gave a semi-solid residue which



(118a)



(118b)

^{1}H n.m.r. spectroscopy revealed as a mixture of at least two compounds. Signals at δ 7.16 and 3.51 appeared consistent with the presence of dibenzyl disulphide. Other signals appeared in the aromatic region at δ 7.21, and further upfield at δ 4.09 and 3.95, the two latter signals being in an approximate 1:2 ratio. All these resonances were singlets.

The signals at δ 7.21, 4.09 and 3.95 may be explained in terms of the presence of the cis,trans-trithiane (118b). The chemical shifts and relative intensities of these signals (approximately 15:2:1) are in good agreement with those reported by earlier workers[88] for this compound. However, the formation of this isomer of (118) is contrary to previous findings. Campaigne and co-workers reported that the ratio of (118a) to (118b) was approximately 23:1 when the trimer was made from thiobenzaldehyde generated from benzaldehyde and hydrogen sulphide. If, indeed, (118b) is being formed, the reaction must be rapid and irreversible, otherwise the more stable all-cis isomer (118a) would be formed.

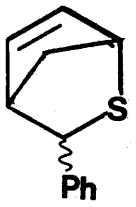
When ethoxycarbonylmethanesulphenyl chloride was treated with triethylamine in benzene, a transient deep pink colour appeared. Intense colours are frequently observed with thiocarbonyl compounds; however, this was the only example of such colour appearing in the treatment of a sulphenyl chloride with triethylamine. The colour persisted for only a few seconds. Within one minute, the reaction mixture was inert to starch-potassium iodide paper, indicating that the sulphenyl chloride had been consumed. The reaction mixture was washed with water to remove triethylamino hydrochloride, and yielded

an amorphous product apparently consisting of one compound, based on analytical t.l.c. Examination of the ^{1}H n.m.r. spectrum of this material indicated that the appropriate disulphide was the only product.

The mechanism whereby disulphides are formed in these reactions is unknown. Armitage and Clark[84] have reported formation of dimethyl and diethyl disulphides by reaction of thioformaldehyde and thioacetaldehyde with dimethylamine (vide supra); however, it seems improbable that triethylamine hydrochloride could react with a thioaldehyde in the same manner.

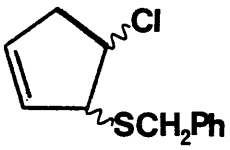
The reaction of thebaine with phenylmethanesulphenyl chloride has also been investigated. Reaction of thebaine and the sulphenyl chloride in 1:1 mole ratio was known to give thebaine hydrochloride and dibenzyl disulphide (vide supra). It was decided to attempt reaction of thebaine with the sulphenyl chloride in a 2:1 ratio in benzene-methanol (1:1) in the hope that one equivalent of thebaine would act as a base to form thiobenzaldehyde, which could then react with the second equivalent of thebaine giving (85). However, no formation of the cycloadduct could be detected; the only materials isolated were thebaine hydrochloride, dibenzyl disulphide and unconverted thebaine. Conceivably this result, together with that of the reaction between phenylmethanesulphenyl chloride and triethylamine, indicates that the strength of the base used in this reaction is of importance.

Finally, an attempt has been made to react cyclopentadiene with phenylmethanesulphenyl chloride and triethylamine. It was hoped that the cycloadduct (119) might be formed if, as was believed,

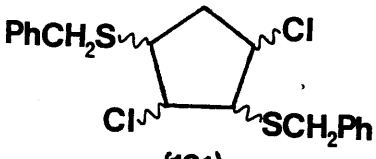


(119)

(98)



(120)



(121)

thiobenzaldehyde was being generated. It was already known that thioformaldehyde and cyclopentadiene reacted to give the adduct (98) (vide supra).[82] However, this reaction gave rise to a complex mixture; it seemed likely that the sulphenyl chloride was reacting with the double bonds of cyclopentadiene giving sulphenylation products such as (120) and (121) faster than elimination to give the thioaldehyde.

In conclusion, studies of the reaction leading to the adducts (85) and (107) have produced little concrete evidence for the formation of thioaldehydes, although the trithiane (118b) appeared to be one of the products formed when phenylmethanesulphenyl chloride reacted with triethylamine. Despite this, there appears to be no credible alternative mechanism for the formation of (85) and (107), and so generation of a thioaldehyde by elimination, followed by its cycloaddition to thebaine, remains the hypothesis advanced to account for the formation of these adducts.

EXPERIMENTAL

Instrumentation

Melting points (uncorrected) :-	Kofler hot-stage apparatus
^{1}H n.mr. spectra:-	Varian T-60 (60 MHz) Perkin-Elmer R32 (90 MHz)
^{13}C n.m.r. spectra:-	Varian XL-100 (25.2 MHz)
i.r. spectra:-	Perkin-Elmer 257 and 197
u.v. spectra:-	Unicam SP 800B.
mass spectra:-	A.E.I. MS12; ionising voltage 70eV.
mass measurements:-	A.E.I. MS902 high-resolution mass spectrometer.

Notes

(i) All solvents and reagents used were of analystical reagent grade unless otherwise stated. 'Ether' refers to diethyl ether. Methylene chloride employed as solvent was dried by distillation from calcium hydride.

(ii) Stirring of reaction media was carried out using magnetic stirrer bars.

(iii) In experiments requiring inert atmospheres, the nitrogen or argon employed was dried by passage through Dreschel bottles containing concentrated sulphuric acid and silica gel.

(iv) Organic solutions were dried over anhydrous magnesium sulphate and evaporated on a Buchi rotary evaporator under water-pump vacuum, unless otherwise stated.

(v) Analytical t.l.c. was carried out on microscope slides coated with 0.25mm layers of Kieselgel G silica gel, with components visualised by iodine staining. Preparative t.l.c. was carried out on 20 x 20cm^2 plates coated with 1mm layers of Kieselgel HF.254 silica with visualisation by u.v. Column chromatography on silica employed 70 - 230 mesh silica under gravity or, in the case of medium-pressure column chromatography, with air pressure applied by means of a hand bellows. Alumina utilised in column chromatography was Woelm basic or neutral alumina of activity grade III.

(vi) ^{13}C and ^{1}H chemical shifts are given on the δ scale relative to trimethylsilane. ^{13}C n.m.r. spectra were recorded with full ^{1}H decoupling; multiplicities are quoted under off-resonance decoupling at δ0.00.

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

Abbreviations :

s, singlet; d, doublet; t, triplet; q, quartet;

m, multiplet (n.m.r.) or medium (i.r.); br, broad; comp, complex.

PART I

1) Acetals of 14 Bromocodeinone

(i) 14-Bromocodeinone dimethyl acetal (28)

Thebaine (15.5g, 0.05 mol) was stirred in methanol (120ml) and N-bromosuccinimide (11.0g, 0.055 mol) was added to the resulting suspension. An intense yellow colour developed and the solid material dissolved. After approximately one minute, a slurry of colourless cyrstals formed. Stirring was continued for a further 30 minutes and the mixture left at 4°C for 16 hours.

The crystals were filtered off, resuspended in water (200ml) and stirred for 15 minutes to remove succinimide, then filtered and dried giving 16.8g of colourless crystals. A further 0.7g of crystalline material was recovered by concentration of the methanolic mother liquors, giving a total yield of 17.5g (83%) of 14-bromocodeinone dimethyl acetal, mp 158 - 160° (lit.[37] 160 - 162°).

^{1}H n.m.r. ($CDCl_3$)

δ 6.65 and 6.49 (2H, ABq, J 8Hz) H-2, H-1; 5.98 and 5.64 (2H, ABq, J 11Hz) H-8, H-7; 4.66 (1H,s), 5-H; 3.87 (3H,s) aromatic -OMe; 3.44 (3H,s) 6α-OMe; 3.17 (3H,s) 6β-OMe; 2.42 (3H,s) -NMe.

i.r. ($CHCl_3$) ν_{max} 1505, 1380, 1050 cm^{-1}

m.s. m/e 423,421 (1:1, M^+), 343,310 (base peak), 296,255,254.

Assignments of the 6-methoxy resonances in the n.m.r. spectrum of this compound were arrived at following labelling studies (see Discussion, pp. 19 - 26).

(ii) 14-Bromocodeinone diethyl acetal (29a)

a) Technical grade ethanol was dried by refluxing with magnesium turnings (10g/litre) and iodine (1g/litre) and distilled. The middle fraction from this distillation was again dried and distilled. To 40ml of the middle fraction from this distillation was added 2ml of redistilled acetyl chloride and 1ml triethyl orthoformate, giving a solution approximately 0.7 M in HCl.

14-Bromocodeinone dimethyl acetal (4.2g, 10mmol) was dissolved in 5ml dry methylene chloride in a 100ml Quickfit conical flask equipped with serum cap and magnetic stirrer. 30ml of the ethanolic HCl prepared as described above was added with stirring and the mixture left at room temperature for 16 hours.

The reaction mixture was basified with solid $NaHCO_3$ and saturated aqueous $NaHCO_3$ solution, then extracted with methylene chloride (2 x 100ml, 2 x 50 ml). The combined organic extracts were dried, filtered and evaporated to give a viscous orange gum. This was chromatographed on grade III basic alumina (50g) in methylene chloride/pentane (2:1 v/v); evaporation of the eluent gave a pale yellow crystalline solid whose ^1H n.m.r. was consistent with 14-bromocodeinone diethyl acetal; 4.2g (94%) mp 112 - 115°. A portion was recrystallised from methanol as colourless prisms, mp 119 - 121°.

Microanalysis: Found : C, 58.59; H, 6.30; N, 2.96; Br, 17.64

$C_{22}H_{28}BrNO_4$ requires : C, 58.67; H, 6.27; N, 3.11; Br, 17.74%.

^1H n.m.r. ($CDCl_3$) δ6.63 and 6.49 (2H, ABq, J 8HZ) H-2, H-1; 5.93 and 5.67 (2H, ABq, J 10Hz) H-8, H-7; 4.66 (1H,s) H-5; 3.82 (3H,s) aromatic -OMe; 3.80 (approx) (2H,m) 6α-OCH_2CH_3; 3.44 (2H,q,J 7Hz) 6β-OCH_2CH_3; 2.40 (3H,s) -NMe; 1.21 (3H,t,J 7Hz) 6α-OCH_2CH_3; 1.16 (3H,t,J 7Hz) 6β-OCH_2CH_3.

m.s. m/e 451,449 (1:1, M^+), 370,324 (base peak), 278.

b) To ethanol dried as above (40ml) was added redistilled acetyl chloride (2.9ml) giving a solution approximately 1 M in HCl. 14-Bromocodeinone (18) (3.3g, 8.9 mmol) was dissolved in methylene chloride (10ml) in a 100ml Quickfit conical flask fitted with serum cap and magnetic stirrer; 8ml of triethyl orthoformate and 40ml of molar ethanolic HCl, prepared as detailed above, were added with stirring and the mixture left at room temperature for 24 hours. The mixture was worked up as for 2(a) above, yielding an orange-red gum; chromatography on alumina as for 2(a) yielded 3.1g (78% recovery) of a pale yellow semi-solid material whose ^1H n.m.r. spectrum was entirely identical with that of the crystalline diethyl acetal isolated in 2(a) above. However, this material could not be crystallised.

iii) 14-Bromocodeinone di-n-propyl acetal (29b)

Reagent grade propan-1-ol was dried over sodium (10g/l) and distilled, the middle fraction (b.p.97 - 98°)being retained. A solution of 0.7 M HCl in propan-1-ol was prepared from 40ml of distillate, 2.0ml of redistilled acetyl chloride and 1ml of triethyl orthoformate.

The reaction was carried out on the same scale as 2(a) above and the reaction mixture left at room temperature for 40 hours, then basified as in 2(a) and extracted with methylene chloride (3 x 100ml). The combined organic extracts were dried, filtered and evaporated leaving 4.5g of yellow gum. This was dissolved in boiling methanol (10ml) and on standing 14-bromocodeinone di-n-propyl acetal (29b) crystallised out as pale yellow prisms, 3.4g, mp 97 - 99°. A further 0.7g of crystalline material, mp 96 - 99°, was obtained from the mother liquors on concentration and seeding, giving a total yield of 4.1g (81%) of crystalline material.

A portion was recrystallised from methanol as colourless prisms, mp 103 - 104°.

Microanalysis: Found : C, 60.14; H, 6.68; N, 2.61; Br, 16.44

$C_{24}H_{32}BrNO_4$ requires C, 60.25; H, 6.74; N, 2.93; Br, 16.70%

^1H n.m.r. ($CDCl_3$) The spectrum is identical with (29a) in all respects except for the resonances due to the n-propyl groups which appear as:

δ3.80 approx (2H,m) 6α-OCH_2-; 3.22 (2H,t,J 6Hz) 6β-OCH_2;

1.4 - 1.9 (4H, complex m)-$OCH_2CH_2CH_3$; 0.91 (6H,t,J 8Hz)-$OCH_2CH_2CH_3$.

m.s. m/e 479, 477 (1:1, M^+), 398,356,338 (base peak), 288

Strong metastable peaks at m/e 338, 287, 279.

(iv) 14-Bromocodeinone ethylene acetal (29c)

Ethylene glycol was distilled through a 30cm Vigreux column and the middle fraction dried for 16 hours over sodium sulphate, then distilled twice through a 30cm Vigreux column under an atmosphere of dry nitrogen. A stock solution of 3 M HCl in dry ethylene glycol was prepared by bubbling hydrogen chloride gas through 200ml of this last distillate, the hydrogen chloride being previously dried by passage through concentrated sulphuric acid. The stock solution was titrated at intervals to check for loss of HCl, and was diluted as required to provide the solution used in the preparation of the ethylene acetal.

To 4.2g (10 mmol) of dimethyl acetal (28) in 10ml methylene chloride, in a 100ml Quickfit conical flask equipped with serum cap and magnetic stirrer, was added 30ml of 0.5 M HCl in dry ethylene glycol, prepared by dilution of the stock solution, and 1ml of triethyl orthoformate. The mixture was stirred at room temperature for 4 hours, then basified as in 2(a) and extracted with methylene chloride (4 x 100ml). The combined organic extracts were washed with brine (2 x 200ml), dried, filtered and evaporated to give a pale yellow gum (4.2g) which, on tritration with methanol, crystallised to give 14-bromocodeinone ethylene acetal (29c) as colourless prisms, 3.7g (88%), mp 136 - 138°. A portion was recrystallised from methanol to mp 137 - 138°.

Microanalysis: Found : C, 56.67; H, 5.24; N, 3.53

$C_{20}H_{22}BrNO_4$ requires C, 57.15; H, 5.28; N, 3.33%.

^1H n.m.r. ($CDCl_3$) δ 6.68 and 6.56 (2H, ABq, J 8Hz) H-2, H-1;
6.13 and 5.62 (2H,ABq,J 8HZ) H-8, H-7; 4.57 (1H,s) H-5;
4.06 (4H,comp.m.)-OCH_2CH_2O-; 3.90 (3H,s) 3-OMe; 2.43 (3H,s)-NMe.

i.r. ($CHCl_3$ solution): ν_{max} 1510, 1450, 1380 cm^{-1}
m.s. m/e 421, 419 (1:1, M^+), 340 (base peak), 278,254.

2) Reduction Methods : Codeinone Enol Ethers

Typical procedures for each reduction method are detailed below. In the case of the dialkyl acetals (29a,b) all three methods have been successfully applied (cf. Discussion, p. 15) while reduction of the cyclic acetal (29c) has been carried out only with sodium dihydrobis(2-methoxyethoxy) aluminate ('Vitride').

(i) Codeinone enol ethyl ether (21a),(6-desmethoxy-6-ethoxythebaine).

14-Bromocodeinone diethyl acetal (29a) (0.9g, 2 mmol) was dissolved in dimethylformamide (50ml) in a 250ml Quickfit three-necked round-bottomed flask fitted with a nitrogen inlet, rubber serum cap and magnetic stirrer. The system was flushed thoroughly with nitrogen over a period of 30 minutes.

An aqueous solution of chromium (II) sulphate (50ml; approx. 0.3 M in chromium (II) was added using a nitrogen-flushed syringe and the reaction mixture stirred under a nitrogen atmosphere for two hours at room temperature.

Saturated aqueous ammonia (20ml) was added and the mixture extracted with methylene chloride (4 x 50ml). The combined organic extracts were back washed with water (4 x 100ml) then concentrated down to approximately 50ml and washed with a further 4 x 100ml of water to remove any residual dimethyl-formamide. The organic phase was dried, filtered and evaporated leaving a colourless solid, which crystallised from ether to give codeinone enol ethyl ether as colourless prisms, 0.4g (62%) mp 122 - 123° (lit.[23] 123 - 124°).

Found : C, 73.48; H, 7.09; N, 4.39.

Calculated for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30%.

^1H n.m.r. ($CDCl_3$) δ 6.57 and 6.55 (2H, ABq, J 8Hz) H-2, H-1; 5.55 (1H, d, J 8Hz) H-7; 5.30 (1H, s) H-5; 4.92 (1H, d, J 8Hz) H-8; 3.87 (3H, s) aromatic-OMe; 3.60 (2H, q, J 7Hz) $-OCH_2CH_3$; 2.49 (3H, s) -NMe; 1.33 (3H, t, J 7Hz) $-OCH_2CH_3$.

i.r. ($CHCl_3$) : ν_{max} 2940, 1660 cm^{-1}.

m.s. m/e 325 (M^+; base peak), 310, 296, 269.

The enol ether (21a) was also prepared from 14-bromocodeinone diethyl acetal using Vitride in benzene (1.3g from 2.25g diethyl acetal (79%) m.p. 122 - 124°) and n-butyl-lithium in tetrahydrofuran (2.4g from 4.0g diethyl acetal (83%) m.p. 119 - 121°) using procedures described below (vide infra).

(ii) Codeinone enol n-propyl ether (21b)(6-desmethoxy-6-n-propoxythebaine).

14-Bromocodeinone di-n-propyl acetal (3.2g, 6.7 mmol) was dissolved in dry tetrahydrofuran (40ml) in a 100ml Quickfit round-bottomed flask fitted with a rubber serum cap and magnetic stirrer, and the solution cooled to -60° in an acetone/Drikold bath. A solution of n-butyl lithium in hexane (4.5ml; approximately 1.6M in organolithium reagent) was added slowly by syringe until the deep crimson colour produced on addition[89] no longer discharged immediately. The colour discharged over a few minutes leaving a clear yellow solution.

The flask was allowed to warm to room temperature and 20ml of 9:1 tetrahydrofuran/water added slowly with stirring. The reaction mixture

was evaporated to a small volume, re-dissolved in methylene chloride (50ml) and washed with water (50ml). The organic layer was dried, filtered and evaporated leaving a yellow gum, which was chromatographed on basic alumina (30g) in 2:1 methylene chloride/pentane v/v. Evaporation of eluent gave a pale yellow solid, 2.2g (97% recovery) m.p. 147 - 150°. The enol ether (21b) recrystallised from ether as colourless prisms, 2.0g (88%) m.p. 154 - 156° (Lit.[23] 155.5 - 156.5°). A portion was further recrystallised from methanol to m.p. 155 - 156°.

Found : C, 74.37; H, 7.42; N, 3.92.

Calculated for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13%.

^1H n.m.r. ($CDCl_3$): δ 6.61 and 6.59 (2H, ABq J 8Hz) H-2, H-1; 5.52 (1H, d, J 8Hz) H-7; 5.26 (1H, s) H-5; 4.98 (1H, d, J = 8Hz) H-8; 3.86 (3H, s) 3-OMe; 3.66 (2H, t, J 7Hz) - $OC\underline{H}_2CH_2CH_3$; 2.42 (3H, s) - NMe; 1.82 (2H, comp. m.) - $OCH_2C\underline{H}_2CH_3$; 0.93 (3H, t, J 7Hz) - $OCH_2CH_2C\underline{H}_3$.

m.s. m/e 339 (M^+; base peak), 324, 310, 296. Significant metastable ions appear at m/e 310 and 258.

Codeinone enol n-propyl ether has also been synthesised from the acetal (29b) using chromium sulphate in aqueous dimethylformamide (0.5g (64%) from 1.1g acetal, m.p. 153 - 156°) and Vitride in benzene (2.2g (86%) from 3.6g acetal, m.p. 152 - 154°).

(iii) Codeinone enol 2-hydroxyethyl ether (21) (6-Desmethoxy-6-(2-hydroxy-ethoxy)thebaine)

To a solution of the cyclic acetal (29c) (3.5g, 8.7 mmol) in dry benzene (100ml) was added 10ml of a 70% solution of sodium dihydrobis(2-methoxyethoxy) aluminate in toluene. The mixture was left at room temperature for 16 hours, then poured into 200ml of 40% aqueous sodium hydroxide solution. The layers were separated and the organic layer washed with brine (4 x 100ml) to neutrality, then dried, filtered and evaporated to give codeinone enol 2-hydroxyethyl ether as a pale yellow solid, 2.2g (78%) m.p. 170 - 172°. A portion was recrystallised from methanol as slightly off-white prisms, m.p. 178 - 179°.

Found : C, 70.18; H, 6.96; N, 4.10.

$C_{20}H_{23}NO_4$ requires C, 70.36; H, 6.79; N, 4.32%.

^1H n.m.r. ($CDCl_3$): δ 6.61 and 6.60 (2H, ABq, J 8Hz) H-2, H-1; 5.51 (1H, d, J 7Hz) H-7; 5.31 (1H, s) H-5; 5.05 (1H, d, J 7Hz) H-8; 3.82 (7H, s) 3-OMe and $-OCH_2CH_2OH$; 3.58 (1H, br.s; exchanges in D_2O)-OH; 2.44 (3H, s) -NMe.

i.r. (CCl_4): ν_{max} 3620(w), 3500 - 3100 (m, br), 2740, 1610 cm^{-1}.

m.s. m/e 341 (M^+; base peak), 326, 296, 280.

u.v. λ_{max} (EtOH) 285 (Log ε 3.59), 223 (Log ε 3.94) nm.

Codeinone enol 2-hydroxyethyl ether has been synthesised only by this reduction method. Employment of n-butyl lithium or chromium (II) sulphate as described for other reductions (vide supra) led only to the isolation of amorphous residues.

3) Mixed Acetals

(i) 14-Bromocodeinone methyl ethyl acetal: (a) 6β-ethoxy epimer (35a)

a) Thebaine (940mg, 3.03 mmol) was suspended in ethanol (10ml) and N-bromosuccinimide (590mg, 3.3 mmol) was added with stirring. A pronounced yellow colour developed and the reagents dissolved over approximately five minutes. Stirring was continued for one hour then the mixture left at 4°C overnight. No crystallisation was apparent.

The reaction mixture was evaporated to dryness and the residue dissolved in methylene chloride (25ml) and washed with water (3 x 25ml) to remove succinimide. The organic phase was dried, filtered and evaporated leaving a pale yellow gum, 1.1g (78% recovery). Although pure by t.l.c., giving a single spot of R_f = 0.8 in 9:1 methylene chloride/methanol, this compound could not be crystallised.

^{1}H n.m.r. ($CDCl_3$): δ 6.63 and 6.49 (2H, ABq, J 7Hz) H-2, H-1; 5.94 and 5.66 (2H, ABq, J 10Hz) H-8, H-7; 4.66 (1H, s) H-5; 3.84 (3H, s) aromatic -OMe; 3.47 (3H, s) 6α-OMe; 3.46 (2H, q, J 7Hz) $-OC\underline{H}_2CH_3$; 2.40 (3H, s) -NMe; 1.17 (3H, t, J 7Hz) $-OCH_2C\underline{H}_3$.

m.s. m/e 437, 435 (1:1, M^+); 356 (base peak), 324, 310.

b) 6α-Ethoxy epimer (35b)

Codeinone enol ether (21a) (170mg, 0.52 mmol) was dissolved in methanol (3ml) and N-bromosuccinimide (120mg, 0.6 mmol) added with stirring. The reagent rapidly dissolved and a

pale yellow colour developed. After approximately two minutes, colourless crystals began to form; stirring was continued for a further 30 minutes then the reaction mixture was left at 4^{o} overnight. The crystals were filtered off, washed with water and air dried, giving the 6α-ethoxy acetal (35a), 130mg (60%), m.p. 167 - 169^{o}, recrystallised from methanol as prisms, m.p. 169 - 170^{o}.

Found : C, 57.70; H, 5.96; N, 3.47; Br, 18.38

$C_{21}H_{26}NO_4Br$ requires C, 57.80; H, 6.01; N, 3.21; Br, 18.37%

^{1}H n.m.r. ($CDCl_3$) δ 6.63 and 6.49 (2H, ABq, J 7Hz) H-2, H-1; 5.94 and 5.66 (2H, ABq, J 10Hz) H-8, H-7; 4.66 (1H, s) H-5; 3.84 (3H, s) aromatic -OMe; 3.80 (2H, m) $-OC\underline{H}_2CH_3$; 3.18 (3H, s) 6β-OMe; 2.40 (3H, s) -NMe; 1.23 (3H, t, J 8Hz) $-OCH_2C\underline{H}_3$.

The resonance due to the 6α-O-methylene group is not a simple quartet, but shows further splitting. The fine structure of this resonance is difficult to ascertain since the 3-methoxy signal is superimposed on it.

m.s. m/e 437, 435 (1:1, M^+), 356 (base peak), 324, 310.

(ii) 14-Bromocodeinone methyl 2-hydroxyethyl acetal

a) To thebaine (311mg, 1 mmol) in 5ml ethylene glycol was added 220mg (1.25 mmol) of N-bromosuccinimide. The mixture was stirred for 30 minutes during which the solid dissolved. The mixture was left at 4^{o} overnight, but no crystallisation

was apparent; 30ml of water was added and the mixture extracted with methylene chloride (2 x 50ml). The organic extracts, on drying and evaporation, yielded 350mg of a colourless, viscous gum, whose ^1H n.m.r. spectrum showed a mixture containing unreacted thebaine as one major component.

b) Thebaine (0.96g, 3.1 mmol) in ethylene glycol (20ml) was treated with N-bromosuccinimide (0.6g, 3.4 mmol) in the presence of 200mg potassium hydroxide. As before, the solids dissolved rapidly and after 30 minutes crystals began to form. After stirring for a further hour, the mixture was left at 4° overnight and the colourless crystals filtered off, washed with water and dried, leaving 0.98g (67%) of the mixed acetal (30c) m.p. 129 - 131°; recrystallised from methanol to m.p. 132 - 133°.

Found : C, 55.50; H, 5.96; N, 3.42; Br, 18.04

$C_{21}H_{26}NO_5Br$ requires C, 55.76; H, 5.79; N, 3.10; Br, 17.67%

^1H n.m.r. ($CDCl_3$): δ 6.64 and 6.48 (2H, ABq, J 9Hz) H-2, H-1; 5.93 and 5.67 (2H, ABq, J 10Hz) H-8, H-7; 4.72 (1H, s) H-5; 3.85 (3H, s) aromatic -OMe; 3.74 (2H, m) $-C\underline{H}_2OH$; 3.55 (2H, m) $-OC\underline{H}_2CH_2OH$; 3.48 (3H, s) 6α-OMe; 2.40 (3H, s) -NMe; 1.94 (br.s, exchanges in D_2O) $-O\underline{H}$.

i.r. (CCl_4) ν_{max} 3540, 2935, 1600 cm^{-1}

m.s. m/e 453, 451 (1:1, M^+); 372, 321, 279.

The O-acetate was formed by treatment of the mixed acetal (110mg, 0.25 mmol) with acetic anhydride (100mg, 1 mmol) in 2ml dry pyridine, and was isolated as a gum on removal of solvent.

N.M.R. : δ 4.33 (2H, t, J 7Hz) $-\underline{CH_2}OAc$; 3.55 (2H, t, J 7Hz) $-O\underline{CH_2}$; 2.15 (3H, s) acetyl-CH_3.

i.r. ($CHCl_3$): ν_{max} 1735 cm^{-1}.

4) Reduction of Mixed Acetals

The mixed acetals (35a) and (30c) were reduced using methods described for the reduction of the dialkyl acetals (29) (vide supra).

(i) Reduction of the methyl ethyl acetal (35a)

The mixed acetal (35a) (220mg, 0.5 mmol) was dissolved in dimethyl-formamide (10ml) under a nitrogen atmosphere, and treated with 0.4M chromium (II) sulphate solution (10ml). After 2 hours concentrated ammonium hydroxide solution (20ml) was added and the mixture extracted with methylene chloride (2 x 50ml). The organic extracts were washed with water (8 x 50ml), dried, filtered and evaporated to dryness, leaving 110mg of pale yellow crystals, m.p. 193 - 194°. The melting point of this material was unchanged both on recrystallisation from methanol and on mixing with thebaine, and the ^1H n.m.r. spectrum showed thebaine as the only product present.

(ii) Reduction of the methyl 2-hydroxyethyl acetal (30c)

The mixed acetal (30c) (285mg, 0.5 mmol) was dissolved in benzene (10ml) and 1ml of a 70% solution of sodium dihydro-bis(2-methoxyethoxy) aluminate added. The mixture was left at room temperature for 16 hours, then washed with 20ml of 1N potassium hydroxide solution and brine (3 x 50ml) until neutral. The organic extracts were dried, filtered and evaporated to leave 100mg of a pale yellow gum which crystallised from methanol as prisms, m.p. 193 - 194°, unchanged on mixing with thebaine. The products of both the above reactions were identical, in both i.r. and n.m.r. spectra, with thebaine:

^{1}H n.m.r. ($CDCl_3$): δ 6.59 and 6.57 (2H, ABq, J 8Hz) H-2, H-1; 5.53 (1H, d, J 7Hz) H-7; 5.26 (1H, s) H-5; 5.01 (1H, d, J 7Hz) H-8; 3.81 (3H, s) aromatic -OMe; 3.56 (3H, s) 6-OMe; 2.42 (3H, s) -NMe.

i.r. ($CHCl_3$) ν_{max} 2940, 1605 cm^{-1}.

5) Stereoselectivity of Reductive Eliminations

(i) 14-Bromocodeinone methyl trideuteriomethyl acetal (33)

This acetal was prepared by treatment of thebaine (1.55g, 5 mmol) with N-bromosuccinimide (0.94g, 5.3 mmol) in d_4-methanol, following the procedure described for the dimethyl acetal (28) (vide supra), and was obtained as colourless prisms, 1.3g (63%) m.p. 159 - 161°.

^{1}H n.m.r. ($CDCl_3$): Identical to that of (28) except for the absence of the δ 3.17 resonance due to the 6β-methoxy group.

i.r. ($CHCl_3$) ν_{max} 1505, 1378, 1050 cm^{-1}.

m.s. m/e 426, 424 (1:1, M^+), 345, 310, 278.

(ii) Reduction of the labelled acetal (33)

a) With chromium (II) sulphate

The labelled acetal (33) (210mg, 0.5 mmol), dissolved in dimethylformamide (10ml) was reduced with chromium (II) sulphate solution following the procedure used for the mixed acetal (35a) (vide supra). Workup of the reaction with aqueous ammonia followed by extraction with methylene chloride led, on evaporation of the organic extracts, to the isolation of 125mg of a yellow solid, which crystallised from methanol as colourless prisms, 105mg, m.p. 190 - 192° (lit. for thebaine 193°). The ^{1}H n.m.r. and i.r. spectra of this material were apparently identical with those of natural thebaine.

b) With sodium dihydrobis(2-methoxyethoxy) aluminate

The labelled acetal (210mg, 0.5 mmol) in dry benzene (10ml) was treated with 1ml of a 70% solution of the complex hydride ('Vitride') in toluene, and left at room temperature for 16 hours. 40% aqueous sodium hydroxide solution (10ml) was added and the layers separated. The organic phase was washed with brine until neutral, dried, filtered and evaporated to give 115mg of pale yellow crystals, m.p. 187 - 191°. On re-

crystallisation from methanol the product was obtained as colourless prisms, m.p. 191 - 192°; identical in ^{1}H n.m.r. spectrum both with an authentic sample of thebaine and with the product of chromium (II) sulphate reduction.

c) With n-butyl-lithium

A solution of the labelled acetal (33) (210mg, 1 mmol) in dry tetrahydrofuran (10ml) was cooled to -78° in an acetone/drikold bath and 0.4ml of a 1.6M solution of n-butyl-lithium in hexane was added with stirring. A pronounced deep pink colour appeared, which discharged after one minute to give a clear yellow solution. The flask was allowed to warm to room temperature and excess organolithium reagent destroyed by addition of 9:1 tetrahydrofuran/water (10ml). The mixture was concentrated to a small volume, redissolved in methylene chloride (25ml) and washed with water (20ml). The organic phase was dried, filtered and evaporated giving an oil which partially crystallised on standing and which crystallised from ether as pale yellow prisms, 110mg, m.p. 189 - 191°.

As before, the ^{1}H n.m.r. spectrum of the recrystallised material was consistent with undeuteriated thebaine, and was identical with those of the products of a) and b) above.

6) Tri-n-butyltin hydride Reduction of the Acetals (28) and (33)

(i) The dimethyl acetal (28) (210mg, 0.5 mmol) was dissolved in dry tetrahydrofuran (5ml) in a 25ml three-necked flask equipped with a serum cap, reflux condenser and nitrogen inlet. Dry nitrogen was bubbled through the solution for

20 minutes, then tri-n-butyltin hydride (150mg, 0.52 mmol) added and the mixture heated at 70° water bath temperature under a nitrogen atmosphere. After 4 hours at 70°, water (2ml) was added and the mixture concentrated to a small volume, redissolved in methylene chloride and washed with water. The organic phase was dried, filtered and evaporated to give a gum which was washed with petroleum ether and crystallised from methanol as pale yellow crystals, m.p. 157 - 160°. The ^{1}H n.m.r. spectrum of this substance was identical with that of the starting material.

(ii) The acetal (28) (210mg, 0.5 mmol) was boiled under reflux in toluene (10ml) with 1.2g (4 mmol, 8 equiv) tri-n-butyltin hydride, under an argon atmosphere. After 4 hours, the solvent was removed and the residue dissolved in acetonitrile (20ml), then washed with hexane (4 x 20ml). The acetonitrile layer was evaporated to leave a colourless gum, 120mg, whose ^{1}H n.m.r. spectrum was consistent with neopinone dimethyl acetal (37) as the sole product of reaction.

^{1}H n.m.r. ($CDCl_3$): δ 6.65 and 6.53 (2H, ABq, J 8Hz) H-2, H-1; 5.38 (1H, dd, J 5.5 and 3 Hz) H-8; 4.66 (1H, s) H-5; 3.89 (3H, s) 3-OMe; 3.48 (3H, s) 6β-OMe; 2.93 (3H, s) 6α-OMe; 2.41 (3H, s) -NMe; 2.27 (1H, d, J 5.5Hz) H-7α; 2.20 (1H, d, J 3Hz) H-7β.

The above reaction was repeated using the labelled acetal (33) and yielded a product whose n.m.r. spectrum was identical with that of (37) except for the absence of the methoxy group resonance at δ 3.48.

Chromium (II) Reduction of the Acetal (28) in Presence of a Thiol

The acetal (28) (420mg, 1 mmol) was dissolved in dimethylformamide (20ml) containing 1-hexanethiol (0.9g, 7.6 mmol) and treated with chromium (II) sulphate, under a nitrogen atmosphere. The reaction was worked up after 2 hours by addition of concentrated aqueous ammonia solution (specific gravity 0.88; 20ml) and extracted with methylene chloride (2 x 50ml). The organic extracts were washed with dilute aqueous sodium hydroxide (4 x 50ml) and water (4 x 50ml), dried, filtered and evaporated to leave a white solid, 195mg, whose ^{1}H n.m.r. spectrum was identical with that of thebaine, and which crystallised from methanol as prisms, m.p. 192 - 194° (lit. 193°).

7) Preparation of the Methyl Ketones (40)

(i) 7α-Acetyl-6,14-endo-ethenotetrahydrothebaine (8)(Thevinone)

The known ketone (8) was prepared by the method of Bentley and coworkers.[6]

Thebaine (3.1g, 10 mmol) was boiled under reflux with redistilled methyl vinyl ketone (10ml) for 1 hour. Excess methyl vinyl ketone was removed by distillation under reduced pressure and the viscous residue crystallised from methanol as prisms, 3.7g (97%) m.p. 118 - 120° (lit. 119 - 121°).

The ^{1}H n.m.r. spectrum of this material was identical in all respects with that of the 7α-acetyl isomer (8) as described by Fulmor et al.[47]

δ 6.60 and 6.51 (2H, ABq, J 8Hz) H-1, H-2; 5.89 and 5.56 (2H, ABq, J 9Hz) H-18, H-17; 4.55 (1H, s) H-5; 3.80 (3H, s) 3-OMe; 3.59 (3H, s) 6-OMe; 2.33 (3H, s) -NMe; 2.11 (3H, s) acetyl-CH_3.

i.r. ($CHCl_3$) ν_{max} 1700 cm^{-1}

m.s. m/e 381 (M^+; base peak), 366, 228, 205.

(ii) 7α-Acetyl-6-desmethoxy-6-ethoxy-6,14-endo-ethenotetrahydrothebaine (40a)

Codeinone enol ethyl ether (3.9g, 10.1 mmol) was boiled under reflux with redistilled methyl vinyl ketone for 2 hours. Removal of excess methyl vinyl ketone left a viscous residue (5.5g) which was chromatographed on grade III basic alumina (50g) in methylene chloride/pentane (2:1 v/v). On evaporation of the eluent from the column, the ketone (39a) was obtained as a pale yellow gum, 4.3g (90% recovery). This compound proved difficult to crystallise, but a portion was eventually obtained from ethanol as needles, m.p. 97 - 99°, rising to 99 - 100° on recrystallisation.

Found: C, 73.11; H, 7.53; N, 3.26

$C_{24}H_{29}NO_4$ requires C, 72.88; H, 7.39; N, 3.54%.

^1H n.m.r. ($CDCl_3$): As for the parent ketone (8) (vide supra) except for the replacement of the 6-methoxy resonance at δ 3.59 by ethoxy resonances: δ 3.85 (2H, q, J 8Hz) $-OCH_2CH_3$; and 1.17 (3H, t, J 8Hz) $-OCH_2CH_3$.

The δ 3.85 signal shows further splitting, although the fine structure is difficult to determine due to the superimposed 3-methoxy resonance.

i.r. ($CHCl_3$): ν_{max} 2940, 1705, 1505 cm^{-1}

m.s. m/e 395 (M^+; base peak), 380, 366, 351, 220.

(iii) 7α-Acetyl-6-desmethoxy-6-n-propoxy-6,14-endo-etheno-tetrahydrothebaine (40b)

Preparation of this adduct was carried out as for (40a) (vide supra), and the product crystallised from methanol as prisms, 2.3g (85%) from 2.2g codeinone enol n-propyl ether, m.p. 122 - 124°, rising on recrystallisation to 126 - 127°.

Found : C, 73.22; H, 7.60; N, 3.15.

$C_{25}H_{31}NO_4$ requires C, 73.32; H, 7.63; N, 3.42.

^1H n.m.r. ($CDCl_3$): As for the parent ketone (8) with the 6-methoxy resonance at δ 3.58 replaced by signals from the n-propyl group: δ 3.78 (2H, comp.m.) $-OCH_2-$; 1.86 (2H, m) $-OCH_2CH_2CH_3$; 0.90 (3H, t, J 7Hz) $-OCH_2CH_2CH_3$.

(iv) 7α-Acetyl-6-desmethoxy-6(2-hydroxyethoxy)-6,14-endo-ethenotetrahydrothebaine (40c)

Preparation of this ketone was carried out as for (ii) and (iii) above, and led to the isolation of 2.4g (90% recovery) of the Diels-Alder adduct from 2.15g of codeinone enol 2-hydroxy-ethyl ether, as a pale yellow solid which crystallised from ethanol/water as needles, m.p. 132 - 133°.

Found: C, 68.63, 68.76; H, 7.38, 7.24; N, 3.26, 3.24.

$C_{24}H_{29}NO_5$ requires C, 70.05; H, 7.10; N, 3.40

$C_{24}H_{29}NO_5 . \frac{1}{2}H_2O$ requires C, 68.55; H, 7.19; N, 3.33%.

^1H n.m.r. ($CDCl_3$): δ 6.62 and 6.52 (2H, ABq, J 8Hz) H-1, H-2; 5.99 (1H, d, J 9Hz) H-18; 5.52 (1H, d, J 9Hz) H-17; 4.52 (1H, s) H-5; 3.96 (2H, comp.m.) $-CH_2OH$; 3.81 (3H, s) 3-OMe; 3.72 (2H, comp.m.) CH_2CH_2OH; 2.94 (1H, br.s, exchanges in D_2O) -OH; 2.40 (3H, s) -NMe; 2.12 (3H, s) acetyl-CH_3.

i.r. ($CHCl_3$): ν_{max} 3700 (w), 3650 - 3550 (br, m), 2940, 1710, 1505 cm^{-1}.

m.s. m/e 411 (M^+), 410, 368, 366, 324, 236 (base peak).

8) Grignard and Related Reactions of the Ketones (40)

(i) 19-Propylthevinol (9a) (7α-[1-(R)-hydroxy-1-methybutyl]-6,14-endo-ethenotetrahydrothebaine).

a) n-Propylmagnesium bromide was prepared from magnesium turnings (350mg, 12.5 mmol) and 1-bromopropane (1.5g, 12.1 mmol) in 20ml of anhydrous ether in a 100ml three-necked round-bottomed flask equipped with gas inlet, pressure-equilibrated dropping funnel, reflux condenser and magnetic stirrer. The flask was flushed repeatedly with dry argon prior to commencement of reaction and the reaction carried out under an argon atmosphere.

When all the magnesium was consumed a solution of thevinone (8) (1.1g, 2.9 mmol) in anhydrous ether (50ml) was added with stirring and the mixture boiled under reflux for 2 hours.

Saturated aqueous ammonium chloride solution (50ml) was added and the layers separated. The ether layer, on drying and evaporation, yielded a gum from which the tertiary alcohol (9a) was crystallised from ethanol as prisms, 0.6g (50%) m.p. 175 - 176° (lit. 176°).

^{1}H n.m.r. ($CDCl_3$): δ 6.59 and 6.50 (2H, ABq, J 8Hz) H-1, H-2; 5.93 and 5.42 (2H, ABq, J 9Hz) H-18, H-17; 4.85 (1H, s, exchanges in D_2O) -OH; 4.53 (1H, s) H-5; 3.80 (3H, s) 3-OMe; 3.76 (3H, s) 6-OMe; 2.35 (3H, s) -NMe; 0.96 (3H, s) 19-CH_3.

i.r. ($CHCl_3$): ν_{max} 3500, 2930, 1630 (m), 1600 (m), 1495 cm^{-1}

ν_{OH} at 3500 cm^{-1} is independent of concentration.

m.s. m/e 425 (M^+).

In similar preparations, 19-benzyl-and 19-methylthevinol (9b,c) were prepared from the ketone (8). The products isolated displayed physical properties identical to those reported in the literature.

b) The Grignard reagent was prepared from 1-bromopropane (0.68g, 5.5 mmol) and magnesium turnings (120mg, 5 mmol) in dry benzene (30ml) containing ether (1.5ml), using the apparatus of a) above, under an argon atmosphere with water-bath heating to 70°. When all the magnesium had dissolved, thevinone (0.45g, 1.2 mmol) in benzene (30ml) was added dropwise with stirring over 10 minutes. The reaction was allowed to proceed at 70° for 2 hours and was then worked up with saturated ammonium chloride solution as in a) above. The organic phase, on drying and evaporation, yielded a

colourless viscous gum from which 19-propylthevinol was obtained by crystallisation from ethanol as prisms, m.p. 175 - 176°, yield 260mg. The mother liquors were concentrated to a small volume and a further 100mg of (9a) crystallised out as prisms, m.p. 173 - 175°, giving a combined yield of 360mg (72%) of the tertiary alcohol, identical in all respects with that prepared by method (a) (vide supra).

(ii) Attempted Grignard Reactions of the Higher Ketones (40)

a) 6-Desmethoxy-6-ethoxy-19-propylthevinol (27a)

The ketone (40a) (0.66g, 1.7 mmol) was dissolved in dry ether (15ml) and added to a solution of n-propylmagnesium bromide, prepared from 1-bromopropane (0.7g, 5.8 mmol) and magnesium turnings (130mg, 5.4 mmol) in 20ml of dry ether. The mixture was boiled under reflux for 3 hours under an argon atmosphere, then aqueous ammonium chloride solution (30ml) was added and the layers separated. The organic layer was dried and evaporated to leave an oil which was shown by analytical t.l.c. to be a mixture.

The product mixture was separated by preparative t.l.c. in 9:1 methylene chloride/methanol, giving two bands of R_f 0.8 and 0.45. The more mobile band yielded an oily yellow solid from which the tertiary alcohol (27a) was obtained by crystallisation from ethanol as colourless prisms, 190mg (25%) m.p. 169 - 170 - 5°.

Found: C, 73.77; H, 8.48; N, 3.60

$C_{27}H_{37}NO_4$ requires C, 73.77; H, 8.48; N, 3.19%.

^{1}H n.m.r. ($CDCl_3$): δ 6.60 and 6.45 (2H, ABq, J 8Hz) H-1, H-2; 5.89 and 5.37 (2H, ABq, J 9Hz) H-17, H-18; 5.11 (1H, s, exchanges in D_2O) -OH; 4.51 (1H, s) H-5; 4.3 - 3.8 (2H, comp.m.) $-OCH_2CH_3$; 3.80 (3H, s) 3-OMe; 2.35 (3H, s) -NMe; 1.22 (3H, t, J 7Hz) $-OCH_2CH_3$; 0.98 (3H, s) 19-CH_3.

b) Attempted Grignard Reaction of the Ketone (40b)

The ketone (40b) (650mg, 1.6 mmol) in ether (30ml) was added to a solution of n-propylmagnesium bromide prepared from magnesium turnings (180mg, 7.5 mmol) and 1-bromopropane (880mg, 7.1 mmol) in 20ml of dry ether. The mixture was refluxed under an argon atmosphere for 2 hours, then worked up with ammonium chloride solution as for the earlier Grignard reactions (vide supra) to yield a gum which proved to be a complex mixture, and which could not be separated by preparative t.l.c. The proton n.m.r. spectrum of the total reaction mixture indicated the presence of only a small proportion of tertiary alcohol.

c) Attempted Grignard Reaction of the Ketone (40c)

The hydroxyethyl ketone (40c) (410mg, 1 mmol) in ether (50ml) was added to a solution of the Grignard reagent prepared from n-propylmagnesium bromide (680mg, 5.5 mmol) and magnesium turnings (140mg, 5.9 mmol) in 20ml of ether. The reaction was carried out under reflux in an argon atmosphere and worked up with ammonium chloride solution after 3 hours to give a gum which proved to be a mixture of at least four compounds. The n.m.r. spectrum of the total reaction mixture showed no trace of the expected tertiary

alcohol; the expected methyl resonance at δ 0.98 was not observed.

(iii) Attempted Grignard Reactions of the Ketones (40a) and (40b) in Tetrahydrofuran

The ketone (40a) (0.55g, 1.4 mmol) in dry tetrahydrofuran (20ml) was added dropwise with stirring to n-propylmagnesium bromide, prepared from 130mg of magnesium turnings and 750mg of 1-bromopropane in 20ml of dry tetrahydrofuran. The apparatus of (i)(a) above was employed and the reaction carried out under an argon atmosphere with water-bath heating at 60°. After 4 hours at 60°, the reaction mixture was worked up with aqueous ammonium chloride solution in the normal manner, to yield a gum which was shown by analytical t.l.c. to be a mixture of several compounds, none of which was the desired tertiary alcohol.

Reaction of the ketone (40b) under identical conditions also gave a complex mixture.

(iv) Reaction of the Ketones (40a-c) with n-Propyllithium

The alkyllithium reagent was prepared in solution in dry ether (20ml) from 1-bromopropane (680mg, 5.5 mmol) and lithium metal (70mg, 10.1 mmol) under a nitrogen atmosphere in a 100ml three-necked round-bottomed flask equipped with a reflux condenser, nitrogen inlet, pressure-equilibrated dropping funnel and magnetic stirrer. When all the lithium was consumed the ketone (40a) (0.5g, 1.26 mmol) in 30ml of dry ether was added dropwise with stirring over a period of approximately 30 minutes. The mixture was then boiled under reflux for 4 hours and worked up with aqueous ammonium chloride solution as for the Grignard reactions (vide supra). Drying and evaporation of the ether layer yielded 460mg of unreacted

ketone (40a) as a gum, identified by its ^{1}H n.m.r. spectrum (vide supra).

Similar results were obtained for the ketones (40b) and (40c), unreacted starting material being recovered.

Reaction of the ketone (40b) with 4.5 equivalents of n-propyllithium in the presence of 4.5 equivalents of N,N,N',N'-tetramethylenediamine likewise ended in the recovery of unreacted starting material, even after reflux for 16 hours in ether.

(v) Grignard Reactions of Ketones (40a-c) in Benzene/Ether: Synthesis of the Tertiary Alcohols (27a-c)

a) 6-Desmethoxy-6-ethoxy-19-propylthevinol (27a)

The Grignard reagent was prepared from magnesium turnings (100mg, 4 mmol) and 1-bromopropane (520mg, 4.2 mmol) in 30ml of dry benzene containing 2ml of ether, in a three-necked 100ml round-bottomed flask equipped with pressure-equilibrated dropping funnel, reflux condenser, gas inlet and magnetic stirrer. The reaction was carried out under an atmosphere of dry argon.

When all the magnesium had dissolved, a solution of the ketone (40a) (395mg, 1 mmol) in dry benzene (20ml) was added with stirring over 30 minutes while the solution was maintained at 65 - 70° by water-bath heating. The reaction was allowed to proceed for 3 hours at 65 - 70°, then worked up by addition of saturated aqueous ammonium chloride solution. The layers were separated and the organic phase dried, filtered and evaporated to leave a yellow gum.

This residue was chromatographed on basic alumina (10g) in methylene chloride, and the eluent evaporated to leave a colourless,

viscous gum from which the tertiary alcohol (27a) was isolated by crystallisation from ethanol as prisms, m.p. 169 - 171°, yield 200mg. A further 40mg of crystalline material was obtained on concentration of the mother liquors, giving a total of 240mg (53%) of the tertiary alcohol (27a). The melting point of this material was unchanged on mixing with (27a) prepared by Grignard reaction of (40a) in ether, and the infrared and n.m.r. spectra of both samples were identical (vide supra, (ii)(a)).

b) 6-Desmethoxy-6-n-Propoxy-19-Propylthevinol (27b)

The ketone (40b) (1.02g, 2.5 mmol) in benzene (70ml) was added to a stirred solution of n-propylmagnesium bromide prepared from 250mg (10 mmol) of magnesium turnings and 1.35g (11 mmol) of 1-bromopropane in 75ml of benzene containing 5ml of ether, in a 250ml three-necked round-bottomed flask equipped as for a) above. The reaction was carried out at 65°, with water-bath heating, and was worked up as for a) after 4 hours. The organic phase, on evaporation, yielded a colourless, viscous gum. This was dissolved in boiling ethanol and left at 4° overnight; the tertiary alcohol (27b) crystallised as colourless prisms, 0.5g, m.p. 132 - 134°.

Evaporation of the mother liquors left a gum from which a further 180mg of (27b), m.p. 132 - 134°, was isolated by preparative t.l.c. in 9:1 methylene chloride/methanol, giving a total of 680mg (60%) of (27b). A portion was recrystallised from ethanol as hexagonal prisms, m.p. 133 - 134°.

Found: C, 74.14; H, 8.67; N, 3.09

$C_{28}H_{39}NO_4$ requires C, 73.90; H, 8.35; N, 3.02%.

^{1}H n.m.r. ($CDCl_3$): δ 6.60 and 6.47 (2H, ABq, J 8Hz) H-1, H-2; 5.90 and 5.33 (2H, ABq, J 9Hz) H-18, H-17; 5.12 (1H, s; exchanges in D_2O) -OH; 4.51 (1H, s) H-5; 4.3 - 3.8 (2H, comp.m.) 6-OCH_2; 3.83 (3H, s) 3-OMe; 2.34 (3H, s) -NMe; 0.99 (3H, s) 19-CH_3.

The protons of the 6-alkoxy substituent (apart from the OCH_2 protons) and of the 19-n-propyl group give rise to a complex series of overlapping resonances in the region 1.3 - 0.9 ppm.

i.r. (CCl_4) ν_{max} 3500, 2930, 1630 (m), 1600 (m), 1495 cm^{-1}.
The 3500 cm^{-1} absorption band is independent of concentration.

m.s. m/e 453 (M^+), 410, 392, 366 (base peak), 278.

c) Attempted Reaction of Ketone (40c) with n-Propylmagnesium Bromide

The Grignard reagent was prepared from magnesium turnings (120mg, 5 mmol) and 1-bromopropane (680mg, 5.5 mmol) in 30ml of dry benzene containing 3ml of dry ether, and the ketone (40c) (0.41g, 1 mmol) added in benzene (20ml) with stirring. After 4 hours at 60 - 65° (water bath heating) the reaction mixture was worked up as for a) above, to yield a gum which proved to be a mixture of at least two compounds.

An attempt was made to separate the mixture by preparative t.l.c., using 5:1 methylene chloride/methanol as developing solvent. However, a series of overlapping bands were obtained from which no tertiary alcohol was isolable.

d) 6-Desmethoxy-6(2-Hydroxyethoxy)-19-methylthevinol (27c)

The Grignard reagent was prepared from 120mg (5 mmol) of magnesium turnings and 780mg (5.5 mmol) of methyl iodide in 30ml of dry benzene containing 3ml of ether. The apparatus and conditions of a) above were employed and the ketone (40c) (410mg, 1 mmol) added with stirring in benzene (20ml) over approximately 20 minutes.

After 4 hours at 60 - 65° the reaction mixture was worked up as for a) above, giving a gum from which the tertiary alcohol (27c) was obtained by crystallisation from ethanol/water as needles, m.p. 207 - 209°, yield 315mg (74%). The product was recrystallised from ethanol/water to m.p. 209 - 211°.

Microanalysis: Found C, 70.38; H, 7.72; N, 3.02.

$C_{25}H_{33}NO_5$ requires C, 70.23; H, 7.78; N, 3.28.

^1H n.m.r. ($CDCl_3$): δ 6.60 and 6.48 (2H, ABq, J 8Hz) aromatic H; 5.92 and 5.41 (2H, ABq, J 9Hz) olefinic H; 4.97 (1H, s, exchanges in D_2O) 19-OH; 4.54 (1H, s) H-5; 4.4 - 4.0 (2H, comp.m.) 6-OCH_2-; 3.9 - 3.6 (2H, comp.m.) CH_2OH; 3.81 (3H, s) 3-OMe; 2.40 (1H, br.s, exchanges in D_2O) CH_2OH; 2.34 (3H, s) -NMe; 1.06 and 1.01 (each 3H, s) 19-gem-dimethyls.

i.r. (CCL_4): ν_{max} 3640, 3520, 2935, 1500 cm^{-1}.
The absorption bands at 3640 and 3520 cm^{-1} are independent of concentration.

m.s. m/e 427 (M^+), 368 (base peak), 252, 59.

PART II

1) Attempted Reactions of Thebaine with Thiols

a) Thebaine (311mg, 1 mmol) was dissolved in benzene (20ml) in a 100ml Quickfit conical flask and oxygen bubbled through the solution for 20 minutes to replace air in the 'dead volume'. 1-Hexanethiol (140mg, 1.2 mmol) was added and the flask stoppered, then stirred vigorously by magnetic stirrer at room temperature. After 72 hours, the reaction mixture was washed with sodium hydroxide solution (2 x 30ml) and water (3 x 50ml), dried, filtered and evaporated to leave unreacted thebaine as pale yellow crystals, m.p. 189 - 191°, 300mg.

b) The reaction was repeated in the presence of t-butyl hydroperoxide (10µl of 70% aqueous solution) and ferrous sulphate (10mg, 0.04 mmol) as radical initiators. As before, the reaction was carried out under an oxygen atmosphere at room temperature; however, no sign of reaction could be detected after 72 hours and, after alkaline workup as for a) above, unreacted thebaine was recovered from the reaction mixture.

c) Thebaine (311mg, 1 mmol) was dissolved in benzene (25ml) in a 100ml three-necked round-bottomed flask equipped with a gas inlet, reflux condenser and magnetic stirrer. Oxygen was bubbled through the mixture for 15 minutes, then 1-hexanethiol (140mg, 1.2 mmol) and bis-azoisobutyronitrile ('AIBN') (25mg) were added and the mixture heated to 60° on a water bath with vigorous stirring and in a stream of oxygen. After 20 hours at 60 - 65° the reaction mixture was worked up as for a) above, and a yellow

oil was obtained which partially crystallised on standing. Thebaine (280mg) was obtained from this residue by crystallisation from methanol, m.p. 190 - 192°.

d) The reaction of c) above was repeated using 370mg (3.1 mmol) of 1-hexanethiol. Again, after prolonged heating at 60° only unreacted thebaine was recovered.

e) Thebaine (311mg, 1 mmol) in benzene (10ml) was treated with thiophenol (340mg, 3.1 mmol) under an oxygen atmosphere in a 50ml Quickfit conical flask fitted with a magnetic stirrer. The mixture was stirred for 24 hours at room temperature, with an oxygen atmosphere maintained by connecting the flask to an oxygen-filled balloon via a tap/cone connector.

The reaction mixture was worked up as for a) above, leaving a yellow gum which gave five spots on analytical t.l.c. 260mg of unreacted thebaine was recovered from this mixture by column chromatography on silica.

Attempted Reactions of Thebaine with Sulphenyl Chlorides

:) Preparation of Sulphenyl Chlorides - General Method

The appropriate thiol (1.2 equiv. based on thebaine used) was added to a stirred solution of N-chlorosuccinimide (1.3 equiv.) in benzene. A yellow colour began to develop, generally within one minute, and succinimide began to precipitate out. The mixture was stirred for 45 - 60 minutes at room temperature, then the crude sulphenyl chloride solution was carefully removed by syringe and used immediately without further purification. In general, external

cooling was not required and care in carrying out transfer of the solution was the only measure required to prevent carrying over of succinimide to the next stage of reaction. In a few larger-scale preparations, filtration under suction was employed as the most convenient method of removing the precipitate. The recovery of succinimide was generally 90 - 95% of the amount expected for total conversion of the thiol.

ii) Attempted Addition of Sulphenyl Chlorides to Thebaine

a) 1-Hexanesulphenyl chloride was prepared from the thiol (145mg, 1.2 mmol) and N-chlorosuccinimide (170mg, 1.27 mmol) in benzene (10ml), and added by syringe to a solution of thebaine (311mg, 1 mmol) in 10ml of dry benzene, with vigorous stirring.

The solution became cloudy almost immediately and, after a few minutes, a white solid began to precipitate out. After 1 hour stirring was stopped and the precipitate filtered off; the n.m.r. spectrum of this material proved to be identical with that of thebaine hydrochloride. The precipitate was dissolved in water and the solution basified with sodium carbonate solution, then extracted with methylene chloride (2 x 25 ml). These extracts, on drying and evaporation, yielded 150mg of thebaine as prisms, m.p. 192 - 194°, unchanged on mixing with an authentic sample.

Evaporation of the filtrate from the above process gave a gum whose n.m.r. spectrum indicated the presence of thebaine hydrochloride; in addition, there were a number of intense and complex resonances in the region δ 0.8 - 2.0, perhaps due to

di-n-hexyl disulphide. This material was dissolved in methylene chloride (20ml) and washed with sodium carbonate solution (20ml) and water (2 x 25ml). Drying and evaporation of the organic phase gave a gum from which a further 115mg of thebaine was obtained as prisms, m.p. 192 - 193°, by crystallisation from methanol. The total recovery of unreacted thebaine was 265mg, (85% recovery).

b) The above reaction was repeated on the same scale with the sulphenyl chloride solution added to a solution of thebaine (311mg) in methylene chloride (10ml). No precipitation was observed; the reaction mixture was stirred at room temperature for 3 days with no apparent conversion of starting material as judged by analytical t.l.c. Sodium hydroxide solution (1M; 25ml) was added and the layers separated; drying and evaporation of the organic phase left a gum, from which thebaine was obtained by crystallisation from methanol as prisms, m.p. 193 - 194°, 298mg (96% recovery).

c) Benzenesulphenyl chloride was prepared from thiophenol (130mg, 1.2 mmol) and N-chlorosuccinimide (165mg, 1.24 mmol) in 10ml benzene, and the solution transferred by syringe to a solution of thebaine (311mg, 1 mmol) in benzene (10ml). Immediately on addition, the solution became cloudy and a precipitate began to form. This was filtered off after one hour and, as in a) above, proved to be thebaine hydrochloride, 250mg. Reconversion of this material to the free base, followed by recrystallisation from methanol, gave 200mg of thebaine, m.p. 193 - 194°.

Evaporation of the filtrate left a semisolid residue whose n.m.r. spectrum indicated a mixture of thebaine hydrochloride and another compound giving rise to complex resonances in the aromatic region. This latter compound was assumed to be diphenyl disulphide; however it could not be isolated in crystalline form. Again, no addition of the sulphenyl chloride to thebaine could be detected.

d) Phenylmethanesulphenyl chloride, prepared from benzyl mercaptan (145mg, 1.17 mmol) and N-chlorosuccinimide (165mg, 1.24 mmol) was added to thebaine (311mg, 1 mmol) in benzene (10ml). As before, the mixture immediately became cloudy and a precipitate formed. This was filtered off and again proved to be thebaine hydrochloride; on reconversion to the free base, 267mg (86% recovery) of thebaine, m.p. 192 - 193°, was obtained. Evaporation of the filtrate left a pale yellow solid which crystallised from ethanol as plates, m.p. 68 - 70°, 95mg. The ^{1}H n.m.r. spectrum of this material consisted of two singlets at δ 7.29 (5H) and δ 3.50 (2H), consistent with dibenzyl disulphide as the byproduct of reaction. The disulphide recrystallised from ethanol to m.p. 70 - 71° (lit. 71 - 72°).

ii) Attempted Addition of Sulphenyl Chlorides to Thebaine Hydrochloride

a) Thebaine hydrochloride was prepared by addition of a small excess of 10% methanolic hydrogen chloride (approx. 4ml) to a solution of thebaine (311mg, 1 mmol) in methanol (10ml). Removal of solvent left a semi-solid residue which was dissolved in methylene chloride (10ml).

To this solution was added, with stirring, a solution of 1-hexanesulphenyl chloride prepared from 1-hexanethiol (145mg, 1.2 mmol) and N-chlorosuccinimide (170mg, 1.27 mmol) in benzene (10ml). The reaction mixture was stirred at room temperature for 3 days, during which no reaction could be observed by t.l.c., then shaken with 2M sodium hydroxide solution (25ml). The organic phase was washed with brine to neutrality, dried, filtered and evaporated to leave a yellow, semicrystalline solid. From this residue unreacted thebaine was recovered by crystallisation from methanol; 292mg (94% recovery) m.p. 191 - 192°, unchanged on mixing with an authentic sample.

b) Reaction under Lewis acid catalysis

The above reaction was repeated on the same scale. When addition of the sulphenyl chloride was complete, the reaction mixture was cooled to -60° in an acetone/drikold bath and a solution of tin (IV) chloride (20mg) in methylene chloride (1ml) added with stirring. The mixture was then allowed to warm gradually to room temperature and left to stand for 16 hours. Analytical t.l.c. at this stage indicated that the mixture was composed mainly of unreacted thebaine.

The mixture was worked up as for a) above and yielded a yellow solid, which was chromatographed on grade III neutral alumina using methylene chloride as eluent. Evaporation of the eluent, followed by crystallisation of the residue from methanol, led to the recovery of 260mg (84%) of unreacted thebaine as slightly yellow prisms, m.p. 190 - 192°.

Repetition of the above procedure, with addition of 270mg (1.04 mmol) of tin (IV) chloride, led to the isolation of an amorphous, deep red solid whose ^{1}H n.m.r. spectrum indicated a complex mixture of products. Analytical t.l.c. showed at least four spots plus considerable streaking; it was concluded that this was due to decomposition of starting material.

3) Addition of Sulphenyl Chlorides to N-(t-butoxycarbonyl)Northebaine

i) Preparation of Northebaine

Northebaine was prepared by a modification of the method of E. Lilly and Co.[11,90] Thebaine (15.5g, 0.05 mmol) was heated under reflux in benzene with diethyl azodicarboxylate (9.6g, 0.055 mmol) for 4 h. Removal of the solvent left the intermediate N-hydrazino derivative as a dark red oil, which was then dissolved in ethanol (100ml), water (70ml) and ammonium hydroxide (0.88sp.g., 50ml). The mixture was heated under reflux for a further 5h., then left to stand at room temperature for 16h. The resulting dark brown solution was extracted with methylene chloride (3 x 100ml), dried and evaporated to leave a dark brown oil. This oil was dissolved in refluxing ethyl acetate from which the byproduct urethane, N,N'-carboethoxyhydrazine, precipitated on cooling and was filtered off. The filtrate was evaporated and the residue dissolved in methanol, then made acidic by addition of 15% methanolic hydrogen chloride. Northebaine hydrochloride precipitated from the solution and was recovered by filtration; yield 6.8g (43%), m.p. 267 - 270° (decomp.)(Lit.,[90] 270 - 272° (decomp.)).

ii) Preparation of N-t-Butoxycarbonylnorthebaine (50)

Northebaine (5g, 16.8 mmol) was suspended in t-butanol (20ml) and water (10ml) together with potassium carbonate (2.36g, 16.8mmol) and di-t-butyl dicarbonate (4g., 18.5 mmol) added with stirring. The mixture became slightly warm and the reactants dissolved.

After 15 minutes, a pale yellow precipitate began to settle out; the reaction mixture was stirred at room temperature for a further 2h, then poured into water and extracted with methylene chloride (2 x 50ml). The organic extracts were dried, filtered and evaporated leaving a pale yellow crystalline solid, which was washed with ice-cold methanol, filtered and dried to give N-t-BOC-northebaine as pale yellow prisms, 5.9g (88%) m.p. 169 - 170° (lit.[36] 165 - 166°).

^{1}H n.m.r. ($CDCl_3$): δ 6.62 and 6.59 (2H, ABq, J 8Hz) aromatic H; 5.55 (1H, d, J 7Hz) H-8; 5.28 (1H, s) H-5; 5.04 (1H, d, J 7Hz) H-7; 5.02 (1H, br.s) H-9; 3.81 (3H, s) 3-OMe; 3.59 (3H, s) 6-OMe; 1.45 (9H, s) $-CO_2(CH_3)_3$.

i.r. ($CHCl_3$): ν_{max} 2980, 1685, 1605 cm^{-1}.

iii) Addition of 1-Hexanesulphenyl Chloride to N-t-BOC-Northebaine: 14β-Hexylthionorcodeinone (52a)

a) 1-Hexanesulphenyl chloride was prepared from the thiol (145mg, 1.2 mmol) and N-chlorosuccinimide (170mg, 1.27 mmol) in 10ml of benzene and added by syringe to a stirred solution of N-t-BOC-northebaine (0.4g, 1.01 mmol) in benzene (10ml). The mixture was stirred at room temperature for 3h.

Saturated aqueous sodium carbonate solution (20ml) was added and the layers separated. The organic phase was dried, filtered and evaporated to give a yellow gum, which appeared to consist mainly of 14β-hexylthio-N-t-BOC-norcodeinone (51a).

^{1}H n.m.r. ($CDCl_3$): δ 6.60 (2H, s) aromatic H; 6.47 and 6.03 (2H, ABq, J 10Hz) olefinic H; 4.54 (1H, s) H-5; 3.80 (3H, s) 3-OMe; 2.60 (2H, comp.m.) $-SCH_2$; 1.48 (9H, s) $CO_2(CH_3)_3$; 1.8 - 1.1 (8H, comp.m.) side chain aliphatic CH_2; 0.83 (3H, t, J 6Hz) $-CH_3$.

The N-protected material was dissolved in ethyl acetate, from which a small quantity of crystalline material was obtained as needles, 25mg, m.p. 223 - 225°. The mother liquors were evaporated and the residue dissolved in benzene (10ml) and treated with 5 ml of saturated ethereal hydrogen chloride at room temperature for 1h. Removal of the solvent left a yellow solid, from which 14 -hexylthionorcodeinone hydrochloride was obtained by crystallisation from ethyl acetate as needles, 208mg, m.p. 223 - 225°; unchanged on mixing with original crystalline material. The total yield of hydrochloride was 233mg (53%); a portion was recrystallised from ethyl acetate as needles, m.p. 224 - 225°.

Microanalysis: Found C, 63.55; H, 6.70; N, 3.21; S, 7.35.
$C_{23}H_{29}NO_3S.HCl$ requires C, 63.36; H, 6.96; N, 2.81; S, 7.29%.

^{1}H n.m.r. ($CDCl_3$): δ 6.71 (2H, s) aromatic H; 6.66 (1H, d, J 10Hz) H-8; 6.13 (1H, d, J 10Hz) H-7; 4.70 (1H, s) H-5; 4.30 (1H, br.d, J 6Hz) H-9; 3.81 (3H, s) 3-OMe; 2.57 (2H, comp.m) $S-CH_2$; 1.9 - 1.1 (8H, comp.m) side chain CH_2; 0.82 (3H, t, J 6Hz) $-CH_3$.

i.r. ($CHCl_3$): ν_{max} 2970, 2940, 2670 - 2580 (br), 1690, 1570, 1510 cm^{-1}.

m.s. m/e 399 (M^+), 315, 284, 216 (base peak). Metastable ion at m/e 202 due to m/e 399 (M^+) breaking down to m/e 284 (M - SC_6H_{13}).

b) The sulphenyl chloride was prepared from 1-hexanethiol (320mg, 2.75 mmol) and N-chlorosuccinimide (405mg, 3 mmol) in benzene (20ml), and added to a stirred solution of N-t-BOC-northebaine (1g, 2.52 mmol) in 20ml of benzene. After 3h, saturated ethereal hydrogen chloride (approx. 6M; 10ml) was added with stirring and the mixture left at room temperature for 1h. Removal of solvent left an orange semi-solid from which the hydrochloride of (52a) was obtained as pale yellow needles by recrystallisation from ethyl acetate; 690mg (64%) m.p. 223 - 224°.

iv) 14β-Phenylthio-N-t-BOC-norcodeinone (51b)

Benzenesulphenyl chloride, prepared from thiophenol (330mg, 3 mmol) and N-chlorosuccinimide (420mg, 3.15 mmol) in 20ml of benzene was added with stirring to a solution of N-t-BOC-northebaine (1g, 2.52 mmol) in benzene (20ml). The mixture was stirred at room temperature for 2h.

Sodium carbonate solution (30ml) was added and the layers separated. The organic phase was washed with water (2 x 50 ml), dried, filtered and evaporated leaving a yellow gum, from which the N-protected enone (51b) was obtained from methanol as prisms, 0.8g (65%), m.p. 217 - 218°. A portion was recrystallised from

methanol to m.p. 218 - 219° (partial decomp.).

Found: C,68.28; H, 5.95; N, 2.85; S, 6.42.

$C_{28}H_{29}NO_5S$ requires C, 68.41; H, 5.95; N, 3.02; S, 6.52%.

^1H n.m.r. ($CDCl_3$): The description given applies at 0°. The spectrum is complex and temperature-dependent (see Discussion, p. 49).

δ 7.40 (5H, m) SPh; 6.65 and 6.63 (2H, ABq, J 8Hz) H-1, H-2; 6.50 and 6.41 (1H, d's, J 10Hz) H-8; 5.92 (1H, d, J 10Hz) H-7; 4.98 and 4.76 (1H, t's, J 4Hz) H-9; 4.34 and 4.19 (1H, s's) H-5; 3.80 (3H, s) 3-OMe; 1.55 and 1.51 (9H, s's) N-Boc.

i.r. (CCl_4): ν_{max} 2985, 1695, 1690 cm^{-1}.

m.s. m/e 491 (M^+), 326, 218, 109 (base peak, PhS^+).

v) 14β-Phenylthionorcodeinone (52b)

The reaction of benzenesulphenyl chloride and N-t-BOC-northebaine was carried out, on the same scale as iv) above, at room temperature for 2h. Saturated ethereal hydrogen chloride solution (20ml, ca. 6M) was added and the mixture left at room temperature for a further hour. Removal of solvent left a semi-solid residue from which the hydrochloride of (52b) was obtained by crystallisation from ethanol as prisms, 0.7g, m.p. 198.5 - 200°. A further 60mg of crystalline material was obtained by concentration of the mother liquors giving a total yield of 0.76g (70%) of the hydrochloride.

Found: C, 64.87; H, 5.30; N, 2.98; S, 8.30; Cl, 7.99.

$C_{23}H_{21}NO_3S.HCl$ requires C, 64.55; H, 5.18; N, 3.29; S, 7.49; Cl, 8.28%.

^1H n.m.r. ($CDCl_3$): δ 7.7 - 7.2 (5H, comp.m.) -SPh; 6.69 (2H, s) H-1, H-2; 6.33 and 6.01 (2H, ABq, J 10Hz) H-8, H-7; 4.42 (1H, br.s.) H-9; 4.27 (1H, s) H-5; 3.79 (3H, s) 3-OMe.

The ammonium protons of this salt could not be detected above δ14.0.

i.r. ($CHCl_3$): ν_{max} 2980, 2840 - 2600 (br.), 1685, 1570(m) cm^{-1}.

m.s. m/e 391 (M^+), 282 (base peak, M - SPh), 240, 205.

vi) 14β-Benzylthionorcodeinone (52c)

N-t-BOC-Northebaine (1g, 2.52 mmol) in benzene (20ml) was treated with phenylmethanesulphenyl chloride, prepared from α-toluene-thiol (360mg, 2.9 mmol) and N-chlorosuccinimide (403mg, 3.07 mmol) in 20ml of benzene. The reaction was allowed to proceed at room temperature for 3h, then saturated ethereal hydrogen chloride (20ml, ca. 6M) was added. The hydrochloride of (52c) precipitated out and after 2h was filtered off; pale yellow microcyrstals, 0.94g (81%) m.p. 181 - 183°. A portion was re-crystallised from ethanol as colourless prisms, m.p. 182 - 183°.

Found: C, 65.01; H, 5.50; N, 3.44; S, 6.99.

$C_{24}H_{23}NO_3S.HCl$ requires C, 65.22; H, 5.43; N, 3.17; S, 7.25%.

^{1}H n.m.r. ($CDCl_3$): δ 10.77 (1H, br.s., $W_{\frac{1}{2}}$ 20Hz) and 8.81 (1H, br.s., $W_{\frac{1}{2}}$ 24Hz) ammonium H, both are exchanged in D_2O; 7.5 - 7.1 (5H, comp. m) CH_2Ph; 6.73 (1H, d, J 11Hz) H-8; 6.69 and 6.67 (2H, ABq, J 8Hz) H-1, H-2; 6.20 (1H, d, J 11Hz) H-7; 4.63 (1H, s) H-5; 4.49 (1H, br.s., $W_{\frac{1}{2}}$ 12Hz) H-9; 4.02 (2H, s) CH_2Ph; 3.82 (3H, s) 3-OMe.

i.r. ($CHCl_3$): ν_{max} 2970, 2800, 2700 - 2580 (br), 1685, 1560 (m) cm^{-1}.

m.s. m/e 405 (M^+), 394, 283, 271, 211, 91 (base peak).

vii) 14β-(2-Phenylethyl)thionorcodeinone (52d)

The sulphenyl chloride was prepared from 2-phenylethanethiol (155mg, 1.12 mmol) and N-chlorosuccinimide (160mg, 1.20 mmol) in benzene (10ml) and added with stirring to a solution of N-t-BOC-northebaine (0.4g, 1.01 mmol) in benzene (10ml). The reaction mixture was stirred at room temperature for 2h, then 10ml of saturated ethereal hydrogen chloride was added and the mixture left for a further hour. Removal of solvent left a pale yellow solid which crystallised from isopropanol after 40h at 4°, giving the hydrochloride of (52d) as needles, 300mg (66%) m.p. 157 - 159°. A portion was recrystallised from isopropanol/water as colourless needles, m.p. 160 - 161°.

Found: C, 63.08; H, 6.08; N, 2.91; S, 6.80; Cl, 7.45.

$C_{25}H_{25}NO_3S.HCl.\frac{1}{2}H_2O$ requires C, 63.48; H, 5.97; N, 2.96; S, 6.78; Cl, 7.50%

^{1}H n.m.r. ($CDCl_3$): δ 7.22 (5H, s)CH_2Ph; 6.73 (2H, s) H-1, H-2; 6.70 (1H, d, J 10Hz) H-8; 6.10 (1H, d, J 10Hz) H-7; 4.72 (1H, s) H-5; 3.81 (3H, s) 3-OMe; 2.80 (4H, m) CH_2CH_2Ph.

i.r. ($CHCl_3$): ν_{max} 2980, 2640 (br), 1690, 1570(m), 1420 cm^{-1}.

m.s. m/e 419 (M^+), 284 (base peak), 206, 91.

viii) 14β-(3-Phenylpropyl)thionorcodeinone (52e).

The sulphenyl chloride was prepared from 3-phenylpropanethiol (430mg, 2.83 mmol) and N-chlorosuccinimide (400mg, 2.99 mmol) in 20ml benzene, and added to a stirred solution of N-t-BOC-northebaine (1g, 2.52 mmol) in benzene (20ml). After 2h at room temperature, 20ml of saturated ethereal hydrogen chloride was added and the mixture left for a further hour. Removal of solvent left an orange solid, which was chromatographed on neutral alumina (20g) in methylene chloride. Evaporation of eluent left the crude nor base (51e) as a gum, which was dissolved in benzene (10ml) and reconverted to the hydrochloride by treatment with 5ml of saturated ethereal hydrogen chloride. Removal of solvent followed by crystallisation from isopropanol gave the hydrochloride of (51e) as colourless microcrystals, 0.76g (65%) m.p. 211 - 212° (partial decomp.).

Found: C, 66.46; H, 5.99; N, 2.98; S, 6.50, Cl, 7.54.
$C_{26}H_{27}NO_3S.HCl$ requires C, 66.44; H, 6.00; N, 2.96; S, 6.50; Cl, 7.80%

(following 1st paragraph of p.137)

4) N-Alkylation of the Nor Bases (52)

i) 14β-(2-Phenylethyl)thiocodeinone (56)

2-Phenylethanesulphenyl chloride was prepared from the thiol (385 mg, 2.78 mmol) and N-chlorosuccinimide (400 mg, 3.0 mmol) in benzene (20 ml) and added to N-t-BOC-northebaine (1 g, 2.52 mmol) in benzene (20 ml). After 2 h, 20 ml of saturated ethereal hydrogen chloride was added and the mixture left for a further hour. Removal of solvent left an orange solid, which was chromatographed on neutral alumina (20 g) in methylene chloride. Evaporation of the eluent left the crude nor-base (52d) as a yellow gum.

The crude base was purified by medium-pressure column chromatography on silica (70-230 mesh; 20 cm x 2 cm i.d.) in methylene chloride/3% methanol as eluent. Evaporation of the eluent gave 0.78 g (74% recovery) of (52d); pure by t.l.c., as a gum. To the purified base was added water (40 ml) containing 4 ml of 98% formic acid and buffered to pH 4 by addition of sodium formate (6.4 g). The mixture was heated at 60^{o} on an oil bath, with stirring, in a 100 ml round-bottomed flask equipped with reflux condenser and magnetic stirrer, and 4 ml of 37% aqueous formaldehyde solution added. Evolution of gas (presumed to be CO_2) began after 2 minutes an continued for approximately 45 minutes. The mixture was stirred and heated at 60^{o} for 16 h.

The reaction mixture was basified with aqueous sodium carbonate solution and extracted with methylene chloride (2 x 50 ml). The organic extracts were dried and evaporated leaving a yellow gum. This was dissolved in isopropanol from which 14β-(2-phenylethyl)thiocodeinone (56) crystallised as pale yellow prisms, 0.52 g, m.p. 138-140°. A further 50 mg of crystalline material was obtained on concentration and cooling of the mother liquors to 4°, giving a total yield of 0.57 g of (56) [71% from (52d); 52% based on N-t BOC-northebaine]. A portion was recrystallised from isopropanol to m.p. 140-141°.

Found: C, 71.85; H, 6.30; N, 3.29; S, 7.65.

$C_{26}H_{27}NO_3S$ requires C, 72.04; H, 6.28; N, 3.23; S, 7.40%.

^1H n.m.r. ($CDCl_3$): δ 7.21 (5H, m) side chain Ph; 6.64 and 6.62 (2H, ABq, J 8 Hz) H-1, H-2; 6.47 and 6.11 (2H, ABq, J 10 Hz) H-8, H-7; 4.55 (1H, s) H-5; 3.82 (3H, s) 3-OMe; 2.86 (4H, m) CH_2CH_2Ph; 2.40 (3H, s) -NMe.

i.r. ($CHCl_3$) ν_{max} 2940, 1678, 1280 cm^{-1}.

m.s. m/e 433(M^+), 298, 255, 138, 104, 91 (base peak).

ii) 14β-(2-Phenylethyl)thio-N-cyclopropylmethylnorcodeinone (57a)

a) The nor base (52d) was prepared from N-t-BOC-northebaine (0.4 g, 1 mmol) by the method described above and purified by column chromatography on silica under identical conditions, giving the pure free base (52d) as a pale yellow gum, 320 mg (76% recovery).

The nor base was treated with cyclopropylmethyl bromide (120 mg, 0.88 mmol) and anhydrous potassium carbonate (200 mg, 1.4 mmol) in 10 ml of anhydrous acetone. The mixture was boiled under reflux for 30 h, then poured into water and extracted with methylene chloride (3 x 25 ml). The organic extracts, when dried and evaporated, yielded 295 mg of unchanged nor base.

b) The nor base (52d) was again prepared from N-t-BOC-northebaine (0.4 g, 1.01 mmol) and was recovered as a gum, 360 mg (86% recovery) after chromatography on silica. This was treated with cyclopropylmethyl bromide (140 mg, 1.04 mmol), potassium carbonate (280 mg, 2.0 mmol) and sodium iodide (200 mg, 1.33 mmol) in 10 ml of anhydrous acetone. The mixture was boiled under reflux for 48 h, then worked up as for (a) above giving 14β-(2-phenylethyl)-N-cyclopropylmethylnorcodeinone (57a) as a gum, 290 mg [71% recovery based on (52d); 61% overall recovery from N-t-BOC-northebaine].

Although this material was homogeneous on analytical t.l.c. (one spot, R_f = 0.61, in methylene chloride/2% methanol) it could not be obtained in crystalline form.

^{1}H n.m.r. ($CDCl_3$): δ 7.15 (5H, m) CH_2Ph; 6.52 and 6.43 (2H, ABq, J 7 Hz) H-2, H-1; 6.33 and 6.01 (2H, ABq, J 10 Hz) H-8, H-7; 4.39 (1H, s) H-5; 3.81 (3H, s) 3-OMe; 3.46 (1H, d, J 5 Hz) H-9; 2.75-2.60 (4H, m) SCH_2CH_2Ph; 2.35 (2H, m) $N-CH_2$; 1.1 - 0.8 (1H, m) cyclopropyl CH; 0.65 (2H, m) and 0.50 (2H, m) cyclopropyl CH_2.

i.r. ($CHCl_3$): ν_{max} 3010, 1680, 1505 cm^{-1}.

m.s. m/e 473 (M^+), 337 (base peak), 164, 139, 91.

Found: m/e 473.2031.

$C_{29}H_{31}NO_3S$ requires M^+ = 473.2040.

iii) 14β-Phenylthio-N-cyclopropylmethylnorcodeinone (57b)

14β-Phenylthionorcodeinone hydrochloride (52b, HCl) (430 mg, 1 mmol) was boiled under reflux in acetone (10 ml) with anhydrous potassium carbonate (350 mg, 2.54 mmol), sodium iodide (200 mg, 1.33 mmol) and cyclopropylmethyl bromide (170 mg, 1.20 mmol) for 24 h.

The mixture was poured into water and extracted with methylene chloride (2 x 25 ml). The organic extracts were dried, filtered and evaporated leaving a dark-brown gum. This was dissolved in ethanol and heated with activated charcoal for one minute, then filtered and evaporated leaving the N-'Cpm' compound (57b) as a pale yellow, resinous solid, 300 mg (67% recovery).

This material was homogeneous on analytical t.l.c. (one spot, R_f = 0.68, in methylene chloride/2% methanol) but could not be obtained in crystalline form.

^1H n.m.r. ($CDCl_3$): δ 7.28 (5H, m) SPh; 6.50 and 6.44 (2H, ABq, J 8 Hz) H-1, H-2; 6.30 (1H, d, J 10 Hz) H-8; 5.69 (1H, d, J 10 Hz) H-7; 4.30 (1H, s) H-5; 3.74 (3H, s) 3-OMe; 3.59 (1H, d, 6 Hz) H-9; 2.35 (2H, m) NCH_2; 1.1 - 0.8 (1H, m) cyclopropyl CH; 0.65 (2H, m) and 0.50 (2H, m) cyclopropyl CH_2.

i.r. ($CHCl_3$) ν_{max} 3010, 1680, 1505 cm^{-1}.

m.s. m/e 445 (M^+), 337, 336 (base peak), 218, 110, 109.

Found: m/e 455.1722; $C_{27}H_{27}NO_3S$ requires M^+ = 445.1733.

^{1}H n.m.r. ($CDCl_3$): δ 8.89 (1H, br.s., $W_{\frac{1}{2}}$ 12Hz, echanges in D_2O) ammonium H; 7.20 (5H, m) side chain Ph; 6.71 (2H, s) H-1, H-2; 6.52 and 6.10 (2H, ABq, J 10Hz) H-8, H-7; 4.63 (1H, s) H-5; 4.20 (1H, br.s., $W_{\frac{1}{2}}$ 10Hz) H-9; 3.84 (3H, s) 3-OMe; 2.74 (2H, t, J 7Hz) $C\underline{H}_2Ph$; 2.60 (2H, t, J 8Hz) $SC\underline{H}_2$; 1.92 (2H, m) $SCH_2C\underline{H}_2CH_2$-.

i.r. ($CHCl_3$): ν_{max} 2970, 2800 (br.), 2680 - 2600 (br.), 1685, 1570 (m), 1510 cm^{-1}.

m.s. m/e 433 (M^+), 314, 283, 240, 214 (base peak), 91.

5) Attempts at Synthesis of the Norcodeinone Acetals (69)

a) By sulphenylation in the presence of methanol

i) Benzenesulphenyl chloride was prepared by the normal method from benzenethiol (130mg, 1.18 mmol) and N-chlorosuccinimide (165mg, 1.24 mmol) in 10ml benzene, and added to a stirred suspension of N-t-BOC-northebaine (0.4g, 1 mmol) in methanol (10ml). The N-t-BOC-northebaine immediately dissolved.

After 1h, the solvent was removed leaving a yellow solid. This crystallised from methanol as prisms, m.p. 214 - 216°, which were identical in melting point, mixed melting point and ^{1}H n.m.r. spectrum with 14β-phenylthio-N-t-BOC-norcodeinone (51b).

ii) The above reaction was repeated on the same scale using as solvents sodium-dried benzene and methanol dried by distillation from magnesium. To the reaction medium was added 0.5ml of triethyl orthoformate, prior to addition of the sulphenyl

chloride. As before, removal of the solvent followed by crystallisation from methanol gave the enone (51b).

In neither of the above reactions was any product other than (51b) detected, either by t.l.c. or by n.m.r. spectroscopy of residues from the total reaction mixture.

iii) 1-Hexanesulphenyl chloride, prepared from the thiol (145mg, 1.2 mmol) and N-chlorosuccinimide (170mg, 1.27 mmol) in 10ml benzene was added to a suspension of N-t-BOC-northebaine (0.4g, 1.01 mmol) in dry methanol (10ml) containing triethyl orthoformate (0.5ml).

The reaction mixture was stirred at room temperature for 4h, then worked up by addition of saturated aqueous sodium carbonate solution and extracted into methylene chloride (50ml). Evaporation of the organic phase left a gum whose ^{1}H n.m.r. spectrum was identical with that of the N-protected enone (51a).

b) By direct acetal formation: 7β-alkylthionorneopinone acetals

i) 14β-Hexylthio-N-t-BOCnorcodeinone (51a) was prepared from N-t-BOC-northebaine (0.4g, 1.01 mmol) in benzene by addition of 1-hexanesulphenyl chloride, following the normal procedure. The N-protected enone was isolated as a gum after alkaline workup and was dissolved in dry methanol (2ml). To the solution was added 1ml of triethyl orthoformate and 20ml of 1M methanolic hydrogen chloride (prepared from dry methanol (20 ml) and redistilled acetyl chloride (1.5ml)).

After 16 hours at room temperature, the solvent was removed leaving an orange gum. Chromatography of this residue on neutral alumina (10g) in methylene chloride yielded, on evaporation of the eluent, 200mg of a pale yellow gum which proved to be 7β-hexylthionorneopinone dimethyl acetal (70a).

^{1}H n.m.r. ($CDCl_3$): δ 6.64 and 6.58 (2H, ABq, J 8.5Hz) H-1, H-2; 5.56 (1H, d, J 8Hz) H-8; 5.14 (1H, s) H-5; 3.87 (3H, s) 3-OMe; 3.51 (3H, s) 6β-OMe; 2.91 (3H, s) 6α-OMe; 2.05 (2H, m) SCH_2; 2.0 approx (1H, br.s., exchanges in D_2O) NH; 1.6 - 1.2 (8H, m) aliphatic CH_2; 0.86 (3H, t, J 6Hz) CH_2CH_3.

m.s. m/e 445 (M^+), 430, 414, 328, 296 (base peak).
Measured mass 445.2284. $C_{25}H_{35}NO_4S$ requires M^+ = 445.3116.

The hydrochloride of this nor base was prepared by treatment of the free base with saturated ethereal hydrogen chloride (2ml) and crystallised from ethyl acetate as needles, m.p. 218 - 220°, 154mg (32%).

A subsequent reaction under identical conditions yielded only the norcodeinone derivative (52a) which was isolated as its hydrochloride, m.p. 223 - 224°, in 45% yield.

ii) Recrystallised 14β-phenylthio-N-t-BOC-norcodeinone (51b) (250mg, 0.51 mmol) was dissolved in dry methylene chloride (3ml) containing triethyl orthoformate (0.5ml). To the solution was added 10ml of 1M methanolic hydrogen chloride (prepared by addition of 0.75ml of redistilled acetyl chloride to 10ml of dry methanol), and the

mixture was left to stand at room temperature for 24h. Removal of solvent left a gum which crystallised from ethanol as prisms, m.p. 197 - 199°, identical in ^{1}H n.m.r. spectrum, melting point and mixed melting point with 14β-phenylthionorcodeinone hydrochloride (52b.HCl). Yield 120mg (60%).

iii) 14β-(2-Phenylethyl)thio-N-t-BOC-norcodeinone (51d) was prepared in the normal way from N-t-BOC-northebaine and was isolated as a gum after alkaline workup. This residue was dissolved in methylene chloride (3ml) and treated with triethyl orthoformate (1ml) and 1M methanolic hydrogen chloride (20ml) prepared as for i) above.

The reaction mixture was left at room temperature for 16h and the solvent removed leaving an orange gum. This was chromatographed on neutral alumina (10g) in methylene chloride. Evaporation of the eluent left a pale yellow gum, 260mg, whose ^{1}H n.m.r. spectrum indicated a 70:30 mixture of the acetal (70d) and the enone (52d).

This mixture was separated by flash chromatography on silica,[91] using methylene chloride/5% methanol as eluent. First fractions eluted yielded 63mg (15%) of 14β-(2-phenylethyl)norcodeinone (52d) which was converted to its hydrochloride by treatment with ethereal hydrogen chloride and crystallised from isopropanol, m.p. 158 - 160°. From later fractions was obtained 180mg (39%) of 7β-(2-phenylethyl)thionorneopinone dimethyl acetal (70d) identified by the similarity of its ^{1}H n.m.r. spectrum to that of (70a).

^{1}H n.m.r. ($CDCl_3$): δ 7.26 (5H, s) $CH_2\underline{Ph}$; 6.67 and 6.59 (2H, ABq, $\underline{J}$ 8Hz) H-1, H-2; 5.64 (1H, d, $\underline{J}$ 8Hz) H-8; 5.16 (1H, s) H-5; 3.88 (3H, s) 3-OMe; 3.52 (3H, s) 6β-OMe; 2.99 (4H, m) $\underline{CH_2}\underline{CH_2}Ph$; 2.87 (3H, s) 6α-OMe.

The acetal (70d) was noncrystalline, as was its hydrochloride.

The above reaction was repeated with reaction time extended to 40h, and a mixture apparently identical to that obtained above was isolated. Separation of the products by flash chromatography led to the isolation of the enone (52d) (55mg, 13%) and the acetal (70d) (160mg, 34%).

iv) 14β-Benzylthio-N-t-BOC-norcodeinone (51c), prepared from N-t-BOC-northebaine (0.4g, 1.01 mmol) and isolated as a gum after alkaline workup, was dissolved in methylene chloride (2ml) and triethyl orthoformate (1ml) and treated with 1M methanolic hydrogen chloride, at room temperature for 16h.

Removal of solvent left a gum which displayed a ^{1}H n.m.r. spectrum consistent with the deprotected enone (52c.HCl) as the principal product. Weak signals at δ 3.50 and 2.98 indicated the presence of traces of the acetal (70c). However, an attempt to isolate this material by chromatography proved unsuccessful.

Similar results were obtained on treatment of the 3-phenylpropyl derivative (51e) with methanolic hydrogen chloride; trace quantities of the acetal (70e) were detectable by n.m.r.,but the acetal could not be isolated.

v) 14β-Hexylthionorcodeinone hydrochloride (51a.HCl) (200mg, 0.44 mmol) was dissolved in 1ml of methylene chloride and treated with triethyl orthoformate (1ml) and 1M methanolic hydrogen chloride (10ml). After 60h at room temperature, solvent was removed to leave a gum. The ^{1}H n.m.r. spectrum of this residue was identical with that of the starting material, and the residue was crystallised from ethyl acetate as needles, m.p. 222 - 223°. 166mg of starting material (83%) was recovered.

vi) 14β-Hexylthio-N-t-BOC-norcodeinone (51a) was synthesised from N-t-BOC-northebaine and isolated as a gum. This residue was dissolved in 2ml of methylene chloride and treated with triethyl orthoformate (1ml) and 1M hydrogen chloride in dry ethylene glycol. The reaction mixture was left at room temperature for 24h, then made alkaline with solid sodium bicarbonate and sodium bicarbonate solution and extracted with methylene chloride (3 x 25ml). The combined organic extracts were washed with brine (2 x 100ml), dried, filtered and evaporated leaving a reddish-brown residue which was chromatographed on neutral alumina (10g) in methylene chloride. Evaporation of the eluent left 210mg of a pale yellow gum, whose ^{1}H n.m.r. spectrum was consistent with the norneopinone acetal (73):

^{1}H n.m.r. ($CDCl_3$): δ 6.44 and 6.38 (2H, ABq, J 8Hz) H-1, H-2; 5.48 (1H, d, J 4Hz) H-8; 5.03 (1H, s) H-5; 3.9 - 3.7 (4H, comp.m.) 6-OCH_2; 3.81 (3H, s) 3-OMe; 2.10 (2H, m) -SCH_2; 1.6 - 1.2 (8H, m) aliphatic CH_2; 0.85 (3H, t, J 6Hz) CH_2CH_3.

6) Attempted Treatment of Thebaine with Other Sulphur Reagents

i) With Benzenesulphonyl Chloride

a) Thebaine (311mg, 1 mmol) was dissolved in acetonitrile (10ml) in a 25ml two-necked round-bottomed flask fitted with a serum cap, reflux condenser and gas inlet. To the solution were added 10mg (0.1 mmol) of copper (I) chloride and 20mg (0.15 mmol) of triethylamine hydrochloride. The flask was then flushed three times with argon and benzenesulphonyl chloride (193mg, 1.1 mmol) in acetonitrile (5ml) added by syringe. The mixture was boiled under reflux, under an argon atmosphere, for 4h. Within 30 minutes a deep purple colour developed and persisted.

The reaction mixture was shaken with sodium carbonate solution (20ml) and extracted with methylene chloride (2 x 50ml). The combined organic extracts were washed with water (2 x 50ml), dried and evaporated leaving a dark-red gum. This was chromatographed on neutral alumina (10g) in methylene chloride; evaporation of the eluent followed by crystallisation from methanol gave 277mg (89%) of unconverted thebaine as pale yellow prisms, m.p. 189 - 192°, unchanged on mixing with an authentic sample.

Repetition of the above procedure with reaction time extended to 16h produced identical results.

b) The above reaction was repeated on the same scale using N-t-BOC-northebaine (0.4g, 1.01 mmol) as substrate. After refluxing for 8h in acetonitrile under an argon atmosphere, the reaction mixture was worked up as for a) above, yielding a yellow gum whose ^{1}H n.m.r. spectrum indicated that it

consisted mainly of unchanged starting material. 330mg (82%) of N-t-BOC-northebaine was recovered by crystallisation from methanol, m.p. 166 - 168°.

ii) With Sulphenimides

a) Preparation of Sulphenimides

N-(n-Hexylthio)phthalimide was prepared by a modification of the method of Behfourouz and Kerwood.[58] 1-Hexanesulphenyl chloride, prepared from the thiol (1.2g, 10.2 mmol) and N-chlorosuccinimide (1.4g, 10.5 mmol) in 20ml of benzene; ice bath cooling was required in the initial stages. After 1h at room temperature the precipitate of succinimide was filtered off. The solution of sulphenyl chloride was added dropwise to a solution of phthalimide (1.47g, 10 mmol) and triethylamine (1.25g, 12.4 mmol) in dimethylformamide (20ml) and the mixture stirred at room temperature for 30 min.

100ml of water was added with stirring and the layers separated. The organic layer was dried and evaporated leaving an oil, which on trituration with ether gave N-(n-hexylthio)phthalimide as a white solid which crystallised from heptane as needles, 1.3g (45%) m.p. 60 - 61° (lit. 60°).

A similar preparation was employed in synthesis of N-phenylthiosuccinimide from benzenesulphenyl chloride and succinimide; the sulphenimide was obtained from aqueous ethanol as plates in 30% yield based on succinimide, m.p. 114 - 116° (lit. 115 - 116°).

b) Attempted Addition to Thebaine

i) Thebaine (311mg, 1 mmol) in methanol (10ml) was boiled under reflux with 325mg (1.15 mmol) of N-(n-hexylthio)phthalimide for 72h. The reaction mixture was concentrated down to ca. 2ml and allowed to cool, whereupon unreacted thebaine crystallised out as prisms, m.p. 193 - 194°, 298mg (96% recovery).

ii) Thebaine (155mg, 0.5 mmol) and N-phenylthiosuccinimide (120mg, 0.58 mmol) were stirred together in methanol (5ml) at room temperature for 4 days. The reaction mixture was poured into water (20ml) and extracted with methylene chloride (2 x 25ml). The organic extracts were dried and evaporated giving a pale yellow solid from which unreacted thebaine was obtained by crystallisation from methanol, 140mg (90% recovery) m.p. 192 - 193°.

Repetition of this reaction in refluxing methanol also gave no reaction; after 72h, unreacted thebaine was obtained in 92% recovery.

7) Oxidation of the Alkylthionorcodeinone Derivatives (51,52): 14β-Alkylsulphonylnorcodeinones.

The m-chloroperbenzoic acid (MCPBA) employed was tested for purity by iodometric titration and found to be 77% pure.

i) Attempted oxidation of 14β(3-phenylpropyl)thionorcodeinone hydrochloride (52e.HCl)

The hydrochloride (52e.HCl) (130mg, 0.3 mmol) was dissolved in methylene chloride (10ml) and the solution cooled to 0° in an ice bath. m-Chloroperbenzoic acid (140mg, 0.64 mmol assuming 77% purity) was added with stirring and the solution allowed to

warm to room temperature over 2h. Analytical t.l.c. at this stage showed no trace of starting material, but the product appeared to be a mixture of at least three compounds.

The reaction mixture was shaken with saturated sodium carbonate solution (20ml) and the layers separated. The organic phase was dried, filtered and evaporated leaving a yellow gum, 110mg, whose ^{1}H n.m.r. spectrum was complex and showed no signals attributable to a codeinone system. Analytical t.l.c. displayed three spots plus considerable streaking.

The reaction was repeated with the temperature of reaction maintained at 0^{o} for 45 min. Once again, a complex mixture was isolated.

This reaction was not further investigated.

ii) 14β-Phenylsulphonyl-N-t-BOC-norcodeinone (77a) and 14β-Phenylsulphonylnorcodeinone (74b)

14β-Phenylthio-N-t-BOC-norcodeinone (51b) (250mg, 0.51 mmol) was dissolved in methylene chloride (10ml) and the solution cooled to 0^{o} in an ice bath. m-Chloroperbenzoic acid (240mg, 1.05 mmol assuming 77% purity) was added with stirring. After 2 min. a white precipitate began to form. The mixture was stirred at 0^{o} for 1h, then allowed to warm to room temperature and stirring continued for a further hour.

The precipitate was filtered off; microcrystals, m.p. 156 - 157^{o} (lit. for m-chlorobenzoic acid 158^{o}) and the filtrate shaken with sodium carbonate solution (20ml) and water (20ml), dried, filtered and evaporated leaving 14β-phenylsulphonyl-N-t-BOC-

norcodeinone (77a) as a white solid which crystallised from methanol as prisms, 160mg (60%) m.p. 221 - 223°.

Found : C, 64.45; H, 5.62; N, 2.63; S, 6.28.

$C_{28}H_{29}NO_7S$ requires C, 64.23; H, 5.58; N, 2.67; S, 6.12.

^1H n.m.r. ($CDCl_3$): δ 7.95 (2H, m) phenyl o - H; 7.58 (3H, m) phenyl m- and p-H; 6.68 and 6.56 (2H, ABq, J 8Hz) H-1, H-2; 6.16 (1H, d, J 10Hz) H-8; 5.62 (1H, d, J 10Hz) H-7; 5.21 (1H, s) H-5; 3.82 (3H, s) 3-OMe; 1.52 (9H, s), $C(CH_3)_3$.

i.r. ($CHCl_3$): ν_{max} 2980, 1680, 1420, 1310, 1160 cm^{-1}.

m.s. m/e 523 (M^+), 467, 383, 327, 326 (1:1, base peak), 239.

The above reaction was repeated and the crude sulphone isolated as an off-white solid. The crude material was dissolved in benzene (5ml) and treated with saturated ethereal hydrogen chloride (2ml; ca. 6M). After 45 min. at room temperature, the solvent was removed leaving a dark-red gum. This was chromatographed on neutral alumina (10g) in methylene chloride. Evaporation of the eluent left 14β-phenylsulphonylnorcodeinone (74a) as a pale yellow gum which crystallised from ethanol as colourless needles, 105mg [49% from (51b)] m.p. 235 - 236° (decomp.).

Found : C, 65.28; H, 5.24; N, 3.38.

$C_{23}H_{21}NO_5S$ requires C, 65.23; H, 5.00; N, 3.31; S, 7.57%.

^1H n.m.r. ($CDCl_3$): δ 8.16 (2H, m) phenyl o-H; 7.66 (3H, m) phenyl m- and p-H; 6.71 (2H, s) H-1, H-2; 6.19 (1H, d, J 10Hz) H-8;

5.63 (1H, d, J 10Hz) H-7; 5.28 (1H, s); 5.03 (1H, d, J 6Hz) H-9; 4.30 (1H, d, J 19Hz) H-10β; 3.85 (3H, s), 3-OMe; 3.20 (1H, br.s., exchanges in D_2O) NH.

m.s. m/e 423 (M^+), 282 (base peak), 240, 77.

iii) 14β-Phenylmethylsulphonyl-N-t-BOC-norcodeinone (77b)

Phenylmethanesulphenyl chloride was prepared from α-toluene-thiol (145mg, 1.17 mmol) and N-chlorosuccinimide (170mg, 1.27 mmol) in benzene (10ml) and added to a stirred solution of N-t-BOC-northebaine (0.4g, 1 mmol) in benzene (10ml). After 4h the reaction mixture was shaken with sodium carbonate solution (20ml) and water (20ml) and the organic phase dried, filtered and evaporated leaving the enone (51c) as a gum. This residue was dissolved in methylene chloride (20ml). The solution was cooled to 0^o in an ice bath and MCPBA (0.5g, 2.2 mmol assuming 77% purity) added with stirring. The mixture was allowed to warm to room temperature and left, with stirring, for 16h. The reaction mixture was then shaken with sodium carbonate solution (20ml) and water (20ml), dried, filtered and evaporated leaving a gum. This was chromatographed on neutral alumina (10g) in methylene chloride and the residue from evaporation of the eluent crystallised from carbon tetrachloride giving 14β-phenylmethylsulphonyl-N-t-BOC-norcodeinone (77b) as needles; apparently a mono-solvate, 373mg (54%) m.p. 142 - 143°.

Found : C, 51.60; H, 4.48; N, 2.00.

$C_{29}H_{31}NO_7S$ requires C, 64.79; H, 5.81; N, 2.61; S, 5.96.

$C_{29}H_{31}NO_7S.CCl_4$ requires C, 52.01; H, 4.49; N, 2.02%.

^{1}H n.m.r. ($CDCl_3$): δ 7.36 (5H, s) Ph; 6.70 and 6.64 (2H, ABq, J 9Hz) H-1, H-2; 6.36 (2H, s) H-7, H-8; 5.05 (1H, s) H-5; 4.62 and 4.19 (2H, ABq, J 13Hz) CH_2Ph; 3.84 (3H, s) 3-OMe; 1.50 (9H, s) $C(CH_3)_3$.

i.r. ($CHCl_3$): ν_{max} 2985, 1685, 1420, 1160 cm^{-1}.

m.s. m/e 537 (M^+), 505, 450, 417 and 415 (1:1), 383, 328, 240 and 239 (1:1), 91 (base peak).

iv) 14β-(3-Phenylpropyl)sulphonylnorcodeinone (74b)

3-Phenylpropylsulphenyl chloride was prepared from the thiol (170mg, 1.13 mmol) and N-chlorosuccinimide (165mg, 1.24 mmol) in benzene (10ml) and added with stirring to a solution of N-t-BOC-northebaine (0.4g, 1 mmol) in 10ml of benzene. After 2h at room temperature, the reaction mixture was worked up by the method of iii) above and the crude enone (51e) isolated as a gum.

The enone (51e) was dissolved in methylene chloride (20ml) and treated with MCPBA (0.5g; 2.2 mmol assuming 77% purity) with ice-bath cooling as for iii) above. A white precipitate began to form within a few minutes. The mixture was allowed to warm to room temperature, with stirring,and left for 4h. The precipitate of m-chlorobenzoic acid was filtered off and the filtrate evaporated to leave a gum. This residue was dissolved in benzene (5ml) and treated with 2ml of saturated ethereal hydrogen chloride, at room temperature for 45 min. The solvent was removed and the residue crystallised from ethanol, giving the hydrochloride of 14β-(3-phenylpropyl)sulphonylnorcodeinone (74b) as needles, 216mg (43% based on N-t-BOC-northebaine), m.p. 222 - 224°.

Found: C, 61.81; H, 5.51; N, 2.60; S, 6.28; Cl, 7.01

$C_{26}H_{27}NO_5S.HCl$ requires C, 62.21; H, 5.62; N, 2.79; S, 6.39; Cl, 7.06%.

^1H n.m.r. ($CDCl_3$): δ 8.90 (1H, $W_{\frac{1}{2}}$ 18Hz, exchanges in D_2O) ammonium H; 7.16 (5H, m) Ph; 6.82 (1H, d, J 10Hz) H-8; 6.73 (2H, s) H-1, H-2; 6.31 (1H, d, J 10Hz) H-7; 5.81 (1H, $W_{\frac{1}{2}}$ 9Hz; becomes d, J 6Hz, in D_2O), H-9; 5.18 (1H, s) H-5; 4.12 (2H, comp.m.) SO_2CH_{21}; 3.83 (3H, s) 3-OMe; 2.79 (2H, t, J 8Hz) $PhCH_2$; 2.19 (2H, comp.m) $PhCH_2CH_2$.

The second ammonium proton of this salt could not be detected above δ 13.0.

i.r. ($CHCl_3$): ν_{max} 3160, 2970, 2580 (br), 1690, 1510, 1450, 1385, 1120, 1110 cm^{-1}.

m.s. m/e 465 (M^+), 282 (base peak), 240, 91.

v) Attempted oxidation of 14β(2-phenylethyl)thio-N-t-BOC-norcodeinone (51d)

The enone (51d) was prepared from N-t-BOC-northebaine (0.4g, 1 mmol) and 2-phenylethanesulphenyl chloride [prepared from the thiol (155mg, 1.12 mmol) and N-chlorosuccinimide (160mg, 1.20 mmol)] and isolated as a gum after alkaline workup. This residue was dissolved in 10ml of methylene chloride and treated with MCPBA (0.5g) with ice-bath cooling as in iii) above.

After 4h, the reaction mixture was worked up with Na_2CO_3 solution as for iii) and iv) above, yielding a yellow gum which proved by t.l.c. to be a mixture of at least three compounds.

The reaction was repeated on the same scale using 95% ethanol as the solvent for the oxidation step. Again, the reaction yielded a complex mixture of products. No crystalline material could be isolated from either of these preparations, either directly or following treatment with ethereal hydrogen chloride.

PART III

Reactions of Thebaine with Sulphenyl Chlorides and Triethylamine

1) Reaction of thebaine with phenylmethanesulphenyl chloride and triethylamine

i) In Benzene

Phenylmethanesulphenyl chloride was prepared by the standard method from α-toluenethiol (145mg, 1.2 mmol) and N-chlorosuccinimide (170mg, 1.27 mmol) in benzene (10ml). The solution of sulphenyl chloride was added by syringe to a stirred solution of thebaine (311mg, 1 mmol) and triethylamine (125mg, 1.23 mmol) in benzene (10ml). The reaction mixture immediately became cloudy; however, no reaction could be detected by analytical t.l.c. The reaction mixture was stirred at room temperature for 20h; however, no conversion of thebaine could be detected.

The reaction mixture was shaken with saturated aqueous sodium carbonate solution (20ml) and the layers separated. The organic phase was washed twice with water (30ml), dried and evaporated leaving a pale yellow solid, 0.4g. From this was obtained 280mg (90% recovery) of unreacted thebaine, by crystallisation from methanol; m.p. 191 - 193°, unchanged on mixing with an authentic sample. The mother liquors were concentrated to a small volume and dibenzyl disulphide, 70mg, m.p. 69 - 71° (lit. 71 - 72°) crystallised out as prisms.

ii) In 1:1 benzene-methanol:6,14-dihydro-6β,14β-[(S)-phenylepithiomethano] thebaine (85).

The sulphenyl chloride was prepared on the scale of i) above in benzene (10ml) and added to a stirred suspension of thebaine

(311mg, 1 mmol) in methanol (10ml) containing triethylamine (125mg, 1.23 mmol). Immediately on addition of the sulphenyl chloride solution, a white smoke appeared and the thebaine dissolved. The smoke faded and disappeared after approximately five minutes. Analytical t.l.c. after 2h indicated partial reaction.

The reaction mixture was left to stand at room temperature for 18h then shaken with sodium carbonate solution (20ml) and the layers separated. The aqueous layer was extracted with methylene chloride (2 x 25ml) and the combined organic extracts dried, filtered and evaporated to leave a pale yellow solid. This residue was dissolved in boiling ethanol from which a crystalline product was obtained, m.p. 174 - 181°. Analytical t.l.c. indicated that this material was a mixture of two compounds. One component of the mixture had R_f identical with thebaine; the other, the major component, was considerably more mobile (R_f = 0.78 in methylene chloride - 2% methanol). This product was recrystallised from ethanol giving the adduct, 6,14-dihydro-6β,14β-[(§)-phenyl-epithiomethano]thebaine, as prisms, 180mg (42%) m.p. 182 - 183°.

Found : C, 71.87; H, 6.32; N, 3.07; S, 7.70.

$C_{26}H_{27}NO_3S$ requires C, 72.02; H, 6.28; N, 3.23; S, 7.39%.

^{1}H n.m.r. ($CDCl_3$): δ 7.50 - 7.14 (5H, comp.m.), Ph; 6.59 and 6.50 (2H, ABq, J 8Hz); 6.31 (1H, dd, J 9 and 2Hz) H-7; 5.71 (1H, s) CHPh; 5.20 (1H, d, J 9Hz) H-8; 5.08 (J 2Hz) H-5; 3.80 (3H, s) 3-OMe; 3.68 (3H, s) 6-OMe; 2.33 (3H, s) NMe.

^{13}C n.m.r. ($CDCl_3$): δ 146.8 (s), 142.0 (s), 139.7 (s), 132.8 (s), 132.5 (d), 130.3 (s), 130.1 (d,2c), 127.6 (d, and d, 2c), 127.1 (s), 119.0 (d), 113.1 (d), 93.0 (d), 88.8 (s), 57.9 (d), 56.4 (q),

53.2 (q), 50.1 (d), 49.0 (s), 48.4 (s), 45.3 (t), 42.8 (q), 33.3 (t), 22.4 (t).

i.r. ($CHCl_3$): ν_{max} 2920, 2840, 2800, 1630 (m), 1600 (m), 1505, 1455, 1380, 1140, 1110 cm^{-1}.

m.s. m/e 433 (M^+, base peak), 311, 255, 230, 203, 122, 121.

Found: M^+ = 433.1710. $C_{26}H_{27}NO_3S$ requires 433.171155.

iii) Improved preparation of the adduct (85)

The sulphenyl chloride was prepared from benzyl mercaptan (840mg, 6.77 mmol) and N-chlorosuccinimide (960mg, 7.19 mmol) in benzene (20ml) and added to thebaine (1.0g, 3.22 mmol) in 20ml of methanol containing 730mg (7.23 mmol) triethylamine. As before, a white smoke appeared which disappeared within five minutes; it was observed that the intense yellow colour due to the sulphenyl chloride discharged within seconds of addition. Analytical t.l.c. after 5 minutes indicated that some starting material remained; the appearance of analytical t.l.c. after a further hour had not changed and the reaction mixture was inert to starch - KI paper, indicating the absence of sulphenyl chloride.

The reaction mixture was shaken with sodium carbonate solution (30ml) and extracted with methylene chloride (2 x 50ml). The organic extracts were dried and evaporated giving a gum which crystallised from ethanol to give the adduct (85), 0.8g (60%) m.p. 182 - 183°, identical in melting point, mixed melting point and ^1H n.m.r. spectrum with the product of i) above.

The above preparation was repeated on the same scale but with the quantity of triethylamine increased to 1.4g (13.9 mmol). After workup as above, the adduct (85) was obtained by crystallisation from ethanol as prisms, 0.85g. A further 220mg of (85) was obtained on concentration of the mother liquors, giving a total yield of 1.07g (77%), m.p. 182 - 184°.

2) Attempted desulphurisation of the adduct (85)

i) With sodium amalgam

The adduct (85) (110mg, 0.254 mmol) was dissolved in dry methanol (5ml) with 1ml of tetrahydrofuran as cosolvent, and the solution cooled to 0° in an ice bath. Disodium hydrogen phosphate (100mg) and pulverised 6% sodium amalgam (400mg) were added with stirring. The mixture was stirred at 0° for 1h, then allowed to warm to room temperature and stirring was continued for a further 16h. The reaction mixture was poured into water and extracted with methylene chloride (2 x 25ml). The organic extracts were dried and evaporated leaving 122mg of a white solid. This was crystallised from ethanol giving 102mg (93% recovery) of unchanged starting material, m.p. 182 - 184°, unchanged on mixing with authentic (85).

ii) With aluminium amalgam

Strips of aluminium foil (ca. 1g) were immersed for 30s in a 2% solution of mercury (II) chloride, then rinsed successively with water, 95% ethanol and ether. The strips were then cut with scissors into a solution of the adduct (85) (110mg, 0.254 mg) in tetrahydrofuran (20ml) and water (1ml). The

mixture was heated under reflux for 1h, then allowed to cool. However, the mixture remained warm for several hours, and evolution of gas was also observed during this period.

After 24h at room temperature, the reaction mixture was filtered and the filtrate evaporated leaving a white solid. This residue crystallised from ethanol as prisms, m.p. 182 - 184°, identical in melting point and ^1H n.m.r. spectrum with starting material. Recovery of unchanged (85) was 100mg (91%).

iii) With lithium aluminium hydride

The adduct (85) (250mg, 0.58 mmol) was dissolved in dry tetrahydrofuran (10ml) in a 25ml two-necked round-bottomed flask equipped with a serum cap, magnetic stirrer and gas inlet. The flask was flushed thoroughly with dry argon and lithium aluminium hydride (110mg, 2.9 mmol) added with stirring.

Stirring was continued at room temperature for 16h, and the hydride then carefully destroyed by dropwise addition of 0.1M hydrochloric acid (ca. 15ml) until the reaction mixture was at pH 9. The mixture was extracted with methylene chloride (3 x 25ml) and the combined organic extracts dried and evaporated leaving 190mg (76% recovery) of the unchanged starting material as a white solid, m.p. 181 - 183°. The ^1H n.m.r. spectrum of this material was identical in all respects with the starting adduct.

iv) With Raney nickel

a) Preparation of W-4 Raney nickel

Sodium hydroxide pellets (13g) were dissolved in 50ml of distilled water in a 250ml conical flask. To the solution was added 10g of 1:1 nickel-aluminium alloy, in small portions with

stirring and water bath cooling to maintain a temperature of 48 - 53°. Vigorous stirring was continued for 1h after addition of the alloy was complete, and the solid allowed to settle. The supernatant liquid was decanted off and the black precipitate washed repeatedly with 100ml portions of distilled water until the washings were neutral to litmus (approx. 1.5 litres of water being employed), then with ethanol (50ml) and absolute ethanol (50ml), and finally stored under absolute ethanol. A portion of the resulting black sludge ignited when allowed to dry in air.

b) Attempted desulphurisation of (85) with Raney nickel

The adduct (85) (250mg, 0.58 mmol) was dissolved in tetrahydrofuran (3ml) and ethanol (5ml). To the solution was added approximately 0.3g of the W-4 Raney nickel prepared in a) above, and a further 5ml of ethanol.

The reaction mixture was stirred under argon for 72h then left to stand until the suspended material had settled. The supernatant liquid was removed by pipette and the precipitate washed with ethanol (2 x 5ml) and ether (2 x 5ml). Evaporation of the combined organic extracts left a yellow gum, 220mg, whose ^{1}H n.m.r. spectrum indicated that it was composed almost entirely of the unchanged adduct.

The reaction was repeated using identical quantities of (85) and Raney nickel, heated together under reflux in ethanol (10ml) under an argon atmosphere. After 16h, the mixture was filtered through a short column of Celite and evaporated to leave a yellow gum. This residue was chromatographed on neutral alumina (10g) in methylene chloride and the eluent evaporated to leave a white solid.

Trituration with ether gave a mass of white microcrystals, rather waxy in appearance; 170mg, m.p. 131 - 134°. Recrystallisation from ethanol produced a pronounced change in the appearance of the product which crystallised as needles, m.p. 261 - 262°. This material was identified from its ^{1}H and ^{13}C n.m.r., i.r. and mass spectra as 5,0-dihydro-5β,14β-[(S)-phenylepithiomethano]codeinone (89); yield 160mg (66%). On further recrystallisation from ethanol the melting point rose to 262 - 262.5°.

Found: C, 70.27; H, 6.12; N, 3.26; S, 7.90.

$C_{25}H_{25}NO_3S$ requires C, 71.58; H, 6.01; N, 3.34; S, 7.63.

$C_{25}H_{25}NO_3S.\frac{1}{2}H_2O$ requires C, 70.07; H, 6.03; N, 3.27; S, 7.48%.

^{1}H n.m.r. ($CDCl_3$): δ 7.25 (5H, m) Ph; 6.53 and 6.51 (2H, ABq, J 8Hz) H-2, H-10; 6.00 and 5.82 (2H, ABq, J 9Hz) H-7, H-8; 5.89 (1H, s, exchanges in D_2O) phenolic-OH; 5.81 (1H, s) PhCH; 4.72 (1H, d, J 1.5Hz) H-5; 3.80 (3H, s) 3-OMe; 3.15 (1H, d, J 15Hz) H-10β; 3.02 (1H, br.s) H-9; 2.41 (3H, s) -NMe.

^{13}C n.m.r. ($CDCl_3$): δ 194.6(s), 148.8(d), 144.8(s), 142.8(s), 135.6(s), 131.1(d), 130.2(s), 130.0 (d,2c), 128.0 (d,2c), 127.6(d), 125.0(s), 118.0(d), 108.8(d), 59.5(d), 56.0(q), 56.0(s), 55.0(d), 53.7(d), 52.4(s), 45.8(t), 42.6(q), 29.6(t), 25.3(t).

i.r. ($CHCl_3$): ν_{max} 3530, 2945, 1675, 1490, 1280, 1060 cm^{-1}.

ν_{OH} at 3530 cm^{-1} is independent of concentration.

m.s. m/e 419 (M^+), 231, 198, 189, 121.

Found M^+ = 419.1555 $C_{25}H_{25}NO_3S$ requires M^+ = 419.1555.

3) Preparation of 5,0-dihydro-6β,14β-[(S)-phenylepithiomethano] codeinone (89)

The adduct (85) (433mg, 1 mmol) was boiled under reflux in ethanol (20ml) with sodium hydroxide (200mg). The reaction mixture was maintained at reflux temperature for 16h, then acidified by addition of 5M hydrochloric acid (2ml), neutralised again by addition of saturated aqueous sodium hydrogencarbonate solution, and extracted with methylene chloride (50ml). The organic extracts were dried and evaporated leaving a yellow gum which crystallised from ethanol giving the 5β,14β-bridged phenol (89) as needles, 285mg (68%) m.p. 261 - 262°, identical in melting point, mixed melting point and ^1H n.m.r. spectrum with the product prepared in iv) b) above.

A portion of the phenol (89), dissolved in ethanol and treated with 2 drops of 10% ethanolic iron (III) chloride gave an intense deep green colour.

The phenol (89) (50mg, 0.12 mmol) was idssolved in dry pyridine (1ml) and treated with acetic anhydride (0.5ml) at room temperature for 16h. Removal of solvent under oil-pump vacuum (ca. 0.2mm Hg) at 60° left a semi-solid residue from which the 4-O-acetate, (90), of (89) crystallised from ethanol as hexagonal prisms, m.p. 290 - 291°.

i.r. (KBr disc) ν_{max} 1770, 1690 cm^{-1}.

m.s. m/e 461 (M^+), 419 ($M-CH_2CO$), 283, 241. Metastable ion at m/e 381.

4) Reaction of N-t-BOC-northebaine with phenylmethanesulphenyl chloride and triethylamine

i) In 1:1 benzene-methanol

Phenylmethanesulphenyl chloride was prepared from the thiol (145mg, 1.17 mmol) and N-chlorosuccinimide (165mg, 1.24 mmol) in 10ml of benzene. 5ml of the resulting solution was added to a stirred suspension of N-t-BOC-northebaine (100mg, 0.25 mmol) in methanol (5ml) containing 70mg (0.69 mmol) of triethylamine. A white smoke appeared and the N-t-BOC-northebaine dissolved; the smoke disappeared after ca.5 minutes.

After 2h the reaction mixture was shaken with sodium carbonate solution (20ml) and extracted with methylene chloride (25ml). The organic extracts, on drying and evaporation, yielded a pale yellow solid which crystallised on trituration with methanol giving 98mg (75%) of 6,14-dihydro-6β,14β-[(S)-phenylepithiomethano]-N-t-BOC-northebaine (101), m.p. 181 - 182°. A portion was recrystallised from methanol as prisms, m.p. 182 - 183°.

Found: C, 69.28; H, 6.59; N, 2.67.

$C_{30}H_{33}NO_5S$ requires C, 69.34; H, 6.40; N, 2.70; S, 6.17%.

^1H n.m.r. ($CDCl_3$): δ 7.22 (5H, s) Ph; 6.67 and 6.58 (2H, ABq, J 7Hz) H-2, H-1; 5.95 and 5.80 (2H, ABq, J 9Hz) H-7, H-8; 4.63 (1H, s) H-5; 4.25 (1H, s) PhCH; 3.82 (3H, s) 3-OMe; 3.36 (3H, s) 6-OMe; 1.47 (9H, s) $C(CH_3)_3$.

i.r. ($CHCl_3$): ν_{max} 2940, 1685, 1170, 1135 cm^{-1}.

m.s. m/e 519 (M^+), 397, 341, 267, 121 (base peak).

ii) In benzene alone

To a stirred solution of N-t-BOC-northebaine (100mg, 0.25 mmol) and triethylamine (70mg, 0.69 mmol) in benzene (5ml) was added a further 5ml of the sulphenyl chloride solution prepared in i) above. As in i), a white smoke appeared and dispersed after ca 5 minutes. After 2h, the reaction mixture was worked up as for i) above and the organic extracts evaporated to leave a gum. On trituration with methanol this residue crystallised as prisms, m.p. 182 - 183°, identical in all respects with the N-protected adduct (101) prepared in i). The yield of (101) was 75mg (57%).

5) Attempted reaction of thebaine with other sulphenyl chlorides and triethylamine

i) With benzenesulphenyl chloride

The sulphenyl chloride was prepared from the thiol (130mg, 1.17 mmol) and N-chlorosuccinimide (165mg, 1.24 mmol) in 10ml of benzene, and added to a stirred suspension of thebaine (311mg, 1 mmol) in 10ml of methanol containing 130mg (1.29 mmol) of triethylamine. The mixture was stirred at room temperature for 16h without any apparent conversion of starting material, then worked up by addition of sodium carbonate solution and extracted with methylene chloride (2 x 25ml). Evaporation of the organic extracts left a semi-solid residue from which 292mg (94% recovery) of unconverted thebaine was obtained by crystallisation from methanol, m.p. 191 - 193°.

ii) With 2-phenylethansulphenyl chloride

The sulphenyl chloride was prepared from 2-phenylethane-thiol (165mg, 1.2 mmol) and N-chlorosuccinimide (170mg, 1.27 mmol) in 10ml of benzene, and added to thebaine (311mg, 1 mmol) and triethylamine (130mg, 1.29 mmol) in methanol (10ml), with stirring. A white smoke formed, which disappeared after approximately 5 minutes. At this stage, the reaction mixture was inert to starch/KI paper, indicating that the sulphenyl chloride had been consumed. However, analytical t.l.c. indicated that little if any reaction had occurred, and no change was apparent after 24h at room temperature. As in a) above, the reaction mixture was worked up by shaking with sodium carbonate solution and extracted with methylene chloride (2 x 25ml). Evaporation of the organic extracts followed by crystallisation from methanol gave 280mg (90% recovery) of unreacted thebaine, m.p. 192 - 193°.

The above reaction was repeated using 2-phenylethylsulphenyl chloride prepared from 320mg (2.33 mmol) of the thiol and 330mg (2.47 mmol) of N-chlorosuccinimide, and in the presence of 260mg (2.59 mmol) of triethylamine. Once again, no reaction could be detected and unreacted thebaine (288mg; 93% recovery, m.p. 192 - 193°) was recovered from the reaction mixture.

6) Reaction of thebaine with non-enolisable thioaldehydes derived from sulphenyl chlorides

i) Synthesis of cinnamyl mercaptan (102)

Cinnamyl bromide (5g, 25.4 mmol) and thiourea (2.0g, 26.3 mmol) were heated together under reflux in 95% ethanol (20ml) for 4h.

On cooling of the reaction mixture to 4°, a crystalline solid, cinnamyl isothiourea hydrobromide, separated out and was removed by filtration; colourless prisms, 4.9g (71%) m.p. 197 - 199°. This material was heated under reflux in ethanol (20ml) with 20ml of water containing 1.5g (38 mmol) of sodium hydroxide.

After 2h, the reaction mixture was made acid with 5M hydrochloric acid and extracted with benzene (2 x 30ml). The organic extracts were dried and evaporated leaving the thiol (102) as a colourless liquid, 1.83g (48% overall yield).

^{1}H n.m.r. (CCl_4): δ 7.19 (5H, s) Ph; 6.25 (1H, s) PhCH; 6.24 (1H, t, J 6Hz)=CHCH$_2$; 1.86 (2H, d, J 6Hz) CH$_2$SH; 1.30 (1H, br.s)SH.

ii) Attempted reaction of thebaine with 3-phenyprop-2-enesulphenyl chloride and triethylamine

Cinnamyl mercaptan (330mg, 2.2 mmol) in benzene (10ml) was treated with N-chlorosuccinimide (310mg, 2.3 mmol) to give the sulphenyl chloride. On completion of reaction, the sulphenyl chloride solution was transferred by syringe to a suspension of thebaine (311mg, 1 mmol) in methanol (10ml) containing triethylamine (250mg, 2.48 mmol). A white smoke appeared which disappeared after ca. 5 minutes, and the thebaine dissolved.

The reaction mixture was stirred at room temperature for 18h, then saturated aqueous sodium carbonate solution (20ml) was added and the mixture extracted with methylene chloride (50ml). The organic extracts were washed with water (2 x 50ml), dried and evaporated to give a yellow gum. This crystallised from methanol to give 288mg (93% recovery) of unreacted thebaine, m.p. 192 - 193°.

iii) Reaction of thebaine with ethoxycarbonylmethanesulphenyl chloride and triethylamine: synthesis of the adduct (107)

The sulphenyl chloride was prepared from ethyl mercaptoacetate (103) (880mg, 7.4 mmol) and N-chlorosuccinimide (1.05g, 7.9 mmol) in benzene (20ml). The solution was added to a stirred suspension of thebaine (1g, 3.22 mmol) in methanol (20ml) containing triethylamine (1.5g, 14.8 mmol). As in previous reactions of this type, a white smoke appeared, which disappeared over the next few minutes. After 30 minutes, analytical t.l.c. revealed that no thebaine remained.

The mixture was shaken with sodium carbonate solution (25ml) and extracted with methylene chloride (2 x 50ml). The organic extracts were dried and evaporated leaving a yellow gum. This residue was chromatographed on silica (30cm x 3cm internal diameter) under medium pressure using methylene chloride - 1.5% methanol as eluting solvent. The principal component of the reaction product was obtained as a gum, 1.2g, on evaporation of eluent and crystallised from isopropanol to give 6,14-dihydro-6β,14β-[(S)-carboethoxymethanoepithio] thebaine (107) as needles, 0.98g (71%) m.p. 131 - 133°. A portion was recrystallised from isopropanol to m.p. 133 - 134°.

Found: C, 64.32; H, 6.34; N, 3.26; S, 7.46.

$C_{23}H_{27}NO_5S$ requires C, 64.32; H, 6.42; N, 3.08; S, 7.79%.

^1H n.m.r. ($CDCl_3$): δ 6.49 and 6.38 (2H, ABq, J 8Hz) H-2, H-1; 5.87 and 5.70 (2H, ABq, J 10Hz) H-7, H-8; 4.38 (1H, s) H-5; 4.06 (2H, q, J 7Hz) OCH_2CH_3; 3.80 (3H, s) 3-OMe; 3.60 (3H, s) 6-OMe; 2.32 (3H, s) -NMe; 1.19 (3H, t, J 7Hz) $-OCH_2CH_3$.

The 3-methoxy resonance at δ 3.80 shows an integration height consistent with 4 protons; it is assumed that the methine proton of the 6β,14β-bridge is under this peak. A small coupling (ca. 0.5Hz) was observed between the δ 5.87 and 4.38 resonances.

^{13}C n.m.r. ($CDCl_3$): δ 169.6(s), 147.1 (s), 142.1 (s), 134.2 (d), 133.6 (s), 127.0 (d), 126.8 (s), 119.7 (d), 114.1 (d), 91.7 (d), 80.7 (s), 61.1 (t), 59.9 (d), 56.6 (q), 52.8 (q), 52.3 (s), 50.8 (d), 48.2 (s), 45.7 (t), 43.3 (q), 33.3 (t), 23.1 (t), 14.0 (q).

i.r. ($CHCl_3$): ν_{max} 2950, 1740, 1505, 1160, 1110 cm^{-1}.

m.s. m/e 429 (M^+), 414, 311 (base peak), 296, 255, 230.

7) Further reactions of the adduct (85) and (107)

i) Rearrangement of the adduct (85) under acidic conditions

a) In ethylene glycol-hydrogen chloride

The adduct (85) (250mg, 0.58 mmol) was dissolved in 2ml of methylene chloride in a 25ml flask fitted with a serum cap. Triethyl orthoformate (1ml) and 1.0M glycolic hydrogen chloride (10ml) were added and the mixture left overnight at room temperature. After 18h, the reaction mixture was basified with solid sodium bicarbonate and saturated aqueous sodium bicarbonate solution, and extracted with methylene chloride (2 x 25ml). The combined organic extracts were washed with brine (100ml) then dried and evaporated leaving 160mg of an amorphous white solid. Crystallisation from ethanol gave the 5β,14β-bridged phenol (89) as needles, 168mg (69%), m.p. 261 - 262°.

The ^{1}H n.m.r. and i.r. spectra of this material were identical with those of (89) prepared by alkaline rearrangement of (85) (cf. Section 3 and 2 iv) b) above) and the melting point was undepressed on mixing with sample of (89) prepared by this method.

The above reaction was repeated on the same scale, but with 2ml of triethyl orthoformate present and with reaction time extended to 40h. After basifying and extraction as above, the phenol (89) was again obtained in 67% yield.

b) In methanolic hydrogen chloride

The adduct (85) (250mg, 0.58 mmol) was dissolved in 2ml of dry methylene chloride and treated with 10ml of 1.0M dry methanolic hydrogen chloride and 2ml of triethyl orthoformate, under identical conditions to those of a) above. After 40h at room temperature, the mixture was worked up as in a) above and yielded 155mg (64%) of (89) as needles on crystallisation from ethanol, m.p. 260 - 261°.

The reaction was repeated using undried methanolic hydrogen chloride; triethyl orthoformate was not added and no precautions were taken to exclude water. After 40h, the solvent was removed to leave the hydrochloride of (89) as an amorphous white solid, 230mg. Treatment of this material with aqueous sodium hydrogen-carbonate solution yielded the free phenol (89), which crystallised from ethanol as needles, 163mg (67%) m.p. 260 - 261°.

The hydrochloride salt was noncrystalline and proved to be insoluable in the majority of solvents. The ^{1}H n.m.r. spectrum was eventually obtained in d_6-dimethylsulphoxide:

δ 8.90 (1H, $W_{\frac{1}{2}}$ 12Hz, exchanges in D_2O) $\overset{+}{N}\underline{H}$; 7.50 (2H, m) and 7.20 (3H, m) Ph; 6.65 and 6.54 (2H, ABq, J 8Hz) H-2, H-1; 6.13 (1H, s, exchanges in D_2O) -O<u>H</u>; 5.96 (2H, s) H-7, H-8; 4.68 (1H, s) H-5; 3.70 (3H, s) 3-OMe; 2.85 (3H, br.s) -$\overset{+}{N}$Me.

ii) Reduction of the adduct (107): 6,14-dihydro-6β,14β-[(R)-hydroxymethylmethanoepithio]thebaine (116)

The adduct (107) (215mg, 0.5 mmol) was dissolved in dry tetrahydrofuran (10ml) in a 50ml round-bottomed flask equipped with a magnetic stirrer and gas inlet. The flask was flushed several times with dry argon and lithium aluminium hydride (20mg, 0.5 mmol) added with stirring under an argon atmosphere. Immediately upon addition of the hydride, the mixture became warm and effervescence occurred.

After 5 minutes, analytical t.l.c. indicated that the starting material had been totally consumed; t.l.c. showed a single spot, R_f 0.11, in methylene chloride - 2% methanol. Excess hydride was destroyed by cautious addition of 10% aqueous sodium hydroxide (2ml) and water (5ml) and the mixture extracted with methylene chloride (2 x 25ml). The combined organic extracts were washed with water (50ml), dried and evaporated to leave the primary alcohol (116) as a crystalline solid, 136mg (70%) m.p. 153 - 155°.

^{1}H n.m.r. ($CDCl_3$): δ6.60 and 6.53 (2H, ABq, J 7Hz) H-1, H-2; 5.86 (2H, s) H-7, H-8; 4.57 (1H, s) H-5; 3.80 (3H, s) 3-OMe;

3.68 (3H, s) 6-OMe; 3.50 (1H, t, J 6Hz) SCHCH$_2$OH; 3.36 (2H, d, J 6Hz) SCHCH$_2$OH; 2.60 approx (1H, br, disappears in D_2O) -OH; 2.36 (3H, s) -NMe.

i.r. ($CHCl_3$): ν_{max} 3520 (m,br), 2845, 1505, 1110 cm^{-1}.

m.s. m/e 387 (M^+), 311 (base peak), 255, 212, 69.

Found: M^+ = 387.1510 $C_{21}H_{25}NO_4S$ requires M^+ = 387.1503.

8) Studies of the thebaine - thioaldehyde reaction

i) Solvent effects in synthesis of the adduct (85)

Phenylmethanesulphenyl chloride was prepared from the thiol (580mg, 4.67 mmol) and N-chlorosuccinimide (650mg, 4.87 mmol) in 20ml of benzene. 5ml aliquots of the resulting solution were added to solutions of thebaine (150mg, 0.48 mmol) in each of the following reaction media:

A : Benzene (10ml), methanol (0.5ml) and triethylamine (155mg,1.5mmol)

B : Methanol (10ml) and triethylamine (155mg, 1.5mmol)

C : Methylene chloride (10ml) and triethylamine (155mg, 1.5 mmol)

All three reaction mixtures were stirred at room temperature for 2h, then worked up by addition of sodium carbonate solution and extracted with methylene chloride (2 x 25ml). Evaporation of the organic extracts followed by crystallisation from ethanol gave the following results:

A : The product crystallised as needles, m.p. 155 - 179°, which were shown by analytical t.l.c. to be an approximately 1:1 mixture of thebaine and the adduct (85). Recrystallisation from ethanol gave the pure adduct (85) as needles, 65mg (31%) m.p. 181 - 182°. Evaporation of the mother liquors from

both crystallisations, followed by crystallisation of the residues from methanol, gave 67mg (45%) of unconverted thebaine, m.p. 191 - 193°.

B : The adduct (85) was obtained as needles, 115mg (55%) m.p. 181 - 182°. Concentration of the mother liquors led to the isolation of 40mg of dibenzyl disulphide, m.p. 69 - 70°.

C : The adduct (85) was obtained as needles, 122mg (59%) m.p. 181 - 182°. The thiobenzaldehyde adduct (85) was identical in all respects with material prepared in 1 ii) and iii) above.

ii) Reaction of phenylmethanesulphenyl chloride and triethylamine

The sulphenyl chloride was prepared from phenylmethanethiol (210mg, 1.7 mmol) and N-chlorosuccinimide (250mg, 1.87 mmol) in benzene (10ml) and added to a solution of triethylamine (180mg, 1.78 mmol) in benzene (10ml).

A white smoke appeared and the yellow colour due to the sulphenyl chloride discharged leaving a pale pink, cloudy solution which was inert to starch/potassium iodide paper. After 10 minutes, the mixture was filtered through a celite plug and evaporated down, leaving a pale pink semi-solid, whose ^{1}H n.m.r. spectrum indicated a mixture of the trithiane (118b) and dibenzyl disulphide in approximately equal amounts (see Discussion, p.88).

iii) Reaction of ethoxycarbonylmethanesulphenyl chloride and triethylamine

The sulphenyl chloride was prepared from ethyl mercaptoacetate (280mg, 2.3 mmol) and N-chlorosuccinimide (320mg, 2.4 mmol) in benzene (10ml) and added to a solution of triethylamine (240mg, 2.35 mmol) in 10ml of benzene.

A transient deep pink colour appeared, and a white smoke formed which disappeared after ca. 2 minutes, by which time the reaction mixture was inert to starch/potassium iodide paper. After a further ten minutes the reaction mixture was washed with water (20ml), dried and evaporated leaving a gum, whose ^{1}H n.m.r. spectrum was consistent with di(ethoxycarbonylmethane)disulphide.

^{1}H n.m.r. (CCl_4): δ 4.17 (2H, q, J 7Hz) $CO_2\underline{CH}_2CH_3$; 3.53 (2H, s) SCH_2CO; 1.29 (3H, t, J 7Hz) $CO_2CH_2\underline{CH}_3$.

iv) Treatment of cyclopentadiene with phenylmethanesulphenyl chloride and triethylamine

The sulphenyl chloride was prepared from the thiol (210mg, 1.7 mmol(and N-chlorosuccinimide (250mg, 1.87 mmol) in benzene (10ml) and added to a solution of triethylamine (180mg, 1.76 mmol) and freshly redistilled cyclopentadiene (104mg, 1.58 mmol) in 10ml of benzene. A white smoke appeared and the colour of the sulphenyl chloride solution discharged leaving a colourless solution. After 30 minutes sodium carbonate solution (15ml) was added; the layers were separated and the organic phase washed with water (2 x 25ml), dried and evaporated to leave 250mg of an off-white solid. Analytical t.l.c. in di-isopropyl ether - petroleum ether 60° - 80° (4:1 v/v) showed three spots plus a certain amount of straking. The ^{1}H n.m.r. spectrum indicated a complex mixture.

Repetition of the reaction using cyclopentadiene and triethylamine in methanol (10ml) gave identical results; again a complex mixture was obtained.

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