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SYNTHESIS OF NEW, SULPHUR-CONTAINING MORPHINAN ANALGESICS

A Thesis presented to the University of Glasgow for the Degree of Doctor of Philosophy

by

Alastair David Sclare

Chemistry Department May, 1988
ACKNOWLEDGEMENTS

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My thanks are also due to the technical staff of the Chemistry Department for elemental analyses and the recording of spectra.
"The unexamined life is not worth living".

(Socrates)
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A new sulphur-containing cycloadduct, 8-thiathevinone, was formed by Diels-Alder reaction of the transient thioaldehyde 2-oxopropanethial with thebaine. The thioaldehyde was best prepared and trapped in situ, from S-(2-oxopropyl)toluene-\(p\)-thiosulphonate and triethylamine.

Two homologous series of epimeric tertiary alcohols, both series having the 7\(\alpha\)-configuration, were prepared by the reaction of 8-thiathevinone with Grignard reagents. These alcohols were generally less potent analgesics than those derived from thevinone (the cycloadduct of thebaine and but-1-en-2-one). However, alcohols from one series, believed to have the (20R-configuration, were generally more potent than their epimers. The reaction of 8-thiathevinone with butyl-lithium gave the corresponding diastereomeric tertiary alcohols; while that with propyl-lithium gave an unexpected rearrangement product.

The thermal isomerisation of the known cycloadduct of thebaine and ethyl thiooxoacetate was reinvestigated. Isomerisation of the 8-thia cycloadduct to give the 7-thia regioisomer was observed, as before, in toluene at 111°C. However, prolonged heating gave a new isomer having sulphur attached to C(5) and oxygen to C(6).

8-Thiathevinone also underwent dissociation and recombination in toluene at 111°C to form the thermodynamically more stable '7-thiaisothevinone', which arises from endo-\(\beta\) addition of the thioaldehyde to thebaine in the alternative regiochemical sense.

The reaction of '7-thiaisothevinone' with methyl magnesium iodide gave an unexpected rearrangement product and not the intended
tertiary alcohol. However, '7-thiaisothetvinone' reacted with propyl-lithium to give one of the corresponding epimeric tertiary alcohols as well as novel rearrangement products. This tertiary alcohol was a less potent analgesic than normorphine, but more potent than either of the corresponding isomeric 8-thia-7α-tertiary alcohols.
INTRODUCTION

1.1 Modifications to the Morphine Nucleus

Since classical times opium, the dried sap of the poppy Papaverum somniferum has been used medicinally for the relief of pain. The accompanying feelings of euphoria have also made opium a drug of abuse, while the effects of acquired tolerance and physical dependence have led to problems of addiction. While morphine (1) is the principal active analgesic constituent, opium also contains lesser quantities of three related alkaloids. Codeine (2) is a weak analgesic and anti-tussive. Thebaine (3), inactive as an analgesic, is a biosynthetic precursor of morphine and codeine. Papaverine (4), another constituent, is a muscle relaxant.

Morphine was isolated in pure crystalline form in 1805.¹ Exactly 120 years after this, the brilliant work of Sir Robert Robinson provided the first formulation of the morphine structure.² Robinson's formula was confirmed by the first total synthesis of morphine in 1956 by Gates and Tschudi.³

Morphine, although in current clinical use, is not the analgesic of choice due to the accompanying physical effects which include respiratory depression, nausea, and physical dependence liability. It is these effects plus the continuing importance of pain relief that encouraged synthetic chemists to structurally modify the morphine skeleton in the pursuit of a non-addictive analgesic. Diacetylmorphine (heroin) synthesised at the end of the last century and marketed as a "non-addictive" analgesic arguably marked the start of a search which continues today. This first attempt at structural modification failed to separate analgesia from its undesirable side effects. However, further modifications to
morphine alkaloids have been made. A representative selection of these is now reviewed.

Later, systematic simplification of the morphine nucleus led to the synthesis of analgesics such as the hydroxymorphinans (5), benzomorphans (6) and phenylpiperidine (7). Each retains the phenylpiperidine structure found in morphine (1) but the benzomorphans lack the C ring, while the phenylpiperidines lack both B and C rings. Although many members of these classes of opiate remain in clinical use, few are selective analgesics. Some indeed are actually more addictive than morphine. Phenazocine [6; $R^1 = (CH_2)_2Ph$, $R^2 = R^3 = Me$] however is a notable exception. It is an orally active analgesic which shows reduced physical dependence liability.

The observation that benzomorphans (6) with 5,9-trans substituted alkyl groups are more potent than the cis isomers led one group of researchers to synthesise trans morphine (8): the structural isomer of morphine in which the B and C rings are trans fused as opposed to the B/C cis fusion seen in natural morphine (1). Unexpectedly, the analgesic potency of (8) was less than that of (1). This was later attributed to restraint by the 4,5α-epoxy bridge which prevents the C ring of trans morphine (8) adopting the half chair conformation.

Methadone (9) retains little of the original morphine structure but still interacts with the opiate receptor. It is orally active, and forty years after its introduction, methadone and some related acyclic analogues remain in clinical use.

By contrast, morphine-like structures of greater complexity were next sought as selective analgesics. The Diels-Alder addition of
substituted alkenes to thebaine (3) led to C ring bridged cycloadducts with additional peripheral functionality.\textsuperscript{6,7} The 6\(\beta\),14\(\beta\)-ethano bridge derived from the alkene confers rigidity on the molecule. Thus the 6\(\alpha\),14\(\alpha\)-etheno bridged (ring C numbering is transferred to the new bridge) cycloadduct thevinone (10) was formed by the addition of methyl vinyl ketone to thebaine.\textsuperscript{6} As an analgesic, thevinone is equipotent with morphine. However, thevinone turned out to be the key starting material for the synthesis of much more potent analgesics since it reacted stereo-selectively with a large number of Grignard reagents (RMgX) to form a series of tertiary alcohols (11).

Many alcohols in this series, known as thevinols\textsuperscript{7} are very potent analgesics. For example, compound (11; \(R = \text{CH}_2\text{CH}_2\text{Ph}\)) is 500 times
as potent as morphine. It was also found that thevinols with \( R \) stereochemistry at C-20 [as in (11); \( R \sim Me \)] were in all cases more potent than the \( \alpha \)-diastereomers, the minor isomers from the Grignard reactions.

Two significant modifications\(^8\) were then made to the thevinol structure (11). 3-O-Demethylation led to a series of phenolic tertiary alcohols (12), the orvinols, which have even greater potency than their 3-methoxy progenitors (11). Thus, the phenol (12; \( R = \text{CH}_2\text{CH}_2\text{Ph} \)) is approximately \( 10^4 \) times as potent as morphine. Etorphine (12; \( R = \text{Pr}^n \)) is approximately \( 10^3 \) times as potent as morphine.

The second modification led not to increased potency but to a significant change in the pharmacological profile. Replacement of the \( N \)-methyl group of (11) or (12) by allyl, dimethylallyl, or cycloalkylmethyl groups was found to confer antagonist properties on the molecule.\(^9\) It was already known that naloxone (13) was essentially a 'pure' antagonist; buprenorphine (14) was found to have 'mixed' agonist-antagonist properties. Naloxone is used for
the reversal of opioid, respiratory depression. Buprenorphine is routinely administered for the relief of moderate to severe pain. The partial-agonist properties of the drug ensure the overdosing is unlikely to lead to dangerous narcosis or dependence. Catalytic reduction to form the 6α,14α-ethano bridge in buprenorphine (14) is a final modification which confers stability on the molecule under physiological conditions. By variation of both the C-20 alkyl and the nitrogen substituent, a complete range of mixed-profile analgesics is now available which covers the spectrum from pure agonist to pure antagonist. Further aspects of the chemistry of the Diels-Alder adducts of thebaine and olefinic dienophiles will be reviewed alongside the chemistry of the corresponding adducts with thioaldehydes (see Discussion).
The synthetic utility of thebaine in the preparation of analgesics arises from the reactive 6-methoxydiene system. The methoxy group results in an electron rich carbon-14. In the general case, the reaction of thebaine (3) with an electrophile (E⁺) takes place preferentially as shown in Scheme 1.

Electrophilic attack at C-14 has given rise to another important class of analgesics: the codeinones and morphinones having a 14β-lipophilic group attached via a heteroatom. For example, 14-acylamino codeinones (16; E = NHCOR) and the corresponding morphinones have high agonist activities. The exact pharmacological profile depends on the nature of the R group and on the nitrogen substituent. The corresponding 7,8-didehydro compounds are also active. The derivatives were first obtained via 14β-nitrocodeinone (16; E = NO₂) and the corresponding dimethyl acetal (15; E = NO₂, R' = Me), prepared by nitration of thebaine with tetranitromethane or dinitrogen tetroxide.

Another route for the introduction of nitrogen at the 14-position of thebaine was developed. Transient nitrosocarbonyl dienophiles (RCON=O) generated in situ by the oxidation of hydroxamic acids (RCONHOH), underwent Diels-Alder cycloaddition with thebaine to form the cycloadducts (17). Ring opening with ethylene glycol gave the acetals (18) (Scheme 2). Reduction and hydrolysis then gave the required 14β-acylamino codeinones.
Scheme 1

(3) $E^+$

(15)

(16)
Analgesics with heteroatoms at position-14 other than nitrogen have also been obtained. As in the formation of 14β-acylamino-codeinones, the initial reaction is electrophilic attack at C-14 of thebaine. Thus, Kirby and McDougall prepared 14β-alkyl-thiocodexinones by the reaction of sulphenyl chlorides with N-protected northebaine. 14β-Phenethylthiocodexinone (16; E = SCH$_2$CH$_2$Ph) prepared in this way has an analgesic activity 70 times that of normorphine. The pure agonist naloxone (13) and the partial agonists naltrexone (19) and nalbuphine (20) are also obtained from thebaine. The initial reaction is the peracid oxidation of thebaine to form 14-hydroxycodeinone (16; E = OH).
Thebaine may also be chlorinated\textsuperscript{16} and brominated\textsuperscript{16,17} at the 14-position. The resulting codeinone and morphine derivatives generally show agonist activity.

Lastly, analgesics have also been obtained from substrates other than thebaine. Kotick and co-workers\textsuperscript{18} obtained 8-\(\alpha\)-alkylmorphinans (22) from codeinone (21) in modest yield by 1,4-addition, followed by 3-O-demethylation (Scheme 3). The major product in each case was the isomer in which the 8-alkyl substituent has the \(\beta\)-configuration and has the thermodynamically more stable equatorial conformation. Minor quantities of the 8-\(\alpha\)-substituted morphinones were obtained in sufficient quantities for pharmacological testing. Neither isomer however, showed promising agonist activity. 7-\(\alpha\)-Alkyl substituted codeinone (23; \(R = \text{Me}\)) and morphinone (23; \(R = \text{H}\)) derivatives have also been investigated.\textsuperscript{19} They, like the 8-substituted derivatives
Scheme 3

(3) \[ \rightarrow \]

(21)

1. \( R_2 CuLi \)
2. 48% HBr

(21) \[ \rightarrow \]

(22)

Scheme 3
(22), lack the conformational rigidity of the thevinols (11). In general the 7-substituted derivatives showed low analgesic activity. A notable exception was the codeinone derivative (24).

![Chemical Structure](image)

(23)  (24)
It is apparent therefore that the most active analgesics are the conformationally rigid orvinols (12). Using thebaine (3) as starting material a wide range of potent analgesics is obtained in only three steps. The flexible 14β-alkylamino and -acylamino derivatives are also readily obtained from thebaine. They have potencies similar to those of the orvinols. By contrast, the 7- and 8-substituted derivatives (22) and (23) obtained by more lengthy chemical sequences are generally less potent analgesics.

1.2 The Opiate Receptor and Natural Peptide Opiates

The analgesic potency of the thevinols (11) and the orvinols (12) was determined using the rat tail flick test. Two other commonly used in vivo assays are the mouse phenylquinone-induced writhing test and the rat tail pressure test. More recently attention has focused on the identification of specific opiate receptors in isolated tissue preparations. The stereospecific binding of opiates to receptors in rat brain and guinea pig ileum was demonstrated around 1973. Only the laevorotary isomers are pharmacologically active, suggesting that receptors bind opiates stereospecifically. The initial attempts to identify the opiate receptor were complicated by the tendency of opiates to bind non-specifically to membranes. This binding is not associated with the receptor and occurs in addition to stereospecific binding. However, specific binding of opiates was demonstrated in the following way. Rat brain homogenates or guinea pig ileum preparations bind naloxone both specifically and non-specifically. The application of a low concentration of (-)-[^3]Hnaloxone favoured specific binding; and washing the tissue preparation thoroughly but
quickly removed any non-specific binding. When the ability of active and inactive isomers of a series of agonists and antagonists to displace stereospecifically-bound \((\text{-}[^3\text{H}]\text{naloxone})\) was then investigated, it was found that only the pharmacologically-active isomers displaced labelled naloxone. Using this technique opiate receptors have since been demonstrated in the central nervous system of all vertebrates.\(^{24-28}\) Receptors are also present in the peripheral nervous system.\(^{27}\) It is the interaction of morphine with receptors in the smooth muscle of the human small intestine which accounts for its ability to cause constipation. The guinea pig ileum is also a rich source of receptors and this tissue is used in an \textit{in vitro} assay to determine the potency of opiates. The system provides a valuable compliment to the \textit{in vivo} assays. In the assay a section of guinea pig ileum or its myenteric plexus-longitudinal muscle is mounted under tension in an organ bath containing physiological solution. The tissue is connected through a transducer to a polygraph which records electrically-stimulated contractions. The effectiveness of an opiate analgesic is measured by its ability to inhibit the contraction. Preparations of mouse and rat vas deferens are similarly used in \textit{in vitro} assays. The correlation between receptor affinity (measured by displacement of \((\text{-}[^3\text{H}]\text{naloxone})\) and \textit{in vivo} analgesia (determined by inhibition of electrically-stimulated contraction) was established in the guinea pig ileum for a series of agonists and antagonists by Snyder.\(^{23}\)

The ability of morphine and related opiates to exert profound physiological effects, by acting at identifiable receptors in the central nervous system implies the existence of endogenous \(^{29}\) opiate-like substances in the body. The existence of such agonists was first described by Hughes and Kosterlitz in 1975.\(^{29}\) Two
related pentapeptides were isolated from pig brain homogenates. They were named enkephalins. Met-enkephalin (25) and Leu-enkephalin (26) were isolated in the ratio 3:1.

\[
\text{H-Tyr-Gly-Gly-Phe-Met-OH} \\
(25)
\]

\[
\text{H-Tyr-Gly-Gly-Phe-Leu-OH} \\
(26)
\]

Enkephalins are inactive when administered orally since they are rapidly hydrolysed by peptidases and do not cross the blood-brain barrier. They show high agonist activity, however, when injected into the brain stem. Both (25) and (26) are derived from a common precursor known as pro-enkephalin.\textsuperscript{30,31} Since this discovery, a further sixteen endogenous opioid peptides have been isolated from brain, pituitary, and adrenal tissues.\textsuperscript{21}

The effects of endogenous opioids and opiate agonists are all naloxone-reversible.\textsuperscript{27} This is one fact which suggests that these structurally diverse compounds all bind to the same opiate receptor. There is however a greater body of evidence to suggest the existence of distinct receptor subtypes. Evidence for receptor heterogeneity is as follows.
1. Certain structurally different opiates showed distinct pharmacological profiles in the chronic spinal dog. This observation by Martin and co-workers was made very shortly after the initial discovery of enkephalins.

2. Certain tissues were found to contain receptors which mediated the actions of certain ligands in preference to others. On this basis, receptors predominating in the guinea pig ileum mediate the actions of morphine and morphine-like structures. These were labelled "μ receptors." Receptors identified in peripheral tissues such as the mouse vas deferens have a high affinity for the naturally occurring enkephalins. These were named "δ receptors." The rabbit vas deferens contains receptors which show highest affinity for ketocyclazocine, [a synthetic opiate of the benzomorphan (δ) type] and dynorphin A. These sites were named "κ receptors." Actions at μ, δ, and κ receptors are naloxone-reversible. However, the amount required to reverse the agonist action of κ-selective opiates at κ receptors is greater than that needed to reverse the action of δ-selective opiates at δ receptors. This in turn is greater than the dose required to reverse the action of μ-selective opiates at μ receptors.

3. Behavioural studies on morphine-dependent monkeys indicate that μ and κ receptors may be structurally more distinct than are μ and δ receptors. This was supplemented by an independent study which suggested the co-existence of μ and δ receptors on the same cell membrane. Other behavioural studies in experimental animals led to the concept of the "κ syndrome" which is characterised by
ataxia and sedation. This is distinct from the analgesic effects mediated at the μ receptors.

4. As mentioned earlier, the major problem associated with continual opiate administration is the development of tolerance. The tolerance effect was exploited in selective tolerance experiments on isolated tissue preparations. For example, the mouse vas deferens is a rich source of δ receptors although there is a smaller population of μ and κ receptors. Prolonged activation of δ receptors with a δ agonist induced tolerance at the δ receptors. The μ and κ receptors showed a normal dose-response curve, indicating that these receptors had not become tolerant to the δ agonist. Similar experiments were conducted in favour of μ and κ receptors and the results provide strong confirmatory evidence for structural differences between receptor types.

5. In related selective protection experiments using irreversible opiate antagonists, Goldstein and co-workers demonstrated the structural dissimilarity between μ and κ receptors.

While all of the above evidence implies receptor heterogeneity, there remain two further possibilities which still account for the different activities shown by different compounds. One explanation is that receptor subtypes are merely interchangeable forms of the same receptor. The other possibility is that the binding sites of receptors are identical but they are associated with different spatially proximate binding regions. Both concepts remain feasible despite the existing evidence for multiple receptors.
There are two current models of receptor structure. The Bentley-Cowan model predates the discovery of endogenous opioids; but it adequately explains the high analgesic activity of the thevinols (11) and orvinols (12). A flat lipophilic binding surface is postulated to accommodate the aromatic A-ring of morphine-related opiates. Closely associated with this is a hydrophilic binding site to fit the 3-hydroxy group of morphines. There is a cavity to accommodate the C-15,16 bridge which is in close proximity to an anionic, amine binding site. Lastly, and most importantly, there is a lipophilic site in the region of the C-ring. It is the chemical modification in this region which leads to the greatest change in agonist activity. This model is compatible with the major groups of opiates: morphinans, benzomorphans, and phenylpiperidines. C-ring substitution will be reviewed in more detail in the Discussion. A newer model was recently proposed by Lee and Smith which is consistent with the binding of opioids. This model proposes two distinct topological sites: a protein enkephalin binding site and a lipid alkaloid binding site.

Despite intensive research efforts, the precise nature of the opiate receptor or receptors remains unknown. It is known that opiates bind to receptors on the membrane of central nervous system neurons and of peripheral neurons. It is also known that guanyl nucleotides are negative modulators of opiate binding in vitro. The recent report that opiates inhibit acetylcholine release at nerve endings is a promising lead. There is strong evidence to show that opiates act at nerve endings to open potassium channels thereby inhibiting the action potential.
These factors alone are insufficient for the complete elucidation of the opiate receptor, the structure of which remains elusive at this stage.

1.3 **Thioaldehydes**

1.3.1 Properties of thioaldehydes and other thiocarbonyl compounds

The chemistry of thiocarbonyl compounds is dominated by their general instability and high reactivity. This is due primarily to limited orbital overlap between the 2p-orbital of carbon and the larger 3p-orbital of sulphur. Thiocarbonyl compounds are influenced to a greater extent by incorporated neighbouring atoms or groups than are carbonyl compounds. For example, the C=S group is stabilised by electron donation, as is the C=O group (though not necessarily to the same extent). Thus, thiono compounds such as dithioesters, thioamides, thiono esters and thioketones are more stable than thioaldehydes. Steric hindrance also stabilises thiocarbonyl compounds by reducing rates of attack at the weak π bond. Thioaldehydes are extremely unstable. Their attempted preparation, until recently, led generally to dimers or polymers. The first stable monomeric thioaldehyde was synthesised by Woodward in 1960. Since then, several other stable monomers have been prepared. Woodward's thioaldehyde (27), which was used in the synthesis of chlorophyll is stabilised by electron donation from the pyrrole nitrogen [see (28)]. Reid and co-workers subsequently synthesised a series of similarly-stabilised heterocyclic thioaldehydes. The indolizine thioaldehyde (29) is a representative example. It was made using a modification of the Vilsmeier-Haak formylation reaction. Several years later,
Thioaldehydes have interesting spectroscopic properties. They show absorbances due to $\pi \rightarrow \pi^*$, $n \rightarrow \sigma^*$ and $n \rightarrow \pi^*$ transitions, though it is only the latter which occurs in the visible region (Table 1) giving the typical pink or purple colours. This transition is found at longer wavelengths than the corresponding carbonyl group due to the lower ionization potential of sulphur 3p electrons relative to oxygen 2p electrons.\(^{52}\)

Thioketones similarly absorb in the visible region due to $n \rightarrow \pi^*$ transition and are characterised by intense colours which vary from yellow-red to deep blue.\(^{52}\) 2,2-Dimethylpropanethial (31) shows an i.r. thiocarbonyl stretching frequency at 1085 cm\(^{-1}\), and tris(trimethylsilyl)ethanethial (32) one at 1120 cm\(^{-1}\). This is within the range observed for aliphatic thioketones.\(^{53,54,55}\) The C=S $\pi$ bond is less polar and the vibration is therefore less intense. Structural identification of thiocarbonyl compounds by infrared spectroscopy is therefore less easy. However, due to the high polarisability of the sulphur atom, vibrations are strong in the Raman spectrum.\(^{53}\) Table 2 shows the chemical shifts for carbon
Japanese workers\textsuperscript{49} reported the first stable thiobenzaldehyde. 2,4,6-Tri-t-butylthiobenzylaldehyde (30) is stabilised by steric hindrance. It is a purple solid which can be stored at room temperature for up to one year. The synthesis of 2,2-dimethylpropanethial (31) was reported in 1983.\textsuperscript{50} The monomer was found to persist in solution for up to 16 h at 20°C. Tris(trimethylsilyl)ethanethial (32) is the first example of an aliphatic thioaldehyde that can be isolated as a monomer.\textsuperscript{51} It is a stable pink, crystalline solid which can be purified by chromatography or crystallisation. It remains stable for up to one week at room temperature.
### Table 1

U.V.-Visible Absorption Bands Arising from

*Thiocarbonyl $n \rightarrow \pi^*$ Transitions in Thioaldehydes

<table>
<thead>
<tr>
<th></th>
<th>$\lambda_{\text{max.}}$ (nm)</th>
<th>Solvent</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 2-2-Dimethylpropanethial (31)</td>
<td>508</td>
<td>CH$_3$CN</td>
<td>50</td>
</tr>
<tr>
<td>2. Tris(trimethylsilyl)ethanethial (32)</td>
<td>518</td>
<td>Hexane</td>
<td>51</td>
</tr>
<tr>
<td>3. 2,4,6-Tri-t-butylthiobenzaldehyde (30)</td>
<td>564</td>
<td>Hexane</td>
<td>49</td>
</tr>
</tbody>
</table>

### Table 2

Chemical Shifts ($\delta$) for Thioformyl Carbon

and Hydrogen in Thioaldehydes

<table>
<thead>
<tr>
<th></th>
<th>$^{13}$C</th>
<th>$^1$H</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 6-Methylpyrrolo[2,1-b]-thiazole-5-thioaldehyde (29)</td>
<td>-</td>
<td>10.32</td>
<td>48</td>
</tr>
<tr>
<td>2. 2,4,6-Tri-t-butylthiobenzaldehyde (30)</td>
<td>250.4</td>
<td>13.02</td>
<td>49</td>
</tr>
<tr>
<td>3. 2,2-Dimethylpropanethial (31)</td>
<td>255.6</td>
<td>11.67</td>
<td>50</td>
</tr>
<tr>
<td>4. Tris(trimethylsilyl)ethanethial (32)</td>
<td>248.2</td>
<td>11.45</td>
<td>51</td>
</tr>
</tbody>
</table>
and hydrogen in thioaldehydes. This summarises the physical properties of thioaldehydes. The remainder of this review is concerned with their synthesis.

1.3.2 Early attempts to synthesise thioaldehydes

Attempts to synthesise monomeric thioaldehydes began last century. These led invariably to the formation of trimers or polymers. Laurent's treatment of benzaldehyde with ammonium sulphide or ammonium bisulphide in 1841 was the first attempt to prepare a thioaldehyde. Although thiobenzaldehyde (PhCH=S) was not obtained, a white powder was isolated in low yield which analysed correctly for \((C_7H_6S)_n\). This implied the formation of transient thiobenzaldehyde. The traditional method of thioaldehyde or thioketone synthesis is thionation of carbonyl compounds. The first step is attack by a nucleophilic sulphur species on electron-deficient sp\(^2\)-carbon bearing a suitable leaving group. Of these, the most widespread approach is the treatment of the corresponding carbonyl compound with acidified hydrogen sulphide (Scheme 4). Baumann first proposed the mechanism outlined in

\[
\begin{align*}
 R^1 R^2 C=O & \xrightleftharpoons{H_2S/H^+} [\ \ \ \ \ ] \xrightarrow{-H_2O} R^1 R^2 C=S \\
 & \quad \quad Dimer, Trimer, Polymer
\end{align*}
\]
Scheme 4. This general route was recently used for the preparation of enethiolisable thiocarbonyl compounds. In addition, a range of stable aliphatic thioketones, alicyclic thioketones, cyclic \( \alpha, \beta \)-unsaturated thioketones and \( \beta \)-thioxoketones were made. Thioaldehydes prepared by this route simply polymerise. Others reasoned that thioaldehydes could be obtained by treating the corresponding aldehydes with different nucleophilic sulphur species. Failure to obtain monomeric thioaldehydes was due not to the method of preparation but to their inherent instability. Thus Vanino obtained polymeric thioformaldehyde, \((CH_2S)_n\), by the reaction of sodium thiosulphate and aqueous formaldehyde. In a similar approach, polymeric thioformaldehyde was obtained by the treatment of di-iodomethane with sodium hydrogen sulphide (Scheme 5). In principle thioaldehydes ought to be obtainable from the

\[
\begin{align*}
\text{CH}_2\text{I} & \quad \xrightarrow{\text{NaHS}} \quad \text{CH}_2\text{SH} \\
\text{I} & \quad \text{SH} \quad \xrightarrow{\text{[CH}_2\text{S] + H}_2\text{S}} \quad \text{Polymer}
\end{align*}
\]
corresponding enethiols by tautomerisation (Scheme 6). Stacey and Harris reported the X-ray-induced radical addition of hydrogen sulphide to mono- and di-substituted acetylenes. Addition to methylacetylene (33) produced a mixture of 1-propene-1-thiol (34), the dithiol (35) and polymer (Scheme 7). The enethiol (34) was

\[
\begin{align*}
\text{R}_1^1 \text{C} &= \text{C} \quad \text{SH} \\
\text{R}_2^2 \\
\end{align*}
\]

\[
\begin{align*}
\text{R}_1^1 \text{H} &\quad \text{C} \quad \text{C} \quad \text{S} \\
\text{R}_2^2 \\
\end{align*}
\]

Scheme 6

\[
\begin{align*}
\text{H}_3\text{C} \quad \text{C} &= \text{C} \quad \text{H} \\
\text{H}_3\text{C} &\quad \text{C} \quad \text{SH} \\
\text{H}_3\text{C} &\quad \text{CH}_2 \quad \text{SH} + \text{Polymer}
\end{align*}
\]

(33) \quad (34) \quad (35)

\[
\begin{align*}
(34) &\quad \times \quad \left[ \begin{array}{c}
\text{H}_3\text{C} \quad \text{CH}_2 \quad \text{C} \\
\text{S} \quad \text{H}
\end{array} \right] \\
\end{align*}
\]

(36)

Scheme 7
isolated as an oil; the infrared spectrum showed only absorptions attributable to the thiol and alkene groups. Tautomerism to propanethial (36) did not occur. The equilibrium is in favour of the enethiol. Strausz et al.\textsuperscript{69} obtained the enethiol (34) in the same way. The proton n.m.r. spectrum of their product showed weak resonances at $\delta 1.0-1.4$ which were tentatively assigned to the trimer of propanethiol (36). Treatment of acetylene (37) with acidified hydrogen sulphide\textsuperscript{70} led only to tri(thioacetaldehyde) (40), showing that although ethanethial (39) was formed it rapidly polymerized to the trimer (40) (Scheme 8). A good preparative route to

\[
\begin{align*}
\text{H-C\equiv C-H} & \xrightarrow{H_2S/H^+} \left[ \text{H}_2\text{C}\equiv\text{C-SH} \right] \xrightarrow{} \text{H}_3\text{C-C=S} \\
(37) & \quad (38) & \quad (39)
\end{align*}
\]

\[
\begin{align*}
(39) & \xrightarrow{} \quad \text{CH}_3
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3 & \quad \text{H}_3\text{C}
\end{align*}
\]

\[
\begin{align*}
(40)
\end{align*}
\]

\textbf{Scheme 8}
thioketones uses β-chloroenones as precursors. However, the route is not useful for the preparation of thioaldehydes. For example, the enethiol (42), obtained from the vinyl chloride (41) (Scheme 9), failed to tautomerise to the hindered thioaldehyde (43).

Reductive methods have also been employed in the attempted synthesis of thioaldehydes. Girard's reduction of carbon disulphide (44) produced 1,3,5-trithian (46). Similarly Hofmann obtained the same product by reduction of ethyl isothiocyanate (45) (Scheme 10). More recently, Mitra obtained tri(thioaldehydes) (49) from the corresponding aldehydes (47) using the enethiol of ethyl acetoacetate under acidic conditions (Scheme 11).

The current phase of thioaldehyde synthesis involves the generation of very reactive species by Thermal, photolytic, and other means. Thioaldehydes of the type...
ZCHS, in which Z is an electron-withdrawing group, have enhanced instability and reactivity. Reactive thioaldehydes have been trapped with dienes to form dihydrothiin derivatives. These are useful in their own right, but are also substrates for ring-growing and ring-contraction reactions, and for the generation of more reactive intermediates. Reactive thioaldehydes also undergo 'ene' reactions with suitable olefins.

1.3.3 Thermal generation of thioaldehydes

Thioacrolein (51) and thiobenzaldehyde (53) were generated by flash thermolysis of allyl sulphides (50) and (52), respectively (Scheme 12). The low-temperature (ca. 77 K) u.v. spectra of (51) and (53) were obtained by deposition on a sodium chloride plate in a cryostat. They showed maxima for the n → π* transition at 580 and 575 nm respectively. These are in the range expected for
Scheme 11
conjugated thialdehydes (cf. saturated thioketones, max. ca. 500 nm), and are in accord with calculated values. Low-temperature monitoring of the infrared spectra showed that thioacrolein (51) decomposed at 77 K, but that thiobenzaldehyde (53) was stable up to 110 K.
The thermolysis of certain alkyl thiosulphinates afford sulphenic acids and thioaldehydes. Although the sulphenic acids were trapped with acetylenes to give α,β-unsaturated sulphoxides, the thioaldehydes were allowed to polymerise. Baldwin and Lopez subsequently employed this reaction in the following way. Thiobenzaldehyde (53), generated by thermolysis of S-benzyl phenylmethanethiosulphinate (54), was trapped with 1,3-dimethylbutadiene

![Chemical Structure](53) ![Chemical Structure](54)

in a Diels-Alder cycloaddition reaction (Scheme 13). The dihydrothiin (56) was obtained in 95% yield. The scheme also shows that the thiosulphinate (54) is regenerated by dehydration of the sulphenic acid (55). When 1,3-dimethylbutadiene was replaced by anthracene, the adduct (57) was obtained in 97% yield. The cycloadduct (57) was subsequently used as a "secondary source" of thiobenzaldehyde. When heated in the presence of 1,3-dimethylbutadiene, the anthracene cycloadduct (57) dissociated and the liberated thiobenzaldehyde was trapped to yield the dihydrothiin (56) (Scheme 14). Thiobenzaldehyde, generated thermally from the thiosulphinate (54), was also shown to undergo an 'ene' reaction with β-pinene (Scheme 15). The isomeric cycloadducts (58) and (59) were obtained in the ratio 2:1.
Scheme 13

Ph\(\text{S}^+\text{S}\text{Ph}\)\(\xrightarrow{\text{toluene, } 100^\circ C, 1\text{h}}\) (53) + \(\text{S}^+\text{Ph}\)OH

(54) (55)

(53) \(\rightarrow\) \[
\begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph}
\end{array}
\]

(56)

\(2 \times (55) \rightarrow (54) + \text{H}_2\text{O}\)

Scheme 13

(57)
Scheme 14

(5.7) \[\text{toluene, } 99°C\] \[\text{sealed tube}\] \[\rightarrow\] (56) + anthracene

Scheme 15

(54) \[\text{toluene, } 99°C, 5h\] \[\rightarrow\] (58) (59)
The thioaldehyde (60) was also generated thermally from the corresponding thiosulphinate. This cyclised in an intramolecular Diels-Alder cycloaddition to give the isomeric thiobicyclononenes (61) and (62) in the ratio 1:1 (Scheme 16).

Scheme 16

1.3.4 Photochemical generation of thioaldehydes

Photochemical cleavage of phenacyl sulphides (63) is a mild, versatile method for generation of thioaldehydes (Scheme 17). The reaction was reported for a range of \( R \) groups although initially no thioaldehyde was generated for \( R=\text{Ph} \). The first reported photolytic cleavage of phenacyl sulphides was in 1966 when ethyl phenacyl sulphide (63; \( R=\text{Me} \)) was irradiated. The thioacetaldehyde (64; \( R=\text{Me} \)) was not trapped and the synthetic potential of thioaldehydes generated in this manner was largely
unrealised. However, Woodward et al.,\(^8^9\) reported the successful trapping of a photochemically-generated thioaldehyde with diphenyldiazomethane. Young\(^9^0\) also generated a thioaldehyde photochemically. This was used as an intermediate in the formation of a possible penicillin precursor. Recently, Vedejs et al.,\(^7^9,8^0,8^7\) have trapped photochemically-generated thioaldehydes with a range of dienes, usually having electron-donating substituents. The use of unsymmetrical dienes permitted a study of the regiochemistry of cycloaddition. For example, generation of the thioaldehydes (64) in the presence of 2-(t-butyl-dimethylsilyloxy)-1,3-butadiene gave two classes of regioisomer, (65) and (66)\(^8^0\) (Scheme 18). The dependence of the ratio of (65) : (66) on the thioformyl substituent, R, is shown in Table 3. When R
### Table 3

The Cycloaddition of Substituted Thioaldehydes (64) with 2-(t-butyldimethylsilyloxy)-1,3-butadiene

<table>
<thead>
<tr>
<th>Thioaldehyde (64)</th>
<th>% Yields of Cycloadducts (65)</th>
<th>(66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R = Ph</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>R = SiMe₃</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>R = (CH₂)₂Ph</td>
<td>23</td>
<td>-</td>
</tr>
<tr>
<td>R = H</td>
<td>67</td>
<td>7</td>
</tr>
<tr>
<td>R = COCH₃</td>
<td>12</td>
<td>43</td>
</tr>
<tr>
<td>R = CN</td>
<td>4</td>
<td>70</td>
</tr>
<tr>
<td>R = SO₂Ph</td>
<td>6</td>
<td>57</td>
</tr>
<tr>
<td>R = COPh</td>
<td>5</td>
<td>59</td>
</tr>
<tr>
<td>R = P(0)Ph₂</td>
<td>-</td>
<td>75</td>
</tr>
</tbody>
</table>
was an alkyl, arylalkyl or other electron-donor group (Table 3, entries 1-3), there was an excess of (65) over (66). Thioformaldehyde (64; R=H) also adds to give an excess of (65). When R was an electron-accepting substituent there was an excess of (66) over (65) (Table 3, entries 5-9). In this case the regioselectivity of cycloaddition is the same as for acceptor-substituted vinyl dienophiles and dithioesters; but opposite to that for acceptor-substituted aldehydes. Representative examples are given in Scheme 19. The yields given in Table 3 (entries 5-9)
show that, in general, photochemically-generated acceptor-substituted thioaldehydes are trapped efficiently. The regioselectivity of addition for donor-substituted thioaldehydes is opposite to that of acceptor-substituted thioaldehydes. Yields of the cycloadducts were also lower; (Table 3, entries 1-3), and are reported to depend to a greater extent on the nature of the diene, the thioformyl substituent, R, and on the reaction conditions.
These differences in regiochemistry and reactivity have been explained in terms of Frontier Molecular Orbital Theory. With thioaldehydes in general, it is the interaction between the diene HOMO and dienophile LUMO (the π* CS orbital of the thioaldehyde) which affords the greatest reduction in transition state energy. Calculation of the atomic orbital coefficients in the HOMO and LUMO led to predictions which are in accord with observed regioselectivity. Trapping of acceptor-substituted thioaldehydes (Table 3, entries 5-9) with 2-(t-butyldimethylsilyloxy)-1,3-butadiene is efficient since the electron-donating t-butyldimethylsilyloxy group raises the HOMO energy. Simultaneously, acceptor substituents on the thioaldehyde dienophile lower the LUMO energy. Acceptor-substituted thioaldehydes have the larger LUMO coefficient on sulphur which is therefore more electrophilic than thioformyl carbon. Cycloaddition therefore takes place between the sulphur atom and the electron-rich C-1 of the diene to form the dihydrothiin (66).

In the cycloaddition reaction of donor-substituted thioaldehydes (Table 3, entries 1-3), with 2-(t-butyldimethylsilyloxy)-1,3-butadiene, the larger LUMO coefficient is on the thioformyl carbon which is therefore more electrophilic than sulphur. This reversal of thioaldehyde LUMO polarisation accounts for the observed reversal in regioselectivity; since the thioformyl carbon forms a new bond with C-1 of the diene to give the dihydrothiin (65). However, donor alkyl substituents raise the energy of the thioaldehyde LUMO thereby raising the HOMO-LUMO energy gap in the transition state. This is reflected in an overall reduction in the efficiency of trapping.
Scheme 20
As an illustration of the synthetic utility of dihydrothiins, the ring-expanded sulphides (68) and (69) were obtained from the dihydrothiin (67) as shown in Scheme 20. Less reactive thio-carbonyl compounds can be trapped efficiently with the reactive dipolar silyl nitronate (70). For example, 2,2-dimethylpropanethial (31) reacts with (70) to yield the heterocycle (71) (Scheme 21). Similarly, photochemically-generated thioketones (73) were trapped with (70). Fluoride ion-induced cleavage of the resulting intermediate (74) yielded the carbonyl compound (75) corresponding to the original thioketone (Scheme 22). The
Scheme 22
sequence was used principally for the oxidative removal of sulphur from thioketone macrocycles. Although the intermediate (74) could be formed from several different thioaldehydes, only two cases of oxidative desulphurisation to the corresponding aldehydes were reported (Scheme 23).

\[
\begin{align*}
\text{[R-CH=S]} & \quad \xrightarrow{} \quad \text{(70)} \\
\text{(64)} & \\
R = & \text{CH}_2\text{CH}_2\text{Ph} \\
& \text{CH(OAc)}\text{Ph}
\end{align*}
\]

Scheme 23

1.3.5 Generation of thioaldehydes by other methods

There are several routes to thioaldehydes involving ionic elimination reactions. In general, they allow the generation of a greater variety of thioaldehydes than the methods just described. Furthermore, the high reactivity of thioaldehydes required that new mild preparative routes be developed. Some of these were developed from thioketone syntheses, but others were developed specifically with thioaldehydes in mind.

In a recent report, \(\alpha\)-oxodithioesters (79) generated from 1,3-dithiolanium-derived sulphur ylides (78) at room temperature, were trapped with 2,3-dimethylbutadiene to yield substituted dihydrothiins (80) (Scheme 24). This cycloreversion route is
Scheme 24
interesting, especially as prior to this there was little in the literature on α-oxodithioesters. Prior to this, however, Vyas and Hay\textsuperscript{92} described the Diels-Alder cycloaddition reactions of methyl cyanodithioformate (81), which showed that electron-acceptor-substituted dithioesters do participate in cycloaddition reactions.

\[
\begin{array}{c}
\text{Me-S} \\
\text{C} \\
\text{C≡N}
\end{array}
\]

(81)

Schaümann\textsuperscript{95} later adapted the above route (Scheme 24) to the generation of thioaldehydes. Cycloreversion proceeded as shown in Scheme 24 because the C-2 proton is the most acidic. Schaümann reasoned that acceptor substituents at C-4 and C-5 of the dithiolanium salt would enhance the acidity of the hydrogen at C-5 thereby leading to a different cycloreversion. Thus, the dithiolanium salts (82) were prepared by thioacetalisation of aldehydes using dimercaptosuccinic acid, followed by esterification and S-methylation. In the presence of lithium di-isopropylamide, (82) was selectively deprotonated at C-5 to give ylide (83). This generated the thioaldehyde (64) by spontaneous cycloreversion (Scheme 25). The 1,4,2-oxathiazoles (84) were obtained by trapping the thioaldehydes (64) with mesitonitrile oxide.

2,2-Dimethylpropanethial (31) was similarly trapped with benzylideneaniline N-oxide to yield the heterocycle (85) which was then used as an auxiliary thioaldehyde precursor in the following way. Heating (85) in toluene, in the presence of 2,3-dimethylbutadiene, regenerated 2,2-dimethylpropanethial.
Scheme 25

R = H, Me, Bu^†, Ph, or CH=CH_2
(31), which was trapped in a [4+2]-cycloaddition reaction to yield the dihydrothiin (86) (Scheme 26). In this [3+2]-cyclodimerization

\[
\text{(83), } R=\text{But} \rightarrow (31) \quad \begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{Ph} \\
\text{O} \\
\text{Bu}^t \quad \text{S} \quad \text{N} \\
\text{Ph} \\
\end{array}
\]

Scheme 26

(85)

\[
\text{(85) } \Delta, \text{toluene} \rightarrow (31) 
\text{Bu}^t \quad \text{But} \quad \text{S} \\
\]

The successful generation and trapping of thioketones from α-oxo-methylene bisxanthates (87) by a German group inspired Vedejs and his co-workers to attempt the analogous generation and
trapping of thioaldehydes. In this way, the previously unknown cyanomethanethial (89) was generated from dibromoacetonitrile in the presence of ethyl xanthate (Scheme 27). Cyanomethanethial (89) was trapped with 2-ethoxybutadiene to afford the cycloadduct (90) in low yield. The regioselectivity is in accord with expectations. This route, involving the attack by nucleophilic sulphur on gem-dihalides is also of historical interest. It is not however preparatively useful in the generation of thioaldehydes.

The most versatile route for generation of thioaldehydes is base-mediated 1,2-elimination of HX from the general class of precursor, Z-CH$_2$-S-X in which X is a suitable leaving group and Z is an acceptor substituent. A large number of such precursors, variable in X and Z have recently been studied by Kirby and
Thioaldehydes were trapped with a variety of conjugated dienes. Several of the new resultant cycloadducts were used as auxiliary sources of the transient thioaldehydes.

Thioaldehydes can be generated from sulphenyl chlorides in the presence of base by 1,2-elimination of hydrogen chloride. For example, Armitage and Clark treated methanesulphenyl chloride with secondary amines. As well as the expected sulphenamides, by-products apparently arising from condensation of the amines with thioformaldehyde were obtained. Thioformaldehyde was thought to have arisen by 1,2-elimination of hydrogen chloride from methanesulphenyl chloride. Phenylmethanesulphenyl chloride (91) was shown by McDougall to undergo 1,2-elimination of hydrogen chloride in the presence of triethylamine. The thiobenzaldehyde (53) which was generated was trapped by the electron-rich diene system of thebaine (3) to form the new cycloadduct (92) (Scheme 28). Ethoxycarbonyl

\[
\begin{align*}
\text{Ph-CH}_2\text{-S-Cl} & \xrightarrow{\text{Et}_3\text{N}} \text{[PhCH= S]} \\
(91) & \quad (53)
\end{align*}
\]

\[
\begin{align*}
\text{(3)} & \quad (92)
\end{align*}
\]
methanesulphenyl chloride (93) underwent 1,2-elimination of hydrogen chloride in the presence of triethylamine to generate ethyl thioacetate (94). This was trapped by a number of conjugated dienes in the comprehensive study by Kirby and co-workers (Scheme 29). [The reaction with thebaine (3) is described later]. The reactions were carried out at room temperature. In the course of this work control experiments were carried out which proved beyond reasonable doubt that ethyl thioacetate was generated by a 1,2-elimination process. The high yield of the dihydrothiin (95) (90% by proton n.m.r., 65% after purification) testifies to the efficient generation and trapping of ethyl thioacetate. Low yields of the cycloadducts (96), (99), and (100) were attributed to competitive 1,2-addition of the sulphenyl chloride (93) to 1,3-cyclohexadiene and to cyclopentadiene. The low yields with anthracene and dimethylanthracene reflect inefficient trapping of the thioaldehyde. Good yields with anthracene have since been obtained using an excess of this trapping agent.

Earlier, Harpp and Back reported that treatment of \( \text{N-\((\text{methoxycarbonylthio})\)phthalimide (101)} \) with two equivalents of benzylamine led not to the expected sulphenamides, but to a mixture of products. One of the components was identified as thioxoamide (103). It was proposed that methyl thioxoacetate (102), generated by 1,2-elimination of phthalimide from (101), was an intermediate in the reaction which led ultimately to the formation of the thioxoamide (103) (Scheme 30). The thiophthalimides were examined by Kirby and Lochead as sources of thioaldehydes. They were found to be excellent thioaldehyde precursors. For example, the anthracene cycloadduct (97) was obtained in 53% yield.
Scheme 29
Scheme 30

Scheme 30 compares with 37% for (97) obtained by direct elimination from sulphenyl chloride (93). Furthermore, the cyclopentadiene adducts (99) and (100) were obtained virtually quantitatively from N-(ethoxycarbonylmethylthio)phthalimide (104) in the presence of triethylamine and cyclopentadiene (Scheme 31). The endo-adduct (99) and the exo-adduct (100) were obtained in the ratio 7:3. They are distinguishable by their proton n.m.r. spectra as follows. In the endo-adduct (99) 3-H resonates at δ 4.42. The signal shows vicinal coupling (J 4.2 Hz) with 4-H. In the exo-adduct (100) 3-H gives a singlet at δ 3.30. Its upfield position is due to shielding by the C-5/C-6 double bond. The dihedral angle (Ø) between 3-H and 4-H is almost 90°. Consequently 3-H appears as a broadened singlet. Heating the kinetically-determined mixture of (99) and (100), or each isomer separately, in toluene, yielded the
same equilibrium mixture of (99) (70%) and (100) (30%). It was thought the mixture of (99) and (100) might act as a source of ethyl thiooxoacetate by thermal dissociation. The known dihydrothiin (95) was obtained when the mixture of (99) and (100) was heated with 2,3-dimethylbutadiene, thus illustrating the role of the cycloadducts as an auxiliary source of ethyl thiooxoacetate. Also, the cycloadduct (106) was obtained in 48% yield upon heating (99) and (100) in xylene with 1,4-diphenylbutadiene (105) (Scheme 32). This compares with a yield of only 9% for (106) obtained directly from the thiophthalimide (104). The precursors (101) and (104) have the further advantage of being stable crystalline solids. Ethoxycarbonylmethanesulphenyl chloride (93), by contrast, is unstable and must be prepared and used without purification.
A new, alternative class of thioaldehyde precursors was found in the thiosulphonates (107). With Z a suitable electron-withdrawing substituent and the toluene-p-sulphinate anion as a leaving group, these precursors were expected to readily undergo base-mediated elimination to generate thioaldehydes.\textsuperscript{101} Indeed this was the first stage in an unexpected rearrangement which led
\[
\text{Scheme 33}
\]
ultimately to the disulphides \((\text{111})\) (Scheme 33). The disulphide \((\text{111})\) is also a thioaldehyde precursor since it undergoes 1,2-elimination of toluene-\(p\)-sulphinate ion to yield 2 equivalents of the thioaldehyde \((\text{108})\). The thiosulphonates \((\text{107})\) were prepared by alkylation of sodium toluene-\(p\)-thiosulphonate.\(^\text{106}\) Improved yields are obtained if the anion is first transferred to an anion-exchange resin.\(^\text{101,107}\)

In a similar manner sodium thiosulphate \(S\)-esters \((\text{112})\) are prepared by the alkylation of aqueous sodium thiosulphate.\(^\text{108,109}\) (Scheme 34). This class of compounds, known as Bunte salts after

\[
\text{Na}_2\text{S}_2\text{O}_3 + \text{Z-CH}_2\text{-X} \rightarrow \text{Z-CH}_2\text{S-S}^-\text{O}^+ \text{Na} + \text{NaX}
\]

\((\text{112})\)
their nineteenth century originator, was extensively studied in the early part of this century. More recently, Milligan and Swan obtained a thioxo-amide from the reaction of a carbamoyl Bunte salt with a secondary amine. In this sequence, as in that reported by Harpp and Black, the first step was thought to be generation of the thioaldehyde by 1,2-elimination. Two subsequent reports, which described generation of thiolketones from Bunte salts, supported the idea that thioaldehydes could be similarly generated. Accordingly, Kirby and co-workers found that thioaldehydes could be generated from Bunte salts by 1,2-elimination of sulphite dianion. The thioaldehydes were trapped in cycloaddition reactions with 2,3-dimethylbutadiene and cyclopentadiene under mild conditions (Scheme 35). High yields of cycloadducts were obtained by carrying out the elimination in the presence of calcium chloride dihydrate, since this removes the sulphite dianion as its sparingly soluble calcium salt. Otherwise, low yields of cycloadducts were obtained together with water-soluble by-products presumed to arise from attack by sulphite on the thioaldehyde (cf Scheme 33). A mixture of endo- and exo-cyclopentadiene adducts was obtained. In each case the endo-isomer predominated. When the Bunte salt (112; R=Ph) was treated with triethylamine and calcium chloride in the presence of cyclopentadiene, no cycloadducts were obtained, although the p-nitrophenyl derivative gave high yields. This illustrates the requirement for an electron-withdrawing, Z, substituent.

The trapping of thioaldehydes generated by another 1,2-elimination process was recently reported. In the presence of fluoride ion, α-silyldisulphides (116) underwent 1,2-elimination
\[
\begin{align*}
\text{Z-CH}_2\text{S-S-O Na} & \xrightarrow{\text{Et}_3\text{N, CaCl}_2\cdot2\text{H}_2\text{O}} [\text{ZCH=S} - \text{SO}_3^- + \text{Na}^+ + \text{Et}_3\text{NH}^+ \\
(112) & \quad (64)
\end{align*}
\]

Z = CN
EtO_2C
PhNHCO
PhCO
O_2N\text{-}[\text{aryl}]\text{-CO}

Scheme 35
of the arylthiolate anion to form thioaldehydes. Trapping with cyclopentadiene yielded the adducts (117) and (118) (Scheme 36). The endo- isomer (117) predominated in each case. The stability of the disulphide (116) and the efficiency of the elimination reaction was controlled by the nature of the aromatic X-substituent. Electron-acceptor substituents stabilise the disulphide (116) and enhance the rate of elimination by stabilising the aryl thiolate anion leaving group. Disulphides (116) with no aromatic substituent, X, are less reactive and required elevated temperatures to effect elimination. Excessive electron withdrawal caused destabilisation of the disulphide. Thus 2,4,6-trichlorodisulphides (116) were too unstable to be useful precursors. Those which gave the highest yields of cycloadducts had an aromatic 2-nitro or 4-chloro substituent. Reactivity therefore is controlled at a position in the precursor which is remote from the potential thioformyl group. This method, like the cycloreversion method of Schaümann,95 (Scheme 25), permits the generation of simple alkyl thioaldehydes which are less accessible by the reactions involving 1,2-elimination of HX rather than $R_3SiX$. The latter methods however have the advantage that the precursors are generally prepared more easily, especially those prepared directly from sulphur-free materials, ZCH$_2$Br.
SiMe₂Ph

\[ R \text{S-S-S-} \text{Ph} \xrightarrow{F^-} [RCH=\text{S}] + \text{PhS}^- \]

(116)  \hspace{5cm} (64)

\[ \text{R} = \text{Me}, \text{Et}, \text{Pr}^n, \text{Pr}^i, \text{Bu}^n, \text{CH}_2\text{Ph} \]

\[ \text{Scheme 36} \]
2. DISCUSSION

2.1 Cycloadducts of Thebaine and Thioaldehydes

2.1.1 Reaction of thebaine with ethyl thioxoacetate

Kirby\textsuperscript{84,99} and co-workers reported the Diels-Alder reaction of thebaine (3) with ethyl thioxoacetate (EtO-CO-CH=S). The latter was generated by 1,2-elimination of hydrogen chloride from ethoxycarbonylmethanesulphenyl chloride (93) at room temperature as described earlier. The resultant cycloadducts (119) and (120) were obtained in high yield although (119) was the major product, there being only a trace of the regioisomer (120) (Scheme 37). This

\[ \text{Et}_3\text{N}, \]
\[ \text{Thebaine} \rightarrow \]

(93)

![Scheme 37](image)

(119)  
(120)

is the first published example of a thebaine cycloadduct possessing a sulphur atom within the newly defined morphine skeleton. Also
reported was the conversion of (119) to (120) by thermal
dissociation and subsequent recombination of thebaine and ethyl
thioxyacetate. As in the case of the cyclopentadiene adducts (99)
and (100), the known dihydrothiin (95) was obtained on heating (119)
in toluene in the presence of 1,3-dimethylbutadiene. It was
concluded that the formation of (119) occurs under kinetic control
and that (120) is the thermodynamically more stable cycloadduct.

When the anthracene cycloadduct (97) was heated in toluene at
100°C for 8 h with an equimolar amount of thebaine, thermal transfer
of ethyl thioxyacetate took place and the thermodynamically more
stable cycloadduct (120) was obtained in 78% yield. The adduct
(120) was also obtained in 86% yield from the 9,10-dimethyl-
anthracene cycloadduct (98) at 100°C after 8 h. Structures (119)
and (120) were assigned by comparison of their proton n.m.r. spectra
with that of (122b) the known6,116 carbon-analogue of (119).

Theoretically, ethyl thioxyacetate could add to the 6,8-diene
system of thebaine to give 8 possible isomers; but a combination of
steric and electronic factors control the cycloaddition in the
following way. Approach by ethyl thioxyacetate takes place from
the exposed β-face of the diene system, the α-face being too
hindered. Electronic effects in the diene and the dienophile then
control the regiochemistry of addition. The sulphur atom of ethyl
thioxyacetate is rendered electrophilic by the carbonyl group.
This, combined with an electron-rich 14-position in the diene system
results in the major regioisomer with sulphur attached at C-14 as in
(119). The configuration at C-7 in (119) is such that the ester
function projects down towards the 18,19-etheno bridge, in accord
with the Diels-Alder endo rule. In the minor adduct (120) the C-8
configuration is also in agreement with the \textit{endo} rule, although the corresponding \textit{exo} adduct would in any case be highly hindered. The regioselectivity of addition of the thioaldehydes is the same as that observed in the addition of acceptor substituted all-carbon dienophiles to thebaine or thebaine analogues. In the addition of substituted alkenes to thebaine the major isomer obtained in each case was the 7α-substituted adduct (121) (Scheme 38).

The C-7 epimers (121) and (122) are distinguishable by their proton n.m.r. spectra. The chemical shift of 5β-H is particularly informative. The signal for 5-H in the 7α-epimers (121; a-f) appears at 6 4.57 ± 0.05. That in the 7β-epimers (122; a-f) is 0.5 ppm downfield at 5.07 ± 0.12. Initially, the downfield shift was attributed to the anisotropic effect of the electron withdrawing 7β-substituent. For example in (122f) the cyano group deshields 5β-H. However, 5β-H in the 7β-tertiary alcohol [122; X = C(OH)Me₂] resonated further downfield than in (122b). The effect is therefore not due solely to anisotropy. The preferred explanation is that steric compression by 7β-substituents causes a downfield shift of 5β-H in the 7β-epimers (122; a-f). This view was supported by independent n.m.r. studies on B/C \textit{cis}-fused octahydrophenanthrenes.

From the reaction of methyl vinyl ketone (MeCO.CH=CH₂) with thebaine (3), Bentley obtained the 7α-ketone (121a) (later named thevinone) in 93% yield. There was only a trace of the epimeric 7β-ketone (122a). In the analogous reaction between thebaine and ethyl acrylate, the major product was the 7α-ester (121b); less than 2% of the epimeric 7β-ester (122b) was formed. There was no evidence for the formation in either of these reactions of the
Thebaine, $R = \text{Me}$

<table>
<thead>
<tr>
<th>$R$</th>
<th>$X$</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>COCH$_3$</td>
<td>6</td>
</tr>
<tr>
<td>Me</td>
<td>EtO$_2$C</td>
<td>6</td>
</tr>
<tr>
<td>Me</td>
<td>COPh</td>
<td>117</td>
</tr>
<tr>
<td>CHO</td>
<td>NO$_2$</td>
<td>118</td>
</tr>
<tr>
<td>Me</td>
<td>CHO</td>
<td>119</td>
</tr>
<tr>
<td>Me</td>
<td>CN</td>
<td>116</td>
</tr>
</tbody>
</table>

Scheme 38
regioisomeric adducts in which the X substituents are attached to C-8. The fact that a small amount of 8α-ester \((120)\) was formed in the reaction of ethyl thioxoacetate with thebaine is attributable to the higher reactivity and therefore lower selectivity shown by ethyl thioxoacetate compared with ethyl acrylate. Bentley compared models of the 7α-substituted adducts \((121); \ a, b, e, \text{ and } f\) with their 7β-epimers and concluded that they were of comparable stability.

The last two observations suggest that, in the reaction of thebaine with ethyl thioxoacetate, some 7β-ester \((123)\) ought to be obtained. It was therefore decided to re-examine this reaction. Since thioaldehydes are conveniently generated\(^{102}\) on a large preparative scale from Bunte salts \((112)\) (Scheme 35) it was decided to develop a route to the required cycloadducts using the Bunte salt \((124)\) as a precursor of ethyl thioxoacetate. The Bunte salt

![Chemical Structure](image-url)
was prepared by the literature method\textsuperscript{121} (Scheme 34). It is known\textsuperscript{102} that elimination of sulphite dianion from Bunte salts is faster in water or hydroxylic solvents but that the yields of cycloadducts are low. The preparation of cycloadducts (119) and (120) was therefore studied to find the best compromise between reaction time and yield. In the exploratory reactions, thebaine was treated with 1.1 equivalents each of Bunte salt (124), calcium chloride, and triethylamine at room temperature. In one experiment the mixture was heated under reflux. The total reaction mixtures, after removal of calcium sulphite by filtration, were examined by \textsuperscript{1}H n.m.r. spectroscopy. The ratio of the cycloadduct (119) to residual thebaine (3) (present as its hydrochloride) was determined from the intensities of the corresponding signals, $\delta$ 4.57 and 5.20 respectively, for 5-H. When methanol was used as a solvent the reaction mixture was found to contain large amounts of the methyl ester corresponding to (119). This was presumably formed by base-catalysed transesterification. The results are summarised in Table 4. The best results

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
Experiment & Solvent & Reaction time (h) & Fraction (119)/(3) \\
\hline
1. & MeOH & 52 & 0.48 \\
2. & MeOH & 160 & 0.56 \\
3. & EtOH & 50 & 0.66 \\
4. & EtOH-C\textsubscript{6}H\textsubscript{6} (1:1) & 160 & 0.77 \\
5. & EtOH-C\textsubscript{6}H\textsubscript{6} (1:1) & 50 & 0.46 \\
6. & EtOH-C\textsubscript{6}H\textsubscript{6} (1:1) & 2 & 0.60\textsuperscript{a} \\
7. & EtOH-C\textsubscript{6}H\textsubscript{6} (1:1) & 160 & 0.83 \\
\hline
\end{tabular}
\caption{}
\end{table}

\textsuperscript{a} heated under reflux
were obtained with a long reaction time at room temperature in ethanol-benzene (1:1). These conditions were therefore adopted for the following larger scale preparation. Thebaine was treated with the Bunte salt (124) and triethylamine, in ethanol-benzene (1:1) in the presence of calcium chloride at room temperature for 160 h. The crude reaction mixture was shown by $^1$H n.m.r. spectroscopy to contain the cycloadduct (119) and thebaine in the ratio 0.81:1, in accord with preliminary experiment 7 in Table 4. However, weak signals for two other products were seen. One was the known cycloadduct (120). The other was later identified as the 7β-ester (123). Chromatography of the mixture on silica gave the cycloadducts (119) (73%), (120) (4%), and (123) (5%). The new product was assigned the constitution and stereochemistry (123) on the basis of its microanalysis, mass spectrum, and $^1$H and $^{13}$C n.m.r. spectra. In particular, $6$-C gave a signal, $\delta$ 80.7, similar in chemical shift to that of the adduct (119), $\delta$ 80.8, and substantially upfield from that of the adduct (120), $\delta$ 88.8. This shows that 7-C rather than sulphur is attached to 6-C. Moreover $15_{\text{ax}}$-H in (123) was even more deshielded, $\delta$ 3.25, than the corresponding proton, $\delta$ 2.74, in (119), by the 7β-ethoxycarbonyl group. The signal for 5-H in (123), $\delta$ 5.55, appeared further downfield than the corresponding signals for (119), $\delta$ 4.57, and (120), $\delta$ 4.98. This shift is even greater than that observed for the epimers (121) and (122). The infrared spectrum (KBr) of the new cycloadduct (123) showed a carbonyl stretching band at 1730 cm$^{-1}$. Those for the known cycloadducts (119) and (120) were at 1740 and 1720 cm$^{-1}$ respectively.
It was conceivable that the new cycloadduct (123) had been formed from the major adduct (119) by base-catalysed epimerisation during the extended, 160 h, reaction time. Furthermore the other minor product (120) also might have been formed by thermal dissociation and recombination from the major adduct (119). To test these possibilities, the adduct (119) was treated with triethylamine, the Bunte salt (124) and calcium chloride, under the standard reaction conditions for 160 h. The reaction mixture, however, contained no detectable (t.l.c. and $^1$H n.m.r. control) amounts of the other adducts. It appears therefore that ethyl thiooxoacetate adds to thebaine to give all three adducts (119), (120), and (123) directly in the approximate ratio 74:5:4.

The analogous reaction between thebaine and methyl thiooxyacetate, generated from the Bunte salt (125), yielded the cycloadducts (126) (64%), (127) (4%), and (128) (6%). These previously

\[
\text{MeO-C-CH}_2\text{-S-SO}_3\text{Na}^+ \\
(125)
\]

\[
\text{MeO-C-CH}_2\text{-S-SO}_3\text{Na}^+ \\
(126)
\]
unknown cycloadducts gave accurate masses and elemental analyses consistent with their molecular formulae. The signal for 5β-H in the 7α-ester (126) appeared at δ 4.54. That in the 7β-ester (127) was downfield at δ 5.57 and that in the isomer (128) was at δ 4.95. The infrared spectra (KBr) of (126), (127), and (128) showed sharp carbonyl stretching bands at 1750, 1735, and 1738 cm⁻¹, respectively.

2.1.2 Base-catalysed epimerisation of thebaine cycloadducts

Bentley treated thevinone (121a) with potassium t-butoxide in t-butanol with the aim of forming an equilibrium mixture of the epimeric ketones (121a) and (122a). Instead thevinone was found to undergo the rearrangement outlined in Scheme 39. Removal of the 7β-proton of (121a) occurs to form a stabilised C-7 carbanion (129).
Scheme 39
This displaces the 4,5-oxide bridge by attack at C-5 to form the cyclopropane derivative (130), which suffers attack by the phenoxide ion to form the acetal (131). Similarly, the nitrile (121f) formed the analogous acetal under the same conditions. However, base treatment of the ester (121b), the cycloadduct of thebaine and ethyl acrylate, yielded the cyclopropane derivative (132). The electron-acceptor ability of the 7α-ethoxycarbonyl group was considered insufficient to effect conversion to the acetal analogous to (131).

Bladon subsequently attempted a similar base catalysed rearrangement of the sulphur-containing cycloadduct (119). Treatment of (119) with potassium t-butoxide in t-butyl alcohol at room temperature led to a mixture of products. The results were inconclusive, and it was therefore decided to re-investigate the attempted rearrangement. When (119) was treated with one equivalent of potassium t-butoxide in dry t-butyl alcohol at room temperature a mixture was obtained. The 1H n.m.r. spectrum of the mixture indicated the absence of starting material. It was decided to reduce the concentration of potassium t-butoxide.
ester (119) was treated with one equivalent of potassium t-butoxide in a greater volume of t-butyl alcohol, the $^1$H n.m.r. spectrum of the crude reaction mixture showed that the $\gamma$-ester (119) and the $\gamma\beta$-ester (123) were present in the ratio 8:2. The two esters were then separated chromatographically and the identity of each was confirmed by their melting points and infrared and $^1$H n.m.r. spectra. The course of the epimerisation was monitored by t.l.c. and, although the reaction time was 30 min, the t.l.c. indicated that epimerisation was complete after less than 1 min. To confirm that epimerisation had occurred, and that an equilibrium is established between (119) and (123) in the presence of base, the pure sample of (123) obtained from the initial epimerisation was again treated with one equivalent of potassium t-butoxide. The $^1$H n.m.r. spectra showed the esters (119) and (123) again to be present in the ratio 8:2.

We conclude that the $\gamma$-ester (119) is deprotonated to form a carbanion at C-7, additionally stabilised by the adjacent sulphur atom. Reprotonation occurs more rapidly, to give either the ester (119) or (123), than attack by the carbanion at C-5. Presumably, under more forcing conditions rearrangement does occur, but this possibility was not investigated further.

2.1.3 Thermal isomerisation of thebaine cycloadducts

A further investigation of the thermal isomerisation of (119) and (120) was undertaken for the following reasons. Since the $\gamma\beta$-ester (123) was formed at room temperature we expected that it should appear as an intermediate during the thermal isomerisation of (119) to (120). A transient intermediate had earlier been
observed by t.l.c. but this was not investigated. When the adduct (119) was heated under reflux in toluene for 30 min, t.l.c. examination of the mixture showed approximately equal amounts of the adducts (119) and (123) to be present. As expected both (119) and (123) had disappeared after 8 h but, unexpectedly, the adduct (120) was accompanied, as judged by $^1$H n.m.r. spectroscopy, by a new compound or mixture of compounds. This compound was later identified as the acetal (134). It could not be separated from its isomer (120) by the t.l.c. on silica plates, but separation was achieved on alumina plates. The acetal (134) could not be crystallised. The corresponding methyl ester (135), which was isolated from the thermal isomerisation of the adduct (126), also did not crystallise. The structure (134) was assigned on the basis of the $^1$H and $^{13}$C n.m.r. and infrared spectra, and by hydrolysis to the corresponding ketone (136). The $^1$H n.m.r. spectrum of (120)
showed a signal at δ 4.98 for 5-H, whereas the corresponding signal for the acetal (134) appeared at δ 3.49. Also, the 13C n.m.r. spectrum of (120) showed a signal at δ 88.8 for 6-C, whereas the corresponding signal for (134) appeared at δ 106.8. The latter value is characteristic of an acetal carbon. The mass spectrum of (134) showed a molecular ion peak at m/z 429 and a peak at m/z 310 (M-119) corresponding to the loss of C4H8O2S, whereas the cycloadducts (119) and (120) fragment readily with loss of C4H6O2S, presumably by a retro Diels-Alder process. When the acetal (134) was heated in 2N hydrochloric acid for 10 min, hydrolysis took place cleanly to yield the corresponding ketone (136) which was obtained as a colourless crystalline solid, m.p. 173-174°C. Elemental analyses were consistent with the molecular formula and the mass spectrum showed a molecular ion, m/z 415, having the appropriate accurate mass for C22H29NO5S. The 1H n.m.r. spectrum showed an AB quartet, δ 5.92 and 6.76 (J 10 Hz) arising from the enone protons 7- and 8- H, respectively. The signal for 7-H showed further splitting (J 1.7 Hz) arising from 'W coupling' with 5-H. A signal at δ 5.85 disappeared upon exchange with D2O and was assigned to the phenolic proton. The presence of a ketonic carbonyl group was
confirmed by a signal at $\delta 194.2$ in the $^{13}$C n.m.r. spectrum of (136). The infrared spectrum of (136), in tetrachloromethane, showed a sharp band at $3530 \text{ cm}^{-1}$ characteristic of a hydroxy group, and a strong band at $1690 \text{ cm}^{-1}$, characteristic of an enone.

Thermal isomerisation of the cycloadduct (120) to give the rearranged acetal (134) was studied as follows. Table 5 shows the relative amounts of (120) and (134) after heating (119) and (120) in refluxing toluene. The ratio of (120):(134) remained essentially constant (at ca. 2:8) after 250 h, suggesting that an equilibrium mixture had been obtained. To verify this, a sample of (134), separated from the mixture by chromatography on alumina, was heated in refluxing toluene for 100 h. The $^1$H n.m.r. spectrum of the resulting mixture showed that the isomers (120) and (134) were again present in the ratio 2:8. A possible mechanism for the reversible rearrangement (120) $\rightleftharpoons$ (134) involves a dipolar intermediate (133) (Scheme 40). To test this possibility, the thermal isomerisation was carried out in solvents of increasing polarity, namely xylene, chlorobenzene, o-dichlorobenzene and nitrobenzene. Simple aromatic solvents were used throughout so that a change of mechanism was unlikely to occur with a change of solvent. All reactions were carried out at 132°C, the boiling point of chlorobenzene, and the ratios of (134):(120) were determined by $^1$H n.m.r. spectroscopy. Measurements were carried out in pairs (Table 6), samples of (120) being heated together in the vapour of refluxing chlorobenzene for times selected to effect incomplete equilibrium. The data indicate that the isomerisation was faster in chlorobenzene than xylene, in o-dichlorobenzene than chlorobenzene, and in nitrobenzene than o-dichlorobenzene. That is, the rate of isomerisation increased
Table 5

Isomerisation of the cycloadducts (119) and (120) in refluxing toluene

<table>
<thead>
<tr>
<th>Reflux Time (h)</th>
<th>Starting Adduct</th>
<th>Products (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(119)</td>
<td>(120)</td>
</tr>
<tr>
<td>8</td>
<td>(119)</td>
<td>90</td>
</tr>
<tr>
<td>20</td>
<td>(119)</td>
<td>64</td>
</tr>
<tr>
<td>72</td>
<td>(119)</td>
<td>26</td>
</tr>
<tr>
<td>160</td>
<td>(119)</td>
<td>19</td>
</tr>
<tr>
<td>250</td>
<td>(119)</td>
<td>20</td>
</tr>
<tr>
<td>100</td>
<td>(120)</td>
<td>21</td>
</tr>
</tbody>
</table>

(120) \rightleftharpoons (134)

Scheme 40
Table 6

The effect of solvent polarity on the rate of isomerisation of (120) into (134) at 132°C

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Dielectric constant</th>
<th>Time (h)</th>
<th>% (120) remaining</th>
<th>% (134) at equilibrium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xylene</td>
<td>2.47</td>
<td>) 4</td>
<td>43</td>
<td>26</td>
</tr>
<tr>
<td>Chlorobenzene</td>
<td>5.62</td>
<td>) 2</td>
<td>29</td>
<td>22</td>
</tr>
<tr>
<td>Chlorobenzene</td>
<td>5.62</td>
<td>) 2</td>
<td>67</td>
<td>22</td>
</tr>
<tr>
<td>o-Dichlorobenzene</td>
<td>9.93</td>
<td>) 1.5</td>
<td>34</td>
<td>24</td>
</tr>
<tr>
<td>o-Dichlorobenzene</td>
<td>9.93</td>
<td>) 1.5</td>
<td>52</td>
<td>24</td>
</tr>
<tr>
<td>Nitrobenzene</td>
<td>34.82</td>
<td>) 1.5</td>
<td>40</td>
<td>-</td>
</tr>
</tbody>
</table>

steadily with increasing solvent polarity. This is consistent with the formation of a dipolar intermediate, although the effects were not very large. For preparative purposes, chlorobenzene was found to be a convenient solvent since the isomerisation was faster than in xylene and the product was cleaner. o-Dichlorobenzene was less convenient because of its low volatility.
2.1.4 Thermal transfer of ethyl thioacetate to thebaire

The anthracene cycloadduct (97), the dimethylantracene cycloadduct (98), and the cyclopentadiene cycloadducts (99) and (100) are known auxiliary precursors of ethyl thioacetate.

Thermal transfer of ethyl thioacetate from (97) and (98) to thebaire gave the thermodynamically more stable adduct (120) in 78% and 86% yields respectively. It was decided to prepare (120), required for future reactions, by thermal transfer of ethyl thioacetate from the cyclopentadiene adducts (99) and (100).

The adducts (99) and (100) were prepared by the literature method from the Bunte salt (124). The cycloadducts (99) and (100) (ratio 7:3) were purified by Kugelrohr distillation. In an initial, small scale reaction, a slight excess of the cycloadducts (99) and (100) was added to thebaire in toluene and the solution heated under reflux under oxygen-free dry nitrogen. The formation
of the thebaine cycloadduct (120) was monitored by t.l.c., since prolonged reflux was expected to cause thermal isomerisation of (120) to the rearranged acetal (134). The reaction was stopped after 13 h. Evaporation of the mixture yielded a solid residue which was judged by $^1$H n.m.r. to consist of the thebaine cycloadduct (120) (75%) and residual cyclopentadiene adducts (25%). The adduct (120), after purification by chromatography and crystallisation from propan-2-ol was obtained in 64% yield. The presence in the crude product of cyclopentadiene adducts was a drawback, since they were not easily separated from the thebaine cycloadduct (120).

It was decided to repeat the reaction using an excess of thebaine, which is readily separated from its adducts, under otherwise identical conditions in the hope that all of the cyclopentadiene adducts would react. Thebaine reacted with the cyclopentadiene adducts (99) and (100) in the molar ratio 2.5:1 in toluene for 13 h to give the thebaine cycloadduct (120) in 54% yield after purification. Unreacted cyclopentadiene adducts were obtained in 3% yield. A third component was also isolated (9%). This was identified as the enone (136) which was earlier obtained from the acetal (134) by acid hydrolysis. The presence of (136) and not of the acetal (134) was somewhat surprising. It was assumed that the acetal (134) which formed had been converted into (136) on the silica.

Next, the experiment with an excess of thebaine was repeated, but the reactants, in the same molar ratio were heated at 100°C in toluene for 8 h. The thebaine cycloadduct (120) was obtained in 62% yield together with the enone (136) (2%). Unreacted
cyclopentadiene adducts were obtained in 3% yield. It appeared therefore that complete transfer of ethyl thioxoacetate from the cyclopentadiene adducts (99) and (100) could not be effected and that the conditions employed in the initial small scale reaction were the most promising. The reaction was scaled up and the reactants heated at 100°C for 8 h. The cycloadduct (120) was obtained in 69% yield after purification on a short silica column. 

$^1$H N.m.r. inspection of the remaining fractions from the column chromatography indicated only a trace of the enone (136).

In conclusion, unexpected problems in purification made this less attractive than established routes. The cycloadduct (120) was more readily obtained from (119) by heating under reflux in toluene for 8 h.

2.1.5 Reaction of thebaine with 2-oxopropanethial

The preparation of thevinone (10) from methyl vinyl ketone and thebaine (3) was first reported by Bentley. The thevinols (11) and orvinols (12), many of which are potent analgesics, were obtained by Grignard addition to thevinone. Our aim was the preparation of the 8-thia-analogue of thevinone (139) by the cycloaddition of 2-oxopropanethial (138) with thebaine. Cycloaddition is expected to take place to give the regiochemistry and stereochemistry seen in the adduct (139). This new sulphur-containing adduct was the subject of subsequent chemical modifications. The Bunte salt (137) was initially chosen as the precursor of 2-oxopropanethial since the Bunte salt (124) was an effective precursor of ethyl thioxoacetate (Scheme 41).
The Bunte salt (137) had been described in the literature, but the degree of hydration was uncertain. In a modification of the reported method, the Bunte salt (137) was prepared by heating commercially-available chloroacetone under reflux with sodium thiosulphate pentahydrate in aqueous ethanol. The salt (137) crystallised from ethanol and gave good micro-analytical values (C, H, and S) for anhydrous material. The yield however was low, possibly due to decomposition to the corresponding disulphide. Bromoacetone was therefore used in place of chloroacetone in an attempt to form (137) under milder conditions.
Bromoacetone, was prepared by acid-catalysed bromination of acetone. It is a more potent lachrymator than chloroacetone. The reaction of bromoacetone with sodium thiosulphate pentahydrate at room temperature for 30 min afforded the Bunte salt (137) in 65% yield (after crystallisation from ethanol). Its purity was checked by comparison of the infrared spectrum with that of a sample which had given accurate micro-analytical results. The best yield of (137) obtained using chloroacetone was 37%.

As in the exploratory reactions of ethyl thiooxoacetate with thebaine, small scale experiments were carried out to optimise conditions for the capture of 2-oxopropanethial (138) by thebaine. The required cycloadduct (139) was readily identified in the reaction mixture by its H n.m.r. spectrum which closely resembled that of the ester cycloadduct (119). Initially, thebaine was treated with a 1:1 molar excess of the Bunte salt (137), triethylamine, and calcium chloride dihydrate in ethanol-benzene (1:1) for 48 h at room temperature. The isolated yield of the adduct (139) was 40%. Increasing the reaction time to 96 h did not improve the yield nor did increasing the ratio of other reactants to thebaine to 2:1. The yield of (139) was essentially the same after only 8 h. It was therefore decided to try a batch addition of the Bunte salt, triethylamine, and calcium chloride to thebaine. When a 1.5 molar excess of these reactants was added three times over a 42 h period the isolated yield of (139) was still only 42%. The adduct (139) was purified by t.l.c. but failed to crystallise from any of the common organic solvents, but it did show the expected molecular ion at m/z 399. The infrared spectrum in bromoform showed a carbonyl stretching band at 1690 cm⁻¹. As mentioned earlier, the presence of calcium chloride in
the reaction mixture removes the nucleophilic sulphite dianion as its sparingly soluble calcium salt, preventing competitive attack on the thioaldehyde. When cobalt(II)chloride was substituted for calcium chloride the yield of (139) was reduced to 25%. When guanidinium chloride was used the yield of (139) fell to 0%. As the yield of (139) was low and the purification difficult, especially when an excess of other reactants was used, another precursor of 2-oxopropanethial was sought.

Thiotosylate esters, e.g. (140), are generally transformed to give α-tosyldisulphides, e.g. (141), in the presence of base or when subjected to 'flash' chromatography (Scheme 33). Since both thiotosylates and α-tosyldisulphides are thioaldehyde precursors it was decided to examine the formation of (139) from the precursors (140) and (141) and to assess the relative advantages and limitations of each. The thiosylate (140) was

\[
\begin{align*}
\text{CH}_3\text{C-CH}_2\text{S-SO}_2\text{-} & \text{Me} \\
\end{align*}
\]  

(140)

\[
\begin{align*}
\text{O} & \\
\text{CH}_3\text{C-CH}_2\text{S-SCH-C-CH}_3 & \text{O} \\
\text{SO}_2 & \\
\text{Me} & \\
\end{align*}
\]  

(141)
prepared from sodium p-toluenethiosulphonate and chloroacetone following the method of Takano et al. in which the toluene-p-thiosulphonate anion is supported on Amberlyst A-26 resin (Scheme 42). A slight excess of resin supported toluene-p-thiosulphonate anion is necessary since the use of equimolar quantities left some residual chloroacetone which was difficult to remove from the thiotosylate (140). Bromoacetone was also used in the preparation of (140) from resin supported toluene-p-thiosulphonate ion. Unfortunately the thiotosylate (140) could not be obtained in a pure form. Purification of (140) was complicated by the formation of (141) (15-20%). Noteably this complication did not occur with the analogous ester compounds (107; R=EtO₂C or MeO₂C). It was expected therefore that (140) would easily fragment and rearrange to (141) on 'flash' silica. However, when (140) was adsorbed onto the silica and left overnight in chloroform-benzene, elution yielded a mixture of (140) (29%) and (141) (61%).
In the elimination of sulphite dianion from the Bunte salts (112), polar solvents were found to increase the likelihood of nucleophilic attack by the sulphite dianion. Addition of calcium chloride dihydrate largely overcame this problem by removing sulphite dianion as its sparingly soluble calcium salt. However, the amount of ethanol present was limited to the minimum required to dissolve the Bunte salt. Since the oily derivatives (140) and (141) are not salts it was possible to use benzene-ethanol (8:2) as solvent for the reaction. This, plus the addition of calcium chloride dihydrate, increased the overall efficiency of elimination and trapping. Consequently the thiosulphonate (140) containing (141) (15-20%) was treated with one equivalent of triethylamine in the presence of calcium chloride dihydrate and thebaine at room temperature. The ratio of the cycloadduct (139) to thebaine in the crude product mixture was found (1H n.m.r.) to be 50:50. Due to difficulties in purification though, the isolated yield remained low.

When the α-tosyldisulphide (141) was treated with two equivalents of thebaine and one each of triethylamine and calcium chloride dihydrate, the ratio of (139) to thebaine was 30:70.

It was decided therefore to optimise conditions using the thiosulphonate (140) as a precursor of 2-oxopropanethial. Increasing the molar ratio of thiosulphonate relative to thebaine combined with a longer reaction time considerably improved the yield of (139). The favoured route was as follows. Three equivalents of thiosulphonate (140), calcium chloride dihydrate and triethylamine were stirred with one equivalent of thebaine in benzene-ethanol (8:2) at room temperature for 120 h. The
cycloadduct (139) was obtained in 74% yield as a yellow oil. A considerable amount of yellow polymeric material, presumably the product of self-condensation of 2-oxopropanethial, hindered the purification of (139). Traces of the regioisomeric adduct (142) were also obtained, but the epimeric 7β-methyl ketone could not be isolated.

Attempts were made to obtain a crystalline derivative of (139). Neither the hydrochloride nor the methanesulphonate was obtained in a crystalline form. An attempt to produce a semicarbazone of (139) was also unsuccessful. Failure to form a crystalline derivative may be due to the presence of contaminants such as polymeric 2-oxopropanethial. It was decided therefore to purify (139) via its bisulphite adduct. A solution of (139) in ethanol was stirred with an aqueous solution of sodium metabisulphite at room temperature for 1 h. The solution was extracted with dichloromethane and the aqueous layer was separated and treated with solid sodium hydrogen carbonate. Extraction with dichloromethane yielded some of the cycloadduct (139), but it again
failed to crystallise. It was decided to use the cycloadduct (139) as it was. For convenience it was named 8-thiathevinone by derivation from the known thevinone (121a). The non-systematic name 7-thiaisothevinone was therefore given to the regioisomeric cycloadduct (142).

2.2 Reactions of 8-Thiathevinone

2.2.1 Thermal isomerisation

The interaction of a site on the opiate receptor with a lipophilic group attached at C-7 of the 6,14-bridged morphine nucleus partly explains the generally high analgesic activity of the thevinols (11).6 The accessibility of C-7 functionalised derivatives contrasts with the inaccessibility of C-8 substituted analogues and is due to electronic factors controlling the addition of dienophiles to thebaine.80,128,129 Indeed, the high potency of compounds such as buprenorphine4 and etorphine4 discouraged attempts to form the less accessible rigid thevinols possessing C-8 lipophilic substituents. Nevertheless, the mild analgesic activity of certain flexible C-8-substituted morphian derivatives18 and of 6-deoxythevinol analogues130 suggested that C-8-substituted rigid thevinol-like structures might have analgesic potential. Thermal isomerisation of the 7α-ester cycloadduct (119) to the regioisomeric adduct (120) was described earlier. It was expected that the 7α-ketone 8-thiathevinone (139) would undergo similar dissociation and recombination of components to form the 8α-ketone (142) (Scheme 43). The new cycloadduct would be a substrate for reactions introducing lipophilic substituents at the C-8 position.
When a sample of (139) was heated under reflux in toluene for 5 h rearrangement took place to give the cycloadduct (142) in 35% yield. The rearrangement is faster than that of the ester (119) due to the higher reactivity of 2-oxopropanethial relative to ethyl thiooxoacetate. The ease of the retro-Diels-Alder reaction may account for the low yield, if a substantial concentration of the thioaldehyde is present during isomerisation. Indeed, a considerable amount of polymeric material arising, presumably, from self-condensation of 2-oxopropanethial was also obtained. Some thebaine was also obtained. The new isomer (142), unlike (139), crystallised and had m.p. 150-151°C. The infrared spectrum (KBr) showed a sharp carbonyl stretching band at 1710 cm\(^{-1}\), cf. 1690 cm\(^{-1}\) in the isomeric ketone (139). The \(^1\)H n.m.r. spectrum of the rearranged ester (120) showed a signal at \(\delta 4.98\) for 5-H, whereas
the corresponding signal for (142) appeared at $\delta$ 4.97. Similarly, fine coupling was observed between 5-H and 18-H in the rearranged ketone (142). The olefinic protons 18-H and 19-H gave a singlet in (139) whereas in (142), as in (120), they gave an AB quartet, $\delta$ 5.72 and 6.09 (J 9 Hz) [cf. $\delta$ 5.73 and 6.21 (J 9 Hz) for (120)]. The mass spectrum of (142) showed a molecular ion at m/z 399 and a peak at m/z 311 (M-88) corresponding to thebaine.

Prolonged reflux of the cycloadduct (139) was expected to cause rearrangement to the acetal corresponding to (134). However, heating (139) in toluene under reflux for 100 h led to a black oil, the $^1$H n.m.r. spectrum of which showed some signals corresponding to thebaine. This indicated that the retro-Diels-Alder reaction had occurred. No signals were seen corresponding to the rearranged acetal.

2.2.2 Formation of tertiary alcohols

Thevinone (10) has been converted into tertiary alcohols (11), known as thevinols (Scheme 44). The analgesic potency of the thevinols depends on the chain length of the lipophilic R group at C-20. One of our initial aims was the synthesis of an analogous series of sulphur-containing tertiary alcohols from 8-thiathevinone (139). In this way the effect of replacing the methylene group at position 8 in (11) with a sulphur atom can be assessed. Bentley found that the reaction of thevinone (10) with Grignard reagents (RMgX) proceeded stereoselectively to give, as the major product, tertiary alcohols having the $R$ configuration at C-20. Scheme 45 illustrates the Grignard addition of n-propylmagnesium bromide to thevinone to give the two diastereomers. The major product was
the (R)-diastereomer, [C-20 stereochemistry as in (11)]. Only a very minor amount of the (S)-diastereomer was obtained. This stereoselectivity was seen for the reaction of thevinone with all the Grignard reagents (RMgX). It was attributed to a six-membered transition state in which the magnesium atom coordinates simultaneously with the oxygen atom of the C-7 carbonyl and the C-6 methoxyl groups (Scheme 45).

Where the alkyl group of the Grignard reagent (RMgX) possesses a β-hydrogen, the diastereomeric secondary alcohols (143) and (144) were also obtained. The major secondary alcohol (143) obtained in each case was that having S stereochemistry at C-20. Formation of (144) was a very minor reaction. The model proposed
Scheme 45
for the normal Grignard reaction (Scheme 45) also accounts for the observed stereochemical preference in Grignard reduction. It is consistent with approach by the Grignard reagent to the 5-face of the C-7 carbonyl group in thevinone (as shown in Scheme 45). Bentley prepared a series of tertiary alcohols (145) from thevinone by Grignard addition. The alcohols having R stereochemistry at C-20 were found to have high analgesic potencies. For example, the thevinol [145; R = Me, R' = (CH2)2Ph] had 500 times the potency of morphine and (145; R = Me, R' = Bu) had 24 times the potency of morphine. By contrast the (S)-diastereomers were generally between 1 and 5 times as potent as morphine.\(^7\) Bentley's initial assignment of C-20 stereochemistry in the thevinols (145) was subsequently confirmed by \(^1\)H n.m.r. spectroscopic studies.\(^{116}\) Furthermore, the
tertiary alcohol (145; \( R = \text{Me}, R' = \text{Pr}^n \)) obtained as the major product from the reaction of propylmagnesium bromide with thevinone (10), was selected as a representative example of the pharmacologically-active thevinols. Its stereochemistry at C-20 was confirmed by X-ray crystallographic analysis of its hydrobromide salt.\(^{131}\) The thevinol (145; \( R = \text{Me}, R' = \text{Pr}^n \)) had the highest analgesic potency within the series (145) where \( R' = \text{Me}, \text{Et}, \text{Pr}^n, \text{Bu}^n, \text{n-pentyl} \). Furthermore, 3-O-demethylation led to the alcohol (146) known as etorphine, which has a potency 1000 times that of morphine. Etorphine is used commercially as an analgesic and sedative in veterinary medicine and for the immobilisation of large game animals. Etorphine (146) illustrates well the importance of
C-20 stereochemistry since its C-20 diastereomer has only 20 times the potency of morphine. For these reasons the n-propyl derivative (147; R = Me, R' = Pr\textsuperscript{n}), the 8-thia analogue of (145; R = Me, R' = Pr\textsuperscript{n}), was selected as our initial synthetic target.

Propylmagnesium bromide was prepared in diethyl ether, and 8-thiaethevinone (139) in an equal volume of benzene was added to a refluxing solution of the Grignard reagent. The reactants were heated under reflux for 4 h. Aqueous work up yielded a residue which was shown by analytical t.l.c. and \textsuperscript{1}H n.m.r. spectroscopy to be a complex mixture. However, two bands of higher \( R_F \) and one of lower \( R_F \) were prominent. The two bands of higher \( R_F \) were present in approximately equal amounts. The component of highest \( R_F \) was isolated. It yielded a solid which crystallised from ethanol.
The $^1$H n.m.r. and infrared spectral data indicated that propylation had taken place, but did not permit the assignment of C-20 stereochemistry. Some of the homologous alcohols (147) were next prepared. It was hoped that a comparison of their physical and spectral characteristics with those of the analogues (145) of known stereochemistry would assist the assignment of C-20 stereochemistry. The series of sulphur-containing tertiary alcohols (147) together with their carbon analogues (145) are shown overleaf. After comparison of physical and spectral characteristics (vide infra), the component of highest $R_f$ isolated from the initial reaction of n-propylmagnesium bromide with 8-thiathevinone (139) was assigned the structure (147d). Its melting point was 175.5-176.5°C, while that of (145d) was 171-173°C (lit. 176°C). The infrared spectrum in bromoform showed both (145d) and (147d) to have intramolecular hydrogen bonded hydroxyl groups, since both gave concentration-independent bands at 3450 cm$^{-1}$. The $^1$H n.m.r. spectra of (145d) and (147d) both showed triplets ($\Delta 6.7$ Hz), at $\delta$ 0.91 and 0.86 respectively, corresponding to the terminal methyl group of the C-20 n-propyl group. The methyl group at C-20 gave a singlet at $\delta$ 1.08 in (147d) but at $\delta$ 0.97 in (145d). The signal for 7-H in (145d) appeared as a multiplet, $\delta$ 2.84. The singlet corresponding to 7-H in (147d) appeared at $\delta$ 3.39 showing the expected downfield shift arising from replacement of the methylene group with a sulphur atom. The signal at $\delta$ 4.88 for (145d) disappeared upon exchange with D$_2$O as did the signal at $\delta$ 4.54 for (147d). Lastly, 18-H in (145d) and (147d) gave doublets of similar chemical shifts, $\delta$ 5.98 and 5.91, respectively. In contrast, the doublets for 19-H appeared at $\delta$ 5.44 for (145d) and 5.77 for (147d), reflecting the proximity of
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<tr>
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sulphur in the latter. The mass spectrum of (147d) showed a molecular ion at \( m/z \) 443 and a peak at \( m/z \) 356 (M-87) corresponding to loss of the 7α-(hydroxypentyl) group. Microanalyses (C, H, and N) were consistent with the molecular formula C\(_{25}\)H\(_{33}\)NO\(_4\)S.

The band of slightly lower \( R_F \) yielded a solid which crystallised from ethanol and had m.p. 118-120°C. This was later identified as the tertiary alcohol (147e). The mass spectrum showed a molecular ion at \( m/z \) 443 and as before, a peak at \( m/z \) 356 (M-87) corresponding to loss of the 7α-(hydroxypentyl) group. Microanalyses were consistent with the formula C\(_{25}\)H\(_{33}\)NO\(_4\)S. The infrared spectrum in bromoform showed an intramolecularly bonded hydroxyl band at 3450 cm\(^{-1}\). The \( ^1H \) n.m.r. spectrum was virtually identical to that of (147d), isolated from the band of higher \( R_F \). One notable difference was that the deuterium-exchangeable proton signal appeared at \( \delta \) 4.13, rather than \( \delta \) 4.54 for (147d). It was evident that the alcohols (147d) and (147e) were diastereomers. However, stereochemical assignments could not be made, especially since both alcohols showed intramolecular hydrogen bonding.

The band of lowest \( R_F \) yielded a mixture of the diastereomeric secondary alcohols (148) and (149) formed by Grignard reduction of 8-thiathevinone (139). The secondary alcohols were identified by their \( ^1H \) n.m.r. and infrared spectral characteristics and by comparison with those of the known secondary alcohols (143) and (144) obtained by sodium borohydride reduction of thevinone (10). The major component was identified as the \((S)\)-diastereomer (148). The minor was the \((R)\)-diastereomer (149). The assignment of stereochemistry in (148) and (149) is discussed in Section 2.2.3.
The tertiary alcohols (145) were referred to as alkyl-thevinols. Individual members of the series bear the prefix of the C-20 alkyl substituent. For example, the alcohols (145c) and (145d) are ethylthevinols. By analogy, the sulphur-containing tertiary alcohols (147) are named alkylthiathevinols. The distereomeric alcohols (147b) and (147c) are therefore ethylthiathevinols and (147d) and (147e) propylthiathevinols.

The alkylthiathevinols (147a-k) were prepared by the reaction of 8-thiathevinone (139) with the appropriate Grignard reagent, prepared as described for propylthiathevinols. All were obtained in low yield along with the diastereomeric secondary alcohols (148) and (149). All but two were crystalline, giving correct elemental analyses (C, H, and N). All gave mass spectra consistent with their molecular formulae. The n-pentylthiathevinol (147h) and the n-hexylthiathevinol (144k) were exceptional in being obtained oily. Isolation of the alkylthiathevinols (147a-k) could only be achieved by extensive chromatography. The best results were obtained by passing the crude product twice through a Florisil column. Selected fractions were then purified using the Harrison Chromatotron. The use of silica columns failed to separate the desired alcohols from highly polar material; although silica was considerably more effective than alumina. Furthermore, when the alkylthiathevinols were purified by preparative t.l.c. further polar material developed during the chromatographic process. For this reason the Chromatotron is advantageous, since separation is effected quickly under oxygen-free nitrogen. The use of dichloromethane-methanol solvent systems for preparative t.l.c. also appeared to increase the amount of base-line material.
Consequently diethyl ether-petroleum ether mixtures were used with the Chromatotron.

The alkylthevinols (145, a, b, d, f, and h) were obtained in high yield by the reaction of thevinone (10) with the appropriate Grignard reagent. The alkylthevinols (145c* and (145e)* were prepared in high yield by the reaction of the ketones (150a) and (150b) with methylmagnesium iodide. The stereochemistry of the alkylthiathevinols (147b-k) was assigned as follows. Initially,

![Chemical Structure](image)

```

\( R = \text{Et} \)  
\( R = \text{Pr}^n \)  
\( R = \text{Ph} \)
```

differences in the \(^1\text{H}\) n.m.r. and infrared spectra of the diastereomeric ethylthiathevinols (147b) and (147c) were compared with those of the ethylthevinols (145b) and (145c) of known stereochemistry. Similarly, the spectral differences between (147d) and (147e) were compared with those of the propylthevinols (145d) and (145e) of

* kindly donated by Reckitt and Colman Ltd., Hull.
known stereochemistry (Table 7). The ethylthevinol (145b) was less polar on silica t.l.c. plates than (145c). The thevinol (145b) showed a signal for a deuterium-exchangeable proton at $\delta$ 4.86 while that of (145c) appeared upfield at $\delta$ 4.39. The signal for the deuterium-exchangeable proton of the less polar ethylthiathevinol (147b) appeared at $\delta$ 4.55 while that of the none polar diastereomer (147c) was upfield at $\delta$ 4.05. The propylthevinol (145d) was less polar than (145c). The thevinol (145d) showed a signal for a deuterium-exchangeable proton at $\delta$ 4.88 while that in (145e) appeared upfield at $\delta$ 4.54. The signal for a deuterium-exchangeable proton of the less polar propylthiathevinol (147d) appeared at $\delta$ 4.54 while that of its more polar diastereomer (147e) appeared upfield at $\delta$ 4.13. Of the remaining higher alkylthevinols, only the (20R)-diastereomers (145f), (145h), and (145j) are literature compounds. However, loss of stereoselectivity was again encountered in the formation of the butylthiathevinols, pentylthiathevinols, and hexylthiathevinols. The n.m.r. signals for hydroxy protons in the less polar diastereomers, presumed to have the (R)-configuration, consistently appeared downfield of those in the more polar, presumably (S), diastereomers, re-affirming the trend observed in the ethylthiathevinols and propylthiathevinols.

The $^1$H n.m.r. spectra of the ethylthevinols (145b) and (145c), the propylthevinols (145d) and (145e), and butylthevinol (145f) each showed a three-proton singlet corresponding to the 3-methoxy group at $\delta$ 3.82. The singlet corresponding to the 6-methoxy group in each case appeared slightly upfield; although it was noticeabably more upfield in the more polar (20S)-diastereomers (145c) and (145e) than in the less polar (20R)-diastereomers (145b)
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and (145d) (Table 7). The absolute chemical shift differences are actually small, but similar differences are observed for the thiathevinols (147b-k). Thus, while the 3-methoxy singlet appeared at 8 3.83 or 3.84 in the series (147b-k); the 6-methoxy singlet, in each case, appeared slightly upfield. It was more upfield, however, in the more polar (20S)-diastereomers (147c, e, g, i, and k) than in the less polar diastereomers (147b, d, f, h, and j) (Table 7).

A weak shielding effect is seen in the 1H n.m.r. spectra of (S)-thiathevinols (147c and g) and (S)-thevinols (145c and g) which is absent in the (R)-diastereomers (147b and f) and (145b and f). The terminal methyl group of the C-20 alkyl side chain (Et, Prn, Bu\textsuperscript{n}, Am\textsuperscript{n}) gives a three-proton triplet in the thiathevinols (147b-i). These signals for the (S)-diastereomers (147c, g, and i) appear at slightly higher field than those in the (R)-diastereomers (147b, f, and i). The signals for the propyl derivatives (147d and e) have the same chemical shift. It appears that in the (S)-diastereomers the alkyl side chain is generally in closer proximity to the 18,19-etheno bridge, perhaps because of intramolecular hydrogen bonding. A corresponding shielding effect is also seen in the signals for the olefinic protons 18-H and 19-H, the propyl derivatives again being exceptional. The (S)-thiathevinols (147c and g) show signals at higher field than those in the (R)-thiathevinols (147b and f). The (S)-pentythiathevinol (147i) showed shielding of the 18-H proton only. Interestingly, the (S)-hexylthiathevinol (147k) did not show any shielding effect. These effects are summarised in Table 7. Shielding effects have been reported in the 1H n.m.r. spectra of related thevinone
derivatives. Thus, shielding of the 20-methyl group and the olefinic protons was observed in (20S)-hydroxymethyl-7α-thevinan (151). Similarly, shielding of the terminal methyl group of the 20-butyl side chain and the olefinic protons was observed in (20S)-20-butyl-21-hydroxy-7α-thevinan (152). A particularly pronounced shielding effect was observed for the 20-methyl group in the (20S)-alcohol (153) formed from nepthenone (150c). This may be due to the increased steric hindrance by the 20-phenyl group which forces the 20-methyl group closer to the 18,19-etheno bridge.
The infrared spectra of the secondary alcohols (143) and (144) showed hydrogen-bonded hydroxyl bands which were diagnostic of C-20 stereochemistry. Examination of the infrared spectra
was also useful in assigning the stereochemistry of the analogous, sulphur-containing secondary alcohols (148) and (149), vide infra. The infrared spectra of the thevinols (145b-f) and the thiathevinols (147b-k) all showed hydrogen bonded hydroxyl bands. A dilution test in each case showed these bands to be concentration independent, indicating hydrogen bonding of the C-20 hydroxy group with the 6-methoxy group. The data are summarised in Table 8. A comparison of the infrared spectra of the ethylthevinols (145b) and (145c) in bromoform showed the (R)-diastereomer (145b) to have a hydroxyl band at 3430 cm$^{-1}$, while the (S)-diastereomer (145c) showed one at 3450 cm$^{-1}$. The ethylthiathevinol (147b) showed a band at 3430 cm$^{-1}$, while the diastereomer (147c) showed a band due to a weaker hydrogen bonded hydroxyl group at 3460 cm$^{-1}$. Both the propylthiathevinols (147d) and (147e) showed bands at 3450 cm$^{-1}$ as did the corresponding propylthevinols (145d) and (145e). The infrared spectrum of the remaining alkylthiathevinols is less useful since only the diastereomeric pentythiathevinols (147h) and (147i) showed a difference in hydrogen bond strengths. It appears therefore that differences are discernible in the i.r. region only when the C-20 substituents are small (H, Me, Et) as in (143); (144), (147b), and (147c) and (148), (149), (145b) and (145c). However, increasing the length of the C-20 alkyl chain within the series (147b-k) causes a general weakening of the hydrogen bond.

Finally, as Table 8 shows, the melting point of the (20R)-ethylthevinol (145b) was lower than that of the (S)-diastereomer (145c). Similar differences apply to the ethylthiathevinols (147b) and (147c). The melting point of (20R)-propylthevinol (145d) was actually higher than that of its diastereomer (145e); but this difference was also observed in the propylthiathevinols (147d) and (147e).
Table 8

I.r. Spectra and Melting Points for the
Tertiary Alcohols (147) and (145) and the
Secondary Alcohols (143), (144), (148), and (149)

<table>
<thead>
<tr>
<th>Stereochemistry</th>
<th>$\nu_{\text{max}}$ $\text{cm}^{-1}$</th>
<th>m.p. ($^\circ$C)</th>
</tr>
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<tbody>
<tr>
<td>147b R</td>
<td>3430</td>
<td>130</td>
</tr>
<tr>
<td>147c S</td>
<td>3460</td>
<td>171</td>
</tr>
<tr>
<td>147d R</td>
<td>3450</td>
<td>179</td>
</tr>
<tr>
<td>147e S</td>
<td>3450</td>
<td>120</td>
</tr>
<tr>
<td>147f R</td>
<td>3460</td>
<td>174</td>
</tr>
<tr>
<td>147g S</td>
<td>3460</td>
<td>126</td>
</tr>
<tr>
<td>147h R</td>
<td>3460</td>
<td>-</td>
</tr>
<tr>
<td>147i S</td>
<td>3480</td>
<td>148</td>
</tr>
<tr>
<td>147j R</td>
<td>3470</td>
<td>-</td>
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<td>147k S</td>
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<tr>
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<td>3450</td>
<td>134</td>
</tr>
<tr>
<td>145f R</td>
<td>3450</td>
<td>150</td>
</tr>
<tr>
<td>143 S</td>
<td>3540$^b$</td>
<td>81</td>
</tr>
<tr>
<td>144 R</td>
<td>3490$^b$</td>
<td>82</td>
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<tr>
<td>148 S</td>
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<td>-</td>
</tr>
<tr>
<td>149 R</td>
<td>3500$^b$</td>
<td>185</td>
</tr>
</tbody>
</table>

a All i.r. spectra were for bromoform solutions unless otherwise stated.

b Carbon tetrachloride solution.
Although the foregoing interpretation of physical data is not conclusive it is reasonable to assign the stereochemistries as shown. The results of pharmacological testing subsequently confirmed the assignments in Tables 7 and 8.

The preparation of methylthiathevinol (147a) completed the homologous series of sulphur-containing tertiary alcohols under discussion. The reaction of 8-thiahevinone with methylmagnesium iodide under the conditions described for the preparation of propylthiathevinols (147d) and (147e) gave methylthiathevinol (147a) in 17% yield. The known methylthevinol (145a) was also prepared in order to permit a comparison of its physical and spectral characteristics. The melting point of (147a) is 162-164°C; while that of (145a) is 166°C. A comparison of the infrared spectra in carbon tetrachloride solution showed (147a) to have a concentration independent band, due to a hydrogen bonded hydroxyl, at 3510 cm\(^{-1}\). In (145a) two bands were apparent; a weaker band at 3630 cm\(^{-1}\) due to a free hydroxyl and a stronger one at 3510 cm\(^{-1}\) due to a hydrogen bonded hydroxyl. The latter band was concentration independent, thus confirming intramolecular hydrogen bonding with the 6-methoxy group. The \(^1\)H n.m.r. spectrum of (145a) showed two three-proton singlets at $\delta$ 0.97 and 1.05 corresponding to the geminal methyl groups. The corresponding methyl groups in (147a) gave a six-proton singlet at $\delta$ 1.09. The signal corresponding to 7-H in (147a) appeared as a singlet at $\delta$ 3.36. The singlet at $\delta$ 4.82 for (145a) disappeared upon exchange with D\(_2\)O as did the singlet at $\delta$ 4.45 in (147a). 18-H in (145a) and (147a) gave doublets of similar chemical shifts ($\delta$ 5.94 and 5.88, respectively) whereas the corresponding doublets for 19-H appeared at $\delta$ 5.42 for (145a) but
downfield at 5.76 for (147a). This shift for 19-H, seen in other members of this homologous series reflects the proximity of sulphur. The mass spectrum of (147a) showed a molecular ion peak at $m/z$ 415 and a peak at $m/z$ 356 (M-59) corresponding to loss of the 7α-(hydroxypropyl) group. A much improved yield of methylthiathevinol (147a) was obtained by the reaction of the ester (119) with methylmagnesium iodide. The major complication in the reaction of Grignard reagents with 8-thiathevinone (139) is the formation of ill-defined, polar material. When the ester (119) was treated with ten-fold excess of methylmagnesium iodide, methylthiathevinol (147a) was obtained in 64% yield. No highly polar material was formed.

In the same way, the reaction of an excess of methylmagnesium iodide with the 7β-ester (123) proceeded cleanly to give the 7β-tertiary alcohol (154). The analogous 7β-tertiary alcohol (156) was prepared by Bentley et al., from methylmagnesium iodide and the 7β-ketone (155). As mentioned in Section 2.1.1, for alkylthevinols epimeric at C-7, the chemical shift of 5β-H is particularly indicative of C-7 stereochemistry. In virtually all the C-7 epimers studied by Bentley, signals for 5-H appeared at $\delta$ 4.57 ± 0.05 in the 7β-epimers but downfield at $\delta$ 5.07 ± 0.12 in the 7β-epimers, with the following exception. The methyl-7β-thethevinol (156) was unusual in that it showed a greater downfield shift (from $\delta$ 4.52 to 5.26) for 5-H than expected. A similarly large shift (from $\delta$ 4.52 to 5.31) was also observed in the methyl-7β-thiathevinol (154). The methyl-7α-thevinol (145a) showed a hydroxyl signal at $\delta$ 4.82, while that of the 7β-epimer (156) was upfield at $\delta$ 4.58. Hydroxyl signals appeared at $\delta$ 4.45 in both the methyl-7α-thiathevinol (147a) and methyl-7β-thiathevinol (154). The infrared
spectrum of the β-epimer (154) in carbon tetrachloride showed a concentration independent band due to hydrogen bonded hydroxyl at 3510 cm⁻¹. The epimer (154) showed a molecular ion peak at m/z 415 and, like the methyl-7α-thiathevinol (147a), a peak at m/z 356 (M-59) corresponding to loss of the 7α-(hydroxypropyl) group.

Thus, the alkylthiathevinols (147a-k) were all obtained in relatively low yields. This was due partly to the formation of secondary alcohols (143) and (144) and partly to the formation of unidentified polar material. Bentley⁷ reported that the addition of alkyl-lithiums to thevinone (10) was generally a useful alternative route to alkylthevinols (145). It was used when reaction with the corresponding Grignard reagent was unsuccessful. Its principal disadvantage is that C-20 stereoselectivity is reduced.⁷,¹³⁰ The likelihood of base-catalysed rearrangement, (Scheme 39), is also increased in this route. However, the formation of the secondary alcohols (143) and (144) was not observed. Since the formation of alkylthiathevinols from Grignard reagents is not stereoselective, alkyl-lithium reagents were seen as attractive alternatives to Grignard reagents.

The addition of commercially available n-butyl-lithium to 8-thiathevinone (139), according to the method of Rapoport,¹³⁰ gave a mixture of the diastereomeric butylthiathevinols (147f) and (147g). However, the (S)-diastereomer (147g) was only a minor component. In the small scale pilot reaction only the (R)-diastereomer (147f) was isolated. The scaled-up reaction afforded the (R)-diastereomer (147f) in 14% yield. The (S)-diastereomer (147g) was obtained in only 4% yield. Formation of the secondary alcohols (148) and (149) was not observed.
Furthermore, none of the polar base line material formed in the Grignard reactions was seen either, suggesting that the use of alkyl-lithiums would present a more efficient route to the desired thiathevinols (147b-e). Preparation of the propylthiathevinols (147d and e) was attempted next.

Propyl-lithium was prepared from lithium metal and 1-bromopropane by a slight modification of the literature method. Initial attempts to prepare propyl-lithium from lithium metal and 1-bromopropane or 1-chloropropane according to the method of Gilman were unsuccessful. A two-fold excess of propyl-lithium was added to a solution of 8-thiathevinone (139) in dry tetrahydrofuran. Aqueous work up followed by chloroform-extraction of the crude reaction mixture yielded a brown oil which was purified by preparative layer chromatography. T.l.c. examination of the crude reaction mixture showed a minor band of high R_f. The (20R)-propylthiathevinol (147d) was isolated from the minor band. No (20S)-propylthiathevinol (147e) was obtained and the major component, isolated from the band of lower R_f, was found to be the ketoacetal (157). This product (157) had m.p. 159-163°C and showed a molecular ion at m/z 399, having an accurate mass corresponding to C_{22}H_{25}NO_4S. Elemental analyses were consistent with this molecular formula and the structure was assigned on the following grounds. Treatment of thevinone (10) with methanolic potassium hydroxide is known to give isothevinone (158; R = Me). Similarly, treatment of nepenthone (150c) with methanolic sodium hydroxide yields isonepenthone (158; R = Ph). Analogous base-catalysed rearrangements were demonstrated with other cycloadducts which bear an electron-withdrawing group at C-7.

A
plausible mechanism which leads to the formation of the ketoacetal (157) is outlined in Scheme 46. The mechanism is similar to that proposed by Bentley for the formation of (158; \( R = \text{Me} \)) from thevinone (10) (Scheme 39, Section 2.1.2). Since (158; \( R = \text{Me} \)) and (158; \( R = \text{Ph} \)) are formed under reversible enolisation conditions, the more stable C-18 epimers predominate. Models showed the 18\( \beta \)-epimer to be more stable. The acetal (134), the preparation of which was described in Section 2.1.3, was useful in assigning the structure of (157). The \(^1\text{H n.m.r. spectrum of 8-thiahevinone (139) showed a signal at } \delta 4.51 \text{ for 5-H, whereas the corresponding signal for (157) appeared upfield at } \delta 2.59 \). The signal for 5-H in (157) showed splitting (\( J = 2.7 \text{ Hz} \)) arising from long-range coupling with 7-H. Long-range coupling (\( J = 2.4 \text{ Hz} \)) was also seen between 5-H and 7-H in the ester (134). However,
Scheme 46
coupling between 5-H and 18-H in (157) was not observed. A model showed that vicinal coupling between the \(5\alpha\) and \(18\alpha\)-protons is likely to be very small since the dihedral angle approaches 90°. A measurable vicinal coupling constant would only be expected between \(5\alpha\)-H and on \(18\beta\)-H. The lack of vicinal coupling indicates that the acetyl group is in the \(\beta\)-position which is in accord with the assignment made by Bentley for the acetals (158; \(R = \text{Me}\)) and (158; \(R = \text{Ph}\)). In the parent ketone, (139), the olefinic protons gave a singlet, whereas in (157) they gave an AB quartet, \(\delta 4.99\) and 6.11 (\(J 9.5\) Hz). Similarly the olefinic coupling constants in the 5,14-bridged ethyl ester (134) and the methyl ester (135) were slightly larger than those in the parent 6,14-bridged esters (120) and (128). In (157), 8-H gave a double-doublet at \(\delta 6.11\) and 7-H a double-doublet at \(\delta 4.99\). The relative positions of the two olefinic proton signals were the same as for the ester (134).
It appeared that under the foregoing conditions the acetal (157) was the major product. Formation of (20R-propylthiathievinol (147d) was only a minor reaction. A possible explanation is the enhanced acidity of 7-H in 8-thiathevinone (139) which is caused by the presence of sulphur. This results in the formation of a lithium enolate which rearranges to the 18,20-enolate of the acetal (157) (Scheme 46). This is protonated to give (157) only during work up. Alternatively, the enolate of the ketone (139) survives the course of the reaction but rearranges to the acetal (157) during work-up. The latter possibility was discounted by the following control experiment. To emulate the conditions of work-up as closely as possible, a two-fold excess of propyl-lithium was prepared as before. To this was added distilled water, then a solution of the ketone (139) in dry tetrahydrofuran. The mixture was stirred at room temperature for 5 min. The $^1$H n.m.r. spectrum
of the crude material showed that no reaction had taken place. The ketone (139) was recovered virtually quantitatively, suggesting that in the initial reaction, rearrangement to the acetal (157) took place during the course of the reaction.

The conditions of the reaction were modified in an attempt to produce (20R)-propylthiathevinol (147d). In the first reaction, addition of propyl-lithium to the solution of 8-thiathevinone (139) at -78°C was rapid due to the sensitive nature of the propyl-lithium. When the propyl-lithium solution was added more slowly to a solution of the ketone (139) in dry tetrahydrofuran at -78°C, the (20R)-propylthiathevinol (147d) was obtained in 39% yield. None of the acetal (157) was obtained. This suggested that keeping the reactants at low temperature promoted tertiary alcohol formation rather than rearrangement. Rather than following Rapoport's original conditions it was more convenient to carry out controlled addition of the ketone (139) to a solution of propyl-lithium in diethyl ether at -78°C. By this method, (20R)-propylthiathevinol (147d) was obtained in 30% yield, and the acetal (157) in 3% yield. To confirm the importance of low temperature in the formation of (147d), propyl-lithium solution was prepared as before and then allowed to reach room temperature. To this was added the ketone (139) over a period of 30 s. The acetal (157) was obtained as the sole product.

Despite the unexpected rearrangement, this alternative route to other (20R)- compounds merits further study.

The reaction of Grignard reagents with 8-thiathevinone (139) to give a diastereomeric mixture of tertiary alcohols was somewhat unexpected, since the corresponding reactions with thevinone (10)
were stereoselective for the (R)-diastereomers. Furthermore, although Bentley\textsuperscript{7} reported that the reaction of alkyl-lithiums with thevinone was less selective than the corresponding reactions with Grignard reagents, we found that the reactions of both n-propyl-lithium and n-butyl-lithium with 8-thiathevinone (139) were selective for the (R)-diastereomers. Also, Rapoport\textsuperscript{130} recently reported the addition of alkyl-lithiums to two 6-demethoxythevinone analogues. In both cases, diastereomeric mixtures of tertiary alcohols were obtained. Only in one case was the reaction stereoselective. It seems therefore that the factors controlling stereoselectivity in the addition of alkyl-lithiums to thevinone and its analogues is another area which warrants further study.

2.2.3 Formation of secondary alcohols

Bentley et al., reported that in the formation of alkyl-thevinols from thevinone (10), Grignard reduction competes seriously with tertiary alcohol formation when the incoming alkyl group possesses a $\beta$-hydrogen.\textsuperscript{7} Both secondary alcohols (143) and (144) are formed, (143) being the major product. This is consistent with approach by the Grignard reagent to the exposed $\beta$-face of the carbonyl group as in Scheme 45.

In the formation of alkylthiathevinols (147b-k) from 8-thiathevinone (139), Grignard reduction was also observed. T.l.c. of the crude product in each case revealed three major bands. The two bands of higher $R_F$ contained the tertiary alcohols and the band of lowest $R_F$ contained a mixture of the two second secondary alcohols. The major component was later identified as the (S)-diastereomer (148). The minor was the (R)-diastereomer (149). The ratio of
(148) to (149) was estimated from the $^1$H n.m.r. spectrum to be 8:2. It is interesting that in the reaction of Grignard reagents with thevinone (10), both the normal Grignard reaction which leads to the alkylthevinols, and Grignard reduction leading to the secondary alcohols are stereoselective. In the reaction of Grignard reagents with 8-thiathevinone (139), however, stereoselectivity of the normal Grignard reaction is lost; but Grignard reduction is stereoselective.

The diastereomeric secondary alcohols (143) and (144) are formed by sodium borohydride reduction of thevinone (10). The stereochemistry at C-20 in these alcohols was assigned by Bentley et al. The infrared spectrum of the (S)-diastereomer (143) in tetrachloromethane solution showed a strong hydroxyl band at 3540 cm$^{-1}$ and a very weak band at 3605 cm$^{-1}$. The former arises from intramolecular hydrogen bonding with the 6-methoxy group, and the latter with the 6,14-etheno bridge. The infrared spectrum of the (R)-diastereomer (144) in tetrachloromethane showed a hydroxyl band at 3490 cm$^{-1}$. Bentley et al. postulated that the stronger hydrogen bond would occur in the (20R)-diastereomer (144). In the (20S)-diastereomer (143) the hydrogen bond is weakened since the C-20 methyl group projects over the 6,14-etheno bridge. This leads to a difference of 50 cm$^{-1}$ in the hydrogen bonded hydroxyl frequencies of (143) and (144). In support of these assignments, the (R)-diastereomer (144) is readily hydrogenated at room temperature and pressure. The (S)-diastereomer (143) is resistant to hydrogenation at room temperature due to steric hindrance of the etheno bridge by the 20-methyl group. The secondary alcohols (143) and (144) were then prepared as described, and the crude product
chromatographed on alumina plates using butanone (multiple elutions). The infrared spectra of the two isolated alcohols showed that the less polar diastereomer was (143) and the more polar one (144). The analogous sulphur-containing alcohols (148) and (149) were also prepared. To determine their stereochemistry, the spectral characteristics and t.l.c. behaviour were compared with those of the known secondary alcohols (143) and (144). This approach had proved useful in determining the stereochemistry of the ethylthiathevinols (147b) and (147c).

A solution of 8-thiathevinone (139) in methanol was boiled under reflux with one equivalent of sodium borohydride for 1 h. T.l.c. of the crude product showed two major fractions which were present in approximately equal proportions. These were separated on alumina plates using butanone (multiple elutions). The less polar fraction could not be crystallised but showed the expected molecular ion at $m/z$ 401. The infrared spectrum in tetrachloromethane showed a hydroxyl band at 3520 cm$^{-1}$. A dilution test showed this to be concentration independent indicating intramolecular hydrogen bonding with the 6-methoxy group. The more polar fraction was isolated and crystallised from ethanol, m.p. 183.5-185°C. It showed a molecular ion at $m/z$ 401 and gave correct microanalytical results. The infrared spectrum in tetrachloromethane showed a concentration independent hydroxyl band at 3500 cm$^{-1}$. Thus a difference in hydrogen bonded hydroxyl frequencies of 20 cm$^{-1}$ was observed between the two sulphur-containing alcohols. As in the case of the known secondary alcohols (143) and (144) the (S)-diastereomer showed the weaker hydrogen bond (Table 9). The weak hydrogen bond with the $\pi$ orbitals of the etheno bridge observed
in (143) was not seen in (148). The less polar sulphur-containing alcohol was then assigned the (S)-stereochemistry on account of its t.l.c. behaviour and its weaker hydrogen bond. The more polar alcohol was assigned the (R)-stereochemistry. The observed chemical shift differences in the $^1$H n.m.r. spectra of the diastereomeric pairs of secondary alcohols also support the stereochemical assignments (Table 9). The signal for 20-H in (148) appeared as a broadened multiplet at $\delta$ 4.21 and in (143) as a broadened multiplet at $\delta$ 4.09. Signals for 20-H were not visible in (144) and (149). When the 20-methyl group is more closely

Table 9

<table>
<thead>
<tr>
<th>Stereom.</th>
<th>$\nu_{max.}$ $^b$ cm$^{-1}$</th>
<th>$\delta$(CDCl$_3$)</th>
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<tr>
<td></td>
<td>C-20</td>
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</tr>
<tr>
<td>(143)</td>
<td>S</td>
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</tr>
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<td>(144)</td>
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<td>3520</td>
</tr>
<tr>
<td>(149)</td>
<td>R</td>
<td>3500</td>
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</table>

a Al$_2$O$_3$, butanone

b tetrachloromethane solution

124
apposed to the etheno bridge as in (143) and (148) a shielding effect is discernible. The 20-methyl group resonates at slightly higher fields in the (S)-alcohols (143) and (148) than in the (R)-alcohols (144) and (149).

The absolute stereochemistry of the secondary alcohols (143), (144), (148), and (149) was then determined by a modification of the Horeau method. The method, which uses the partial kinetic resolution of racemic 1-phenylbutyric anhydride was originally employed by Horeau and Kagan to determine the absolute configuration in steroid alcohols. It proved to be more consistent than contemporary circular dichroism methods. In the Horeau method, optical rotation measurements were used to determine the configuration. This required typically 100 μmole of sample. More recently a gas chromatographic method of measurement has permitted the determination to be carried out on very small samples (ca. 2 mg). Each of the chiral secondary alcohols (143), (144), (148), and (149) was esterified with an excess of racemic 1-phenylbutyric anhydride. Using the usual Horeau convention C-7 is taken to be the 'large' group (L) [see (159)] in the (R)-secondary alcohol (149). The 20-methyl group is the 'medium' group (M) in (159). We would expect that alcohols such as (159) would react preferentially with the (R,R)-phenylbutyric anhydride (160) as in Scheme 47. Under kinetic conditions, the reaction of the (R,R)-phenylbutyric anhydride (160) with the alcohols (161) would be much slower (Scheme 48). When the alcohols (159) react preferentially with the (R,R)-anhydride, this leads to an excess of (S,S)- over (R,R)-phenylbutyric anhydride. Two diastereomeric
MeO

OH

Me

HO—  |— m

L

(159)

MeO

O

Me

HO

Me (R)

(149)

R = OCOCH(Ph)Et

(159)

(160)

Scheme 47
amides were then formed by the addition of (+)-(1R)-1-phenyl-ethylamine to the remaining anhydride. The (R,S)-amide, which should be produced in excess for the secondary alcohol (159) has a longer retention time in the gas chromatograph than the (R,R)-amide. For each determination, cyclohexanol was treated in parallel. This gave two peaks of approximately equal area. In each case the area under the curve (a.u.c.) for the (R,S)-amide obtained with cyclohexanol was subtracted from that of the (R,S)-amide obtained with the chiral secondary alcohol to give a corrected value for the alcohol (159). A corrected value was likewise obtained for the alcohol (161). Table 10 shows that the (R)-alcohols (144) and (149), the corrected a.u.c. for the resultant (R,S)-amide is greater than that for the (R,R)-amide. The inverse is true for the (S)-alcohols (143) and (148). (1R)- and (1S)-Menthol were used as
Table 10

Results of Modified Horeau Determinations
of Secondary Alcohols (143), (144), (148), and (149)

<table>
<thead>
<tr>
<th>Stereochem.</th>
<th>C-20</th>
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<th>(R,S)-</th>
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<td>255</td>
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<tr>
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<tr>
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</tbody>
</table>

controls and gave results of the expected sign and magnitude. The results shown in Table 10 confirm the earlier assignments for the sulphur-containing secondary alcohols (148) and (149) which were based solely on relative methods. Furthermore, assignments based on t.l.c. behaviour and shielding effects alone, which have now been proved correct for the secondary alcohols, are thus more likely to be valid for the tertiary alcohols (147b-k) discussed in Section 2.2.2., where no comparable method for the determination of their absolute stereochemistry exists.
Thus Grignard reduction of thevinone (10) is stereoselective; the (S)-diastereomer (143) being formed preferentially. Grignard reduction of 8-thiathevinone (139) is similarly stereoselective; the (S)-diastereomer (148) being formed preferentially. In both cases this is consistent with approach of the Grignard reagent to the β-face of the carbonyl group of thevinone or 8-thiathevinone as in Scheme 45.

2.2.4 Pharmacological screening of tertiary alcohols

The principal requirements for analgesic activity in the thevinols (11) were mentioned in Section 1.1. Tertiary alcohols with the _R_ configuration at C-20 were in all cases more active than those with the _S_ configuration. The observed difference was originally explained by intramolecular hydrogen bonding between the C-20 hydroxy group and the 6-methoxy group. Quantum mechanical calculations showed that in both (R) - and (S) -diastereomers, the conformation with the lowest energy is that in which intramolecular hydrogen bonding takes place. It was therefore proposed that hydrogen bonding caused conformational stabilisation. The superior analgesic potency of the (R) -diastereomers is due to interaction of the C-20 alkyl group with a lipophilic site on the opiate receptor. This interaction was thought to be maximised in the hydrogen bonded conformation. A similar interaction cannot take place in the _S_ configuration.

Rapoport proved that intramolecular hydrogen bonding is not necessary for analgesic potency. Further, he suggested that in the biologically active conformation the C-20 alkyl substituent is actually remote from the 6-methoxy group. Thus the conformation
of the molecule on the receptor is not the one corresponding to the Bentley hydrogen bonded conformation. This conclusion was reached as follows. In the diastereomeric 6-methoxybutylorvinols (162) and (163) intramolecular hydrogen bonding is not possible and there is increased rotational freedom about the C(7)-C(20) bond. The relative agonist potencies of the 6-demethoxybutylorvinols (162) and (163), the diastereomeric butylorvinans (164) and (165), and the diastereomeric butylfurans (166) and (167) are shown in Table 11. That of the butylorvinal (12; R = Bu\textsuperscript{H}) is also given for comparison. The (R) diastereomer (162) is a more potent agonist than the (S)-diastereomer (163). As well as the hydrophobic binding site, Rapoport\textsuperscript{138} proposed an additional hydrophilic site on the surface of the opiate receptor. The C-20 hydroxy group of the 6-demethoxylorvinols interacts with this latter site. The relative
Table 11

Relative Potencies of the 6-Demethoxyorvinols (162) and (163), the Orvinans (164) and (165), and the Furans (166) and (167)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Agonism (XM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(162)</td>
<td>420</td>
</tr>
<tr>
<td>(163)</td>
<td>10</td>
</tr>
<tr>
<td>(164)</td>
<td>187</td>
</tr>
<tr>
<td>(165)</td>
<td>4</td>
</tr>
<tr>
<td>(166)</td>
<td>206</td>
</tr>
<tr>
<td>(167)</td>
<td>19</td>
</tr>
<tr>
<td>(12; R = Bu\textsuperscript{n})</td>
<td>5200\textsuperscript{b}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Analgesia determined by the rat tail flick test unless otherwise stated.

\textsuperscript{b} Analgesia determined by the rat tail pressure test.

Agonist activities of the diastereomeric butylorvinans (164) and (165) support this hypothesis. In the absence of a C-20 hydroxyl group the (R)-diastereomer (164) is more active than the (S)-diastereomer (165). The higher activity of the former is attributed to interaction of the butyl group with the hydrophobic site on the receptor surface. This interaction is not possible in the (S)-diastereomer (165) since interaction of the butyl group with
the hydrophobic site places the 20-methyl group in the hydrophilic area. This leads to destabilisation. Further proof is provided by the diastereomeric furans (166) and (167). The (20S)-furan is the more active diastereomer. This implies that the C-20 butyl group is in the α-position below C-7 and near the etheno bridge. This is opposite to the position it would be in the corresponding orvinol (12; R = Bu<sup>n</sup>) if there were intramolecular hydrogen bonding. On this basis, Rapoport proposed that in the orvinols (12), the lipophilic site on the surface of the receptor accommodates the C-20 alkyl group. The hydrophilic site for the 20-hydroxy group is now above the bicyclic ring system of the orvinol molecule and remote from the 6-methoxy group. Rapoport concluded that interaction of both C-20 substituents (R and OH) with their different sites is a prerequisite for high agonist activity. It is evident that the stereochemical requirements for analgesia are very precise. Failure to interact at these sites is likely to render a structure ineffective as an analgesic.
Formerly, the favoured laboratory methods for assessing analgesia were the rat tail flick test,\textsuperscript{20} the mouse writhing test,\textsuperscript{21} and the rat tail pressure test.\textsuperscript{22} More convenient in vitro testing methods have since been developed.\textsuperscript{140} For the thevinols (11) analgesic activity was measured using the rat tail pressure test, with the alcohols being injected subcutaneously as an aqueous solution of the hydrochloride salts.\textsuperscript{7} In the thevinols (11) increasing the length of the C-20 alkyl group from methyl to ethyl to propyl causes an increase in analgesic activity. Increasing the chain length further, causes a decrease.\textsuperscript{7} In the orvinols (12) a peaking of analgesic activity is seen for butylorvinol\textsuperscript{8} (Figure 1).

The analgesic activities of the 8-thia-7α-alkylthevinols (147a-k) and the 8-thia-7β-methylthevinol (154) were determined in the electrically-stimulated guinea pig ileum preparation using the method of Kosterlitz and Watt.\textsuperscript{140} The method was modified so that the agonist dose response curves were prepared using a cumulative dosing method. The dose response curve for each test compound was bracketed by dose response curves to normorphine as internal standard. The results are shown in Table 12. In vitro testing results for (20R)-n-propyl-, n-butyl-, n-pentyl, and n-hexylthevinols are shown for comparison. The following conclusions are drawn from Table 12.

Replacement of the methylene group at C-8 in the thevinol skeleton with sulphur led to a marked reduction in analgesic potency. The results for diastereomeric pairs of thiathevinols showed that in each case the (R)-diastereomer is more active, suggesting that the stereochemical assignments made earlier are correct. Propylthevinol (145d) was earlier found to be the most
### Table 12

8-Thiathevinols (147) and Thevinols (145); in vitro Analgesic Potency in the Guinea Pig Ileum

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>Stereochem.</th>
<th>Agonism (XN)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C-20</td>
<td></td>
</tr>
<tr>
<td>147a</td>
<td>Me</td>
<td>Me</td>
<td>-</td>
</tr>
<tr>
<td>154</td>
<td>Me</td>
<td>Me</td>
<td>-</td>
</tr>
<tr>
<td>147b</td>
<td>Me</td>
<td>Et</td>
<td>R</td>
</tr>
<tr>
<td>147c</td>
<td>Et</td>
<td>Me</td>
<td>S</td>
</tr>
<tr>
<td>147d</td>
<td>Me</td>
<td>n-Pr</td>
<td>R</td>
</tr>
<tr>
<td>147e</td>
<td>n-Pr</td>
<td>Me</td>
<td>S</td>
</tr>
<tr>
<td>147f</td>
<td>Me</td>
<td>n-Bu</td>
<td>R</td>
</tr>
<tr>
<td>147g</td>
<td>n-Bu</td>
<td>Me</td>
<td>S</td>
</tr>
<tr>
<td>147h</td>
<td>Me</td>
<td>n-pentyl</td>
<td>R</td>
</tr>
<tr>
<td>147i</td>
<td>n-pentyl</td>
<td>Me</td>
<td>S</td>
</tr>
<tr>
<td>147k</td>
<td>n-hexyl</td>
<td>Me</td>
<td>R</td>
</tr>
<tr>
<td>145d</td>
<td>Me</td>
<td>n-Pr</td>
<td>R</td>
</tr>
<tr>
<td>145f</td>
<td>Me</td>
<td>n-Bu</td>
<td>R</td>
</tr>
<tr>
<td>145h</td>
<td>Me</td>
<td>n-pentyl</td>
<td>R</td>
</tr>
<tr>
<td>145j</td>
<td>Me</td>
<td>n-hexyl</td>
<td>R</td>
</tr>
</tbody>
</table>
Relative Potencies of Thevinols (11), Orvinols (12), and Thiathevinols (147)
potent in the series of thevinols (145a-k). In the corresponding thiathevinols, maximum analgesic potency is obtained for the n-pentylthiathevinol (147h) (Figure 1). The 8-thia-7α-methylthevinol (147) had no analgesic activity. However, 8-thia-7β-methylthevinol (154) showed an agonist activity between that of propylthiathevinol (147d) and butylthiathevinol (147f). This derivative is the first 7β-tertiary alcohol to undergo this testing. The result is somewhat unexpected; but is in accord with Rapoport's hypothesis that the hydrophilic site on the receptor surface is in an area above the bicyclic ring system of the thevinol structure and not in the area of the 6-methoxy group.

Reasons for the overall low analgesic potencies of the thiathevinols are not immediately apparent. A contributory factor may be the increased length of the C(7)-sulphur bonds and C(14)-sulphur bonds in the thiathevinols which is accompanied by a change in the bond angles. The result is that the C-20 substituents do not fit their respective lipophilic and hydrophilic sites on the receptor surface as they do in the corresponding thevinols. Another possibility is that the introduction of sulphur into the molecule somehow reduces the bioavailability of the thevinols even in tissue preparations.
2.3 **Reactions of 7-Thiaisothevinone**

2.3.1 **Reaction with methylmagnesium iodide**

The preparation of 7-thiaisothevinone (142) from the kinetically favoured 8-thiathevinone (139) was described in Section 2.2.1.

Our aim was to prepare a series of 8α-tertiary alcohols, isomeric with the tertiary alcohols (147a-k) and to determine their analgesic potencies in the electrically-stimulated guinea pig ileum preparation.

A solution of methyl magnesium iodide in diethyl ether was prepared as described earlier. To this was added a solution of 7-thiaisothevinone (142) in dry benzene and the reactants were heated under reflux for 2 h. The product was shown by t.l.c. to be a mixture. The only isolable product was the rearranged exocyclic diene (168). It had m.p. 261-264 °C and gave a molecular ion $m/z$ 399, having an accurate mass corresponding to $C_{23}N_{29}NO_3S$. Elemental analyses were consistent with this molecular formula and
the structure was assigned on the following grounds. The $^1$H n.m.r. spectrum of (168) showed two three-proton singlets at $\delta$ 1.22 and 1.43 for the geminal methyl groups. The corresponding methyl groups gave a six-proton singlet at $\delta$ 1.09 in the methyl-7α-thiathetinol (147a). The slight downfield shift in (168) may be due to the deshielding effect of the nitrogen lone pair. In the parent 7-thiaisothevinone (142), the olefinic protons gave an AB quartet, $\delta$ 5.72 and 6.09 ($J$ 9 Hz) for 18- and 19-H respectively; whereas in (168) they gave an AB quartet at $\delta$ 5.93 (7-H) and 5.74 (8-H) ($J$ 9.6 Hz). A similarly large coupling constant was observed in the 5,14-bridged esters (134) and (136) than in the 6,14-bridged ester (120). The signal for 5-H in (168) showed splitting ($J$ 1.5 Hz) arising from long range coupling with 7-H; whereas the signal for 8-H showed no long range coupling. Thus the relative position of the two olefinic proton signals is reversed in (168) compared to the parent 7-thiaisothevinone (142). A signal at $\delta$ 5.68 disappeared upon exchange with D$_2$O and was assigned to the 4-hydroxy proton. The corresponding signals in the esters (134)
and (136) appeared at $\delta$ 5.53 and 5.85 respectively. The signal for the 20-hydroxy group in (168) appeared upfield at $\delta$ 2.99. The vinylmethylene protons gave broad singlets at $\delta$ 4.66 and 4.80. 19-H in (168) gave a singlet at $\delta$ 4.74. The corresponding signals for the esters (134) and (136) appeared at $\delta$ 5.53 and 5.93 respectively. The $^{13}$C n.m.r. spectrum showed signals for the conjugated diene system as follows. 8-C and 7-C gave doublets at $\delta$ 128.6 and 132.5 respectively. 6-C gave a singlet at $\delta$ 147.98.
Scheme 49
The exocyclic vinyl carbon gave a triplet at δ 109.93. The infrared spectrum of (168) in trichloromethane showed a sharp band at 3540 cm\(^{-1}\), characteristic of a hydroxy group. The corresponding band for the ester (136) appeared at 3530 cm\(^{-1}\). Three bands at 1635, 1618, and 1590 cm\(^{-1}\) corresponded to the conjugated diene system. A plausible mechanism for the formulation of (168) from the ketone (142) is shown in Scheme 49.

A ten-fold excess of methylmagnesium iodide was used in the initial reaction leading to the formation of (168). Chromatographic separation of the crude reaction mixture was difficult and the diene was obtained in only 17%. If the Grignard reaction takes place preferentially at the carbonyl group, as is most likely (Scheme 49), some of the desired tertiary alcohol (169) ought also to be obtainable. Although (168) was the only isolated component, a minor band of higher \(R_F\) yielded an oil which was shown by t.l.c. to be a mixture. The \(^1\)H n.m.r. spectrum showed some of the features which are compatible with the structure (169) but the oil could not be purified. When the reaction was repeated, again using a
ten-fold excess of methylmagnesium iodide, the exocyclic diene (168) was similarly obtained in 15% yield. A small amount of impure material of higher $R_f$ was isolated but it could not be purified.

In an attempt to form the tertiary alcohol (169) exclusively, the ketone (142) was refluxed for 1 min with a three-fold excess of methylmagnesium iodide. The reaction product was obtained as a pink oil which crystallised on standing. The product, obtained in 45% yield, was the new cyclopropyl methyl ketone (170). It had m.p. 220-222°C and showed a molecular ion at $m/z$ 399 having an accurate mass corresponding to $C_{22}H_{25}NO_4S$. Elemental analyses were consistent with this molecular formula. The structure was assigned as follows. The $^1H$ n.m.r. spectrum of the selenium-containing cyclopropyl ester (172) was particularly useful. The seleno derivative (172) was obtained by heating a mixture of C-7 epimers (171) in toluene (Scheme 50). The $^1H$ n.m.r. spectrum of (170) showed a signal at $\delta$ 5.90 which disappeared on exchange with $D_2O$ and was assigned to the 4-hydroxy group. The corresponding signals in the ester (136) and the seleno adduct (172) appeared at $\delta$ 5.85 and
5.90 respectively. The signal for 5-H in (170) appeared at δ 4.49 and showed allylic coupling (J 2.3 Hz) with 7-H. The signal for 5-H in (172) appeared at δ 4.69 and showed allylic coupling (J 2.4 Hz) with 7-H. 7-H gave a double-doublet, δ 4.61 (J 6.9 and 2.3 Hz) for (170). 8-H gave a signal at ca. δ 2.5 but this was obscured by other signals. In the seleno ester (172) signals for 7-H and 8-H appeared at δ 4.65 and 2.47 respectively (J 6.9 Hz). The singlet corresponding to the 6-methoxy group in the parent ketone (142) appeared at δ 3.58. The corresponding signal in (170) appeared upfield at δ 3.39 and in (172) at δ 3.41. The acetyl signal appeared at δ 2.10 in the ketone (142); but was slightly downfield in (170) at δ 2.27. The infrared spectra in trichloromethane also showed the expected difference in carbonyl stretching frequencies. The ketone (142) showed a band at 1710 cm⁻¹. The corresponding band in the cyclopropyl ketone (170) was at 1680 cm⁻¹. When the Grignard reaction was repeated under identical conditions the cyclopropyl methyl ketone (170) was obtained as the sole product. A plausible mechanism for the rearrangement is shown in Scheme 51 in
Scheme 51
which (170) is formed via the thiolate anion (174). In this scheme
the Grignard reagent is assumed to act first as a base, generating
the enolate (173). In a control experiment a three-fold excess of
methylmagnesium iodide was prepared in dry ether. This was
quenched by the addition of distilled water and cooled to 30°C.
The ketone (142) in the minimum amount of benzene was then added,
followed by saturated ammonium chloride, thus reproducing as far as
possible the conditions of work up used in the formation of the
cyclopropyl methyl ketone (170). The organic layer was separated
and the solution evaporated and dried. The residue contained only
unreacted 7-thiaisothevinone (142); indicating that rearrangement
to (170) had occurred during the course of the reaction rather than
by base catalysis on work up.

Since a three-fold excess of methylmagnesium iodide led to the
cyclopropyl methyl ketone (170) but a ten-fold excess led to the
exocyclic diene (168) it was decided to treat a sample of the
cyclopropyl methyl ketone (178) with a ten-fold excess of methyl-
magnesium iodide under reflux for 1 h. Under these conditions
however (170) was not converted to (168). There was evidence of
some decomposition, but the $^1$H n.m.r. spectrum of the total reaction
mixture showed signals at $\delta$ 2.27 and 3.39 corresponding to 20-H and
the 6-methoxy group, respectively, in the cyclopropyl methyl ketone
(170). Furthermore, signals characteristic of the exocyclic diene
(168) were not seen. This suggests that the ketone (142) reacts
with methylmagnesium iodide by two divergent routes to give two
products depending on the ratio of Grignard reagent to ketone. The
same volumes of ether and benzene were used in each of the Grignard
reactions. With a three-fold excess of methylmagnesium iodide
enolisation of the methyl ketone occurs as the first step. In the presence of a ten-fold excess of methylmagnesium iodide however, addition to the 8α-carbonyl group occurs. In both cases rearrangement takes place by attack of sulphur at C-5 and displacement of the epoxide bridge. [This type of rearrangement took place in the 7-thia-8α-esters (120) and (128)].

2.3.2 Reaction of 7-thiaisothevinone (142) with propyl-lithium

Since the reaction of the ketone (142) with methylmagnesium iodide gave only rearranged products, the reaction of (142) with a two-fold excess of n-propyl-lithium was next investigated in an attempt to form propyl-7-thiaisothevinols. Propyl-lithium was prepared in sodium-dried ether from 1-bromopropane and lithium pieces as before. The solution was cooled to -78°C and the ketone (142) in dry tetrahydrofuran was added slowly and with stirring. Chromatography of the residue on silica plates developed with diethyl ether yielded the crystalline tertiary alcohol (175) in 18% yield along with a small amount of unreacted ketone (142) and some highly polar products. The mass spectrum of (175) showed a
molecular ion at m/z 443 having an accurate mass corresponding to C$_{25}$H$_{33}$NO$_4$S and a peak at m/z 357 (M-86) corresponding to the loss of C$_5$H$_{10}$O. The same fragmentation was observed for the propyl-8-thiathevinols (147d) and (147e). Elemental analyses were consistent with the above formula. A comparison of the $^1$H n.m.r. spectrum with that of the propyl-8-thiathevinols (147d) and (147e) was especially useful. The tertiary alcohol (175) showed a three-proton singlet at $\delta$ 1.04 and a three-proton triplet ($\delta$ 7 Hz) at 0.92 for the 20-methyl group and the terminal methyl group of the propyl group, respectively. The corresponding signals in both (147d) and (147e) appeared at $\delta$ 1.08 and 0.86 ($\delta$ 7 Hz) respectively. 5-H in (175) gave a singlet at $\delta$ 4.70. The corresponding signals for (147d) and (147e) appeared as upfield doublets ($\delta$ 1.1 Hz) at $\delta$ 4.54. The olefinic protons in (175) gave an AB quartet, $\delta$ 6.19 and 5.49 ($\delta$ 10 Hz, 18- and 19-H, respectively). In (147d) and (147e) the corresponding signals appeared at $\delta$ 5.91 and 5.77, respectively. The downfield shift for 18-H in (175) reflects the proximity of sulphur. The olefinic coupling constant in (175) ($\delta$ 10 Hz) was greater than that ($\delta$ 9 Hz) for (147d) and 147e). Similarly, the olefinic coupling constant in the 7-thia-8α-ester (120) was slightly larger than in the 8-thia-7α-ester (119). The signal for 8-H in (175) appeared at $\delta$ 4.99 while the signal for the corresponding proton (7-H) in (147d) and (147e) was obscured by other resonances but was thought to be upfield at ca. $\delta$ 3.8. The downfield position for 8-H in (175) reflects the deshielding effect of the nitrogen lone pair. A similar effect was reported for the 7-thia-8α-ester (120). On the basis of $^1$H n.m.r. spectroscopy it was not possible to assign the stereochemistry at C-20. Examination of the
mother liquors from the crystallisation of (175) by $^1$H n.m.r. spectroscopy showed no sign of the C-20 diastereomer, suggesting that the reaction had proceeded stereoselectively. The tertiary alcohol (175) was tested for analgesic activity in the electrically-stimulated guinea pig ileum preparation. It had a potency 0.17 times that of normorphine. As Table 12, Section 2.2.4 showed, this value is greater than that for the propyl-8-thiathevinols (147d) and (147e). The result confirms earlier indications that codiene and morphine derivatives having tertiary alcohol groups at C-8 are potential morphine agonists.

As in the reaction of 8-thiathevinone (139) with propyl-lithium, the temperature and the rate of addition of 7-thiaisothevinone (142) were found to be crucial to the course of the reaction. When the ketone (142) in dry tetrahydrofuran was added rapidly to a solution of propyl-lithium in dry diethyl ether at $-10^\circ C$, a mixture of products was obtained. The $^1$H n.m.r. spectrum of the crude mixture showed little in common with that of the earlier reaction carried out at $-78^\circ C$. Analytical t.l.c. showed three distinct major bands and several minor ones. The crude mixture was purified on silica plates developed with diethyl ether. The band with $R_F$ 0.32 contained the cyclopropyl methyl ketone (170), which had earlier been obtained in the reaction of (142) with methylmagnesium iodide. The two bands of higher $R_F$ contained the rearranged tertiary alcohols (176). The two alcohols, diastereomeric at C-20, were presumably formed by propylation of the ketone (170). Both alcohols showed virtually identical $^1$H n.m.r. and infrared spectra. Both showed molecular ions at $m/z$ 443 having accurate masses corresponding to $C_{25}H_{33}NO_4S$. It was not possible
to assign the stereochemistry at C-20. The band with $R_F$ 0.88 contained a yellow oil which crystallised from ethanol and had m.p. 199-202°C. This was raised to 208-210°C on recrystallisation and the crystals reformed into long needles from 185°C onwards. The $^1$H n.m.r. spectrum of this alcohol (176) showed signals at $\delta$ 5.80 and 4.24 which disappeared upon exchange with $D_2O$. A one-proton double-doublet ($J$ 6.5 and 2 Hz) at $\delta$ 4.28 was assigned to 7-H. The corresponding signal for the cyclopropyl methyl ketone (170) appeared at $\delta$ 4.61 (dd, $J$ 6.9 and 2.3 Hz). The three-proton singlet at $\delta$ 3.46 was assigned to the 6-methoxy group. This appeared at $\delta$ 3.39 in the ketone (170) but downfield at 3.62 in the tertiary alcohol (175). The less polar alcohol (176) showed a three-proton triplet ($J$ 7 Hz) at $\delta$ 0.92 and a three-proton singlet at 1.31 for the terminal methyl of the propyl group and the 20-methyl group respectively. The corresponding signals for the tertiary alcohol (175) were at $\delta$ 0.92 ($J$ 7 Hz) and 1.04 respectively. The infrared spectra, in trichloromethane, of both tertiary alcohols (176) showed hydroxyl stretching bands at 3540
cm\(^{-1}\). The band with \( R_f 0.85 \) gave the other alcohol (176) which had m.p. 206-209°C. This was raised to 212-214°C on recrystallisation from ethanol. The crystals reformed into long needles from 175°C onwards. The \(^1\)H n.m.r. spectrum was identical to that of the less polar diastereomer except that the signals that disappeared on exchange with D\(_2\)O appeared at \( \delta 5.95 \) and 4.25. To confirm that the reaction of the ketone (142) with propyl-lithium is dependent on temperature the reactions were repeated as follows. When the ketone (142) in dry tetrahydrofuran was added rapidly to a solution of propyl-lithium in ether at \(-10^\circ\)C the rearranged products (170) and (176) were again obtained. When the temperature was maintained at \(-78^\circ\)C with slow addition of the ketone (142), the 7-thia-8\(\alpha\)-tertiary alcohol (175) was obtained as the sole product.

2.4 Conclusions and Future Work

The difficulties encountered with the preparation of the sulphur-containing alkyl-8-thiathevinols (147) contrast with the relatively straightforward synthesis of the familiar alkylthevinols. A persistent problem was the completing rearrangement to 5,14-bridged cycloadducts. The new sulphur-containing tertiary alcohols were obtained as diastereomeric mixtures. The stereochemistry of individual members of the 8-thia series (147) was determined mainly by n.m.r. studies. Data for the corresponding secondary alcohols, whose stereochemistry had been confirmed by absolute means, were also valuable. The alkyl-8-thiathevinols were less potent analgesics than their carbon analogues, the thevinols (145).
The carbon analogues of alkyl-7-thiaisothevinols [e.g., (175)] are inaccessible, since thevinone, unlike 8-thiathevinone, does not isomerise thermally to give the required precursor, 'isothevinone'. There is scope for producing additional members of the new series of alkyl-7-thiathevinols. The propyl derivative (175) has already shown promising analgesic properties. Furthermore, 7-thiaisothevinone (142) potentially provides a simple route to other new structural types. For example, reductive desulphurisation of alkyl-7-thiaisothevinols would lead to a new series of 14-substituted derivatives with analgesic potential.

3-O-Demethylation of thevinols (11) generally gave phenolic orvinols having greater analgesic. Similarly, demethylation of the new alkyl-8-thiathevinols (147) is likely also to give more potent phenolic derivatives.
3. EXPERIMENTAL

3.1 Instrumentation and General Notes

Melting points were determined on a Reichert Kofler hot-stage apparatus. All melting points are corrected.

Stirring of reaction media was carried out using magnetic stirring bars except that in large scale preparations a mechanical stirrer was used.

I.r. spectra were recorded on either a Perkin-Elmer 580 or 953 spectrometer.

$^1$H n.m.r. spectra were recorded, except where stated, at 90 MHz on a Perkin-Elmer R32 or Jeol 90 FT spectrometer. Certain spectra were recorded at 200 MHz on a Bruker WP 200 SY spectrometer. $^{13}$C n.m.r. spectra were recorded on a Bruker WP 200 SY instrument at 50.3 MHz. Chemical shifts throughout are quoted as p.p.m. downfield from tetramethysilane.

Low resolution mass spectra were determined by E.I. (70 eV) on an A.E.I. MS 12 instrument and high resolution spectra on an A.E.I. MS 9 instrument coupled to a GEC-905 computer for data capture and processing.

Analytical t.l.c. was carried out on silica (0.25 mm, Merck GF$_{254}$). Compounds were detected by u.v. light (254 nm).

Preparative t.l.c. was carried out on 20 x 20 cm glass plates coated with silica (0.5 mm, Merck GF$_{254}$) with detection by u.v. light.

Short column chromatography was carried out on silica (Merck HF$_{254}$) under suction applied by a water pump.
Chromatography using the Harrison Chromatotron was carried out under oxygen-free nitrogen at 4 p.s.i. with the detection of compounds by u.v. light.

All solvents used were of analytical reagent grade. Ether refers to diethyl ether. Dry ether refers to ether dried over sodium wire. Light petroleum refers to the fraction b.p. 40-60°C. Solutions in organic solvents were dried over anhydrous magnesium sulphate and evaporated on a rotary evaporator at ca. 40°C under water pump vacuum.

In experiments requiring inert atmospheres nitrogen or argon was dried by passage through Dreschel bottles containing potassium hydroxide pellets and silica gel.

Abbreviations used are as follows:

s singlet
d doublet
dd double doublet
m multiplet
t triplet
q quartet
br broad

3.2 Thioaldehyde Precursors

Sodium S-ethoxycarbonylmethyl thiosulphate (124)

The Bunte salt (124), prepared from ethyl bromoacetate and aqueous sodium thiosulphate according to the literature method,\textsuperscript{121} had m.p. 152-161°C (decomp.) (from ethanol) (lit.\textsuperscript{121} 155°C).
(Found: C, 21.44; H, 2.95; S, 28.76. Calc. for $C_7HNaO_4S_2$: C, 21.62; H, 3.15; S, 28.83%); $\nu_{\text{max}}$ (KBr) 1716 cm$^{-1}$; $\delta_H$ (D$_2$O) 1.31 (t, $J$ 7 Hz, Me), 3.98 (s, CH$_2$), and 4.25 (q, $J$ 7 Hz, CH$_2$CH$_3$) (t-butanol, $\delta$ 1.29, as internal standard).

**Sodium S-methoxycarbonylmethyl thiosulphate (125)**

Freshly distilled methyl chloroacetate (5.0 g, 46 mmol) was added dropwise with stirring at room temperature to sodium thiosulphate pentahydrate (17.9 g, 72.1 mmol) in water (10 ml). The mixture was stirred for 8 h then was evaporated. The residue was extracted with hot methanol (150 ml) and the extracts were filtered. The filtrate, upon cooling, deposited the Bunte salt (125), which was recrystallised from methanol (4.9 g, 51%). The salt had m.p. 150°C (decomp.), (lit. wide m.p. beginning at 150°C) (Found: C, 17.41; H, 2.42; S, 30.73. Calc. for $C_7HNaO_4S_2$: C, 17.31; H, 2.40; S, 30.71%); $\nu_{\text{max}}$ (KBr) 1715 cm$^{-1}$; $\delta_H$ (D$_2$O) 3.75 (s, OMe), and 3.86 (s, CH$_2$) (t-butanol, $\delta$ 1.29 as internal standard).

**Sodium S-(2-oxopropyl) thiosulphate (137)**

**Method A**

Redistilled chloroacetone (3.7 g, 40 mmol) was heated under reflux for 1 h in ethanol (25 ml) containing sodium thiosulphate pentahydrate (14.9 g, 60 mmol). The mixture was evaporated and the residue extracted with hot ethanol to give the salt (137) (2.84 g, 37%). The salt had m.p. 215°C (decomp.) (Found: C, 18.58; H, 2.56; S, 33.71. $C_3HNaO_4S_2$ requires C, 18.75; H, 2.60; S, 33.33%); $\nu_{\text{max}}$ (KBr) 2900, 1710, 1385, 1353, 1255, and 1205 cm$^{-1}$;
Bromoacetone (1.37 g, 10 mmol) in ethanol (5 ml) was added with stirring to sodium thiosulphate pentahydrate (3.89 g, 15 mmol) in water (4 ml) at room temperature. After 5 min, the mixture turned pale yellow. Stirring was continued for 25 min. The mixture was cooled, diluted with ethanol (70 ml) and evaporated to yield a yellow crystalline solid. This was extracted with hot absolute ethanol (50 ml) and the extract was filtered. The Bunte salt (137) (1.24 g, 65%) crystallised from the cooled filtrate.

Bromoacetone

Bromine (50 ml) was added dropwise with stirring to redistilled acetone (71 ml) and glacial acetic acid (52.5 ml) in distilled water (175 ml). The temperature of the reaction mixture was maintained at 65°C. The solution quickly decolourised after each addition of bromine. After 2 h the mixture was cooled in an ice bath. Bromoacetone formed a lower oily layer. Solid Na₂CO₃ (49 g) was added over a 6 h period until the solution was just alkaline. The lower layer was then separated off and dried over anhydrous CaCl₂ which was then filtered off. The filtrate, an orange oil (59 ml) was fractionally distilled. The fraction b.p. 59-70°C (90 mm Hg) was bromoacetone (39.4 g, 34.6%) (lit. 126 43%); δH (CDCl₃) 2.30 (s, COCH₃), and 3.88 (s, CH₂Br).
S-(2-Oxopropyl) toluene-p-thiosulphonate (140)

Following the method of Takano et al., sodium toluene-p-thiosulphonate (21.9 g, 10 mmol) was stirred with Amberlyst A-26 resin (Cl⁻ form, 6.5 g) in distilled water (9.5 ml) for 15 h at room temperature. The resin was then washed with water (4 x 25 ml) to remove sodium chloride, then acetone (4 x 25 ml). The resin-supported toluene-p-thiosulphonate was stirred with 1-chloro-2-propanone (0.694 g, 7.5 mmol) in benzene (7 ml) for 15 h at room temperature. The resin was filtered off and washed with chloroform-benzene (1:1) (50 ml) and the combined filtrate and washings were evaporated to yield the thiosulphonate ester (140) as a yellow oil (1.72 g); H n.m.r. spectroscopy indicated the product composition to be (140) (78%) and 2-oxopropyl 1-(toluene-p-sulphonyl)-2-oxopropyl disulphide (141) (22%). The thiosulphonate ester (140) gave δ_H (CDCl₃) 2.24 (s, tosyl-CH₃), 2.47 (s, Ac), 3.89 (s, CH₂), and 7.39 and 7.82 (4H, ABq, J 9 Hz, aryl-H).

2-Oxopropyl 1-(toluene-p-sulphonyl)-2-oxopropyl disulphide (141)

S-(2-Oxopropyl) toluene-p-thiosulphonate (140) (1.768 g) [containing 22% (141)] was adsorbed onto silica (Merck 60, 'flash' chromatography grade) (50 g) for 48 h in chloroform-benzene (1:1) at room temperature. The silica was eluted with chloroform (200 ml). The eluant contained 29% (140) and 61% (141). It was not possible to separate the two components chromatographically even though they have different R_F values when chromatographed on alumina plates developed with ether-light petroleum. The disulphide (141) gave δ_H (CDCl₃) 2.24 (s, tosyl-CH₃), 2.47 (s, Ac), 3.79 (s, CH₂), 5.18 (s, CH), and 7.38 and 7.81 (4H, ABq, J 9 Hz, aryl-H).
Ethyl 2-thiabicyclo[2.2.1]hept-5-ene-3-carboxylates (99) and (100)

Redistilled triethylamine (141 g, 14 mmol) was added dropwise with stirring to a solution of the Bunte salt (124) (3.11 g, 14 mmol), and calcium/chloride dihydrate (1.71 g, 11.7 mmol) in ethanol (35 ml) containing cyclopentadiene (924 mg, 14 mmol). The reactants were stirred at room temperature. After 24 h 5% aqueous hydrochloric acid (5 ml) was added and the mixture extracted with chloroform. The organic layer was washed successively with dilute hydrochloric acid, dilute sodium hydroxide, and distilled water. The product was a clear oil which contained the endo-cycloadduct (99) and the exo-cycloadduct (100) in the ratio 7:3. The mixture of adducts was purified by Kugelrohr distillation (107°C, 0.02 mbar) (lit. 100 95°C, 0.02 mbar) (1.38 g, 64%) (lit. 100 57%).

3.3 Cycloadducts of Thebaine and Thioaldehydes

Preparation of cycloadducts (119), (120), and (123) from thebaine (3)

Redistilled triethylamine (0.55 g, 5.5 mmol) was added with stirring at room temperature to calcium chloride dihydrate (0.809 g, 5.5 mmol), the Bunte salt (124) (1.32 g, 5.5 mmol), and thebaine (1.56 g, 5.0 mmol) in ethanol-benzene (1:1) (25 ml). Stirring was continued at room temperature for 160 h and the mixture was then diluted with chloroform (100 ml) and filtered through celite. The filtrate was evaporated and the residue (2.8 g) was chromatographed on a silica column (3 x 30 cm) (Merck 60 'flash' chromatography grade) using chloroform-diethyl ether (7:3) (1200 ml). Elution of the cycloadducts was monitored using silica plates developed with diethyl ether. Typical R_F values for the cycloadducts (119), (123),
and (120) were 0.54, 0.61 and 0.72 respectively. Early fractions rich in the minor products (120) and (123) were combined and re-chromatographed on a short silica column using ether-light petroleum (65:35). The 7α-8-thia cycloadduct (119) (1.58 g, 74%) had m.p. 116-118°C (from propan-2-ol) (lit. \textsuperscript{84} 116-118°C), the 8α-7-thia cycloadduct (120) (0.11 g, 5%) had m.p. 126-128°C (from propan-2-ol) (lit. \textsuperscript{84} 125-128°C), and 7β-ethoxycarbonyl-6,7,8,14-tetrahydro-8-thia-6α,14α-ethanothebaine (123) (0.087 g, 4%) had m.p. 139-142°C (from propan-2-ol) (Found: C, 64.51; H, 6.50; N, 3.16; S, 7.45. \( \text{C}_{23} \text{H}_{27} \text{NO}_{5} \text{S} \) requires C, 64.33; H, 6.29; N, 3.26; S, 7.46%); \( \nu_{\text{max}} \) (KBr) 1730 cm\(^{-1} \); \( \delta_{\text{H}} \) (CDCl\(_3\), 200 MHz) 1.32 (t, J 7.1 Hz, OCH\(_2\)-), 1.78 (ddd, J 13.1, 3.5, and 1.0 Hz, 15\( \alpha \)-H), 2.41 (s, NMe), 3.25 (dt, J 12.8 and 5.7 Hz, 15\( \beta \)-H), 3.30 (d, J 18.7 Hz, 10B-H), 3.38 (d, J 6.6 Hz, 9-H), 3.60 (s, 6-OMe), 3.77 (s, 7-H), 3.82 (s, 3-OMe), 4.23 (q, J 7.1 Hz, OCH\(_2\)-Me), 5.55 (d, J 1.6 Hz, 5-H), 5.81 (d, J 9.0 Hz), 19-H), 6.00 (dd, J 9.0 and 1.7 Hz, 18-H), 6.54 (d, J 8.2 Hz, 1-H), 6.64 (d, J 8.2 Hz, 2-H); \( \delta_{\text{C}} \) (CDCl\(_3\)) 14.1 (CH\(_3\)), 23.1 (CH\(_2\)), 30.9 (CH\(_2\)), 43.4 (CH\(_3\)), 45.7 (CH\(_3\)), 49.6 (C), 52.9 (C), 53.2 (CH\(_3\)), 56.7 (CH\(_3\)), 60.2 (CH), 61.7 (CH\(_3\)), 80.7 (C), 89.9 (CH), 114.2 (CH), 119.3 (CH), 125.8 (CH), 126.7 (C), 134.3 (C), 136.2 (CH), 142.3 (C), 147.4 (C), and 170.8 (S) (Found: \( m/z \) 429.1614. \( \text{C}_{23} \text{H}_{27} \text{NO}_{5} \text{S} \) requires \( m/z \) 429.1610).

Control Experiment on the Stability of the Cycloadduct (119)

Redistilled triethylamine (91 mg, 0.9 mmol) was added with stirring at room temperature to calcium chloride dihydrate (132 mg, 0.9 mmol), the Bunte salt (124) (215 mg, 0.9 mmol), and the cycloadduct (119) (350 mg, 0.82 mmol) in ethanol-benzene (1:1) (4 ml). The mixture was stirred for 144 h, then diluted with
chloroform and filtered through celite. The filtrate was evaporated and examination of the residue by t.l.c. and $^1$H n.m.r. spectroscopy showed no significant amounts of the adducts (120) and (123). Chromatography of the mixture on a short silica column gave the cycloadduct (119) (284 mg, 81%).

8α-Ethoxycarbonyl-6,7,8,14-tetrahydro-7-thia-6α,14α-ethanothebaine (120)

Method A

The cycloadduct (119) (2.15 g, 5 mmol) was heated under reflux in redistilled toluene (50 ml) for 6 h. Evaporation of the solution and crystallisation of the residue from propan-2-ol yielded the cycloadduct (120), m.p. 126-128°C (lit. 125-128°C) (1.66 g, 77%) (lit. 84% 82%).

Method B

The mixture of cycloadducts (99) and (100) (7:3) (920 mg, 5 mmol) was heated in toluene at 100°C with thebaine (3) (1.41 g, 4.5 mmol) for 8 h. Evaporation of the solution yielded a residue which was purified on a short silica column using ether-light petroleum (7:3). The cycloadduct (120) had m.p. 126-128°C (1.34 g, 69%).

Base-catalysed Epimerisation of the Esters (119) and (123)

Potassium t-butoxide (0.6 mmol) in t-butyl alcohol (3 ml) was added with stirring to the 7α-8-thia ester (119) (284 mg, 0.66 mmol) in t-butyl alcohol (2 ml). The solution was stirred for 30 min during which time it turned from colourless to dark orange. Saturated ammonium chloride (6 ml) and dichloromethane (10 ml) were added. Evaporation of the solution yielded a yellow oil which was
a mixture of the 7α-8-thia ester (119) and the 7β-8-thia ester (123). The ratio of (119) to (123), as determined by $^1$H n.m.r. spectroscopy and t.l.c. [neutral Merck 60 GF254 Al $\text{O}_3$ developed with ether-light petroleum (65:35)], was 85:15. The mixture was separated by t.l.c. using ether. The minor band, $R_F$ 0.71, contained the 7β-8-thia ester (123) (0.07 g, 25%) m.p. 140-142°C (from propan-2-ol) (expected, 139-142°C). The major band $R_F$ 0.57, contained the ester (119) (0.06 g, 21%), m.p. 116-118°C (from propan-2-ol) (lit. $^{84}$ 116-118°C). To confirm that equilibrium had occurred under basic conditions the 7α-8-thia ester (123) was stirred with potassium t-butoxide (0.3 mmol) in t-butyl alcohol (3 ml) at room temperature. After 30 min saturated ammonium chloride (5 ml) and dichloromethane (5 ml) were added. The organic layer gave a yellow oil. $^1$H n.m.r. spectroscopy showed that the residue contained the 7α-8-thia ester (119) and the 7β-8-thia (123) in the ratio 80:20.

Ethyl 7,8-didehydro-3β,6β-dimethoxy-17-methyl-4,6α-epoxy-5β,14β-thiaethanomorphinan-(19R)-carboxylate (134)

The 8α-7-thia cycloadduct ester (120) (200 mg, 0.46 mmol) was heated in refluxing chlorobenzene (25 ml) for 30 h. Evaporation of the solvent yielded a 2:8 mixture of (120) and the acetal (134) which was separated by t.l.c. [neutral Merck 60 GF254 Al $\text{O}_3$ using ether-light petroleum (65:35)]. The $R_F$ values for isomers (120) and (134) were 0.7 and 0.6 respectively. The minor isomer (120) (33 mg, 16%), eluted from the plates with CHCl$_3$ had m.p. 126-128°C (lit. $^{84}$ 125-128°C). The acetal (134) (127 mg, 64%), eluted with CH$_2$Cl$_2$, was obtained as a colourless oil which did not crystallise;
\[ \text{Vmax. (KBr)} 2919, 1728, 1490, 1278, 1222, 1150, \text{and } 1055 \text{ cm}^{-1}; \delta_H \]

(CDC\(_1\)\(_3\), 200 MHz), 1.24 (t, J 7.1 Hz, OCH\(_2\)CH\(_3\)), 2.38 (s, NMe), 3.38 (d, J 19.0 Hz, 10-H), 3.49 (d, J 2.4 Hz, 5-H), 3.50 (d, J 6 Hz, 9-H), 3.59 (s, 6-OMe), 3.80 (s, 3-OMe), 4.12 (m, OCH\(_2\)CH\(_3\)), 5.24 (dd, J 2.4 and 10.0 Hz, 7-H), 5.53 (s, 19-H); 6.05 (dd, J 10.0 and 0.6 Hz, 8-H), 6.62 (s, 1-H and 2-H), \(\delta_C\) (CDC\(_1\)\(_3\)) 14.1 (CH\(_3\)), 25.5 (CH\(_2\)), 30.6 (CH\(_2\)), 43.2 (CH\(_3\)), 44.8 (CH\(_2\)), 49.6 (C), 50.9 (CH or CH\(_3\)), 51.5 (CH or CH\(_3\)), 54.3 (CH or CH\(_3\)), 56.2 (C), 56.3 (CH or CH\(_3\)), 57.1 (CH or CH\(_3\)), 61.2 (CH\(_2\)), 106.8 (C), 109.9 (CH), 118.5 (CH), 124.8 (CH), 128.6 (C), 130.7 (C), 138.0 (CH), 143.0 (C), 146.6 (C), 170.1 (C)

(Found: m/z 429.1620 and 310.1432. C\(_{23}\)H\(_{27}\)NO\(_5\)S and C\(_{19}\)H\(_{20}\)NO\(_3\) require M, 429.1610 and 310.1444, respectively).

Ethyl 7,8-didehydro-4-hydroxy-3-methoxy-17-methyl-6-oxo-5ß,14ß-thiaethanomorphinan-(19R)-carboxylate (136)

The acetal (134) (75 mg, 0.175 mmol) was heated in 2N-hydrochloric acid (15 ml) at 100°C for 5 min. The reaction mixture was treated with aqueous 5% sodium bicarbonate until effervescence ceased and the solution was slightly alkaline. The solution was then extracted with chloroform and the extracts were washed with distilled water (2 x 10 ml). Evaporation of the solvent yielded the ketone (136) as a white crystalline solid (49 mg, 67%), m.p. 173-174°C (from 50% aqueous methanol) (Found: C, 63.51; H, 5.87; N, 2.95. C\(_{22}\)H\(_{25}\)NO\(_5\)S requires C, 63.61; H, 6.02; N, 3.37%; \(\nu\) \(_{\text{max.}}\) (KBr) 1733, 1685, 1490, and 1282 cm\(^{-1}\); \(\delta_H\) (CCl\(_4\)) 3530, 1729, 1690, 1484, and 1280 cm\(^{-1}\); \(\delta_C\) (CDC\(_1\)\(_3\), 200 MHz) 1.24 (t, J 7.1 Hz, OCH\(_2\)CH\(_3\)), 2.36 (s, NMe), 2.74 (dd, J 18.7 and 5.8 Hz, 10\(\alpha\)-H), 3.17 (d, J 18.7 Hz, 10\(\beta\)-H), 3.68 (d, J 5.0 Hz, 9-H), 3.75
Thermal Equilibrium of the 8α-7-thia Cycloadduct Ester (120) and the Acetal (134)

Two ground-glass thermometer tubes were adapted for Subaseal stoppers and placed in the sidearms of a 100 ml three-necked flask so that the tubes were immersed in the vapour of refluxing chlorobenzene (15 ml). Each tube contained the 8α-7-thia cycloadduct ester (120) (25 mg) in the appropriate solvent (1 ml) (see Table 6). Dry nitrogen was bubbled into the solutions through 10 cm syringe needles prior to heating. Thus, the conversions of (120) to (134) were compared at 132°C in xylene and chlorobenzene, chlorobenzene and o-dichlorobenzene, and o-dichlorobenzene and nitrobenzene, for selected periods for each pair of solvents. Each conversion was followed by t.l.c. [neutral Merck 60 GF254 Al₂O₃ developed with ether-light petroleum (65:35)]. The Rₚ values for the isomers (120) and (134) were 0.7 and 0.6 respectively. After the times shown in Table 6, Section 2.1.2, the solvents were evaporated. The ratio of (134) to (120) was determined from the
relative intensities of the $^1$H n.m.r. signals at $\delta$ 5.53 for isomer (134) and 4.98 for isomer (120).

Preparation of the Cycloadducts (126), (127), and (128) of Thebaine (3) and Methyl Thiooxacetae

Redistilled triethylamine (0.55 g, 5.5 mmol) was added with stirring at room temperature to calcium chloride dihydrate (0.809 g, 5.5 mmol), the Bunte salt, sodium S-methoxycarbonylmethyl thiosulphate (125) (1.09 g, 5.5 mmol) and thebaine (1.56 g, 5.0 mmol) in methanol-benzene (1:1) (25 ml). Stirring was continued at room temperature for 160 h. The mixture was diluted with chloroform (100 ml) and filtered through celite. The filtrate was evaporated and the residue (2.4 g) was chromatographed on a short column using ether-light petroleum (65:35). Elution of cycloadducts was monitored using silica plates developed with ether.

7α-Methoxycarbonyl-6,7,8,14-tetrahydro-8-thia-6α,14α-ethenothebaine (126) ($R_F$ 0.59) (1.52 g, 73%) had m.p. 142-144°C (from propan-2-ol) (Found: C, 63.47; H, 5.89; N, 3.15; S, 7.55. C$_{22}$H$_{25}$NO$_5$S requires C, 63.61; H, 6.02; N, 3.37; S, 7.71%); $\nu$ (KBr) 2920 (m), 2840, 2800, 1750, 1725, 1630, 1600, 1500, 1440, and 1325 cm$^{-1}$; $\delta$ (CDCl$_3$) 2.37 (s, NMe), 3.22 (d, $\downarrow$ 19 Hz, 10β-H), 3.40 (d, $\downarrow$ 7 Hz, 9-H), 3.63 (s, 6-OMe), 3.68 (s, CO$_2$CH$_3$), 3.81 (s, 3-OMe), 4.54 (s, 5-H), 5.86 (br s, 18-H and 19-H), 6.57 (d, $\downarrow$ 8 Hz, 1-H) and 6.63 (d, $\downarrow$ 8 Hz, 2-H); (Found: m/z 415.1460. C$_{22}$H$_{25}$NO$_5$S requires M, 415.1454).

7β-Methoxycarbonyl-6,7,8,14-tetrahydro-8-thia-6α,14α-ethanothebaine (127) ($R_F$ 0.62 (0.079 g, 4%), had m.p. 154-156°C (from propan-2-ol) (Found: C, 63.56; H, 6.00; N, 3.12; S, 7.98. C$_{22}$H$_{25}$NO$_5$S requires C, 63.61; H, 6.02; N, 3.37; S, 7.71%);
\[ \nu_{\text{max.}} \text{(KBr)} \quad 2950 \, \text{m}, \quad 2845, \quad 2810, \quad 1735, \quad 1629, \quad 1600, \quad 1500, \quad 1450, \quad 1380, \quad \text{and} \quad 1330 \, \text{cm}^{-1}; \quad \delta_{\text{H}} \text{(CDCl}_3\text{)} \quad 2.39 \, \text{(NMe)}, \quad 3.22 \, \text{(d, J 19 Hz, 10\text{β}-H)}; \quad 3.40 \, \text{(d, J 8 Hz, 9-H)}, \quad 3.59 \, \text{(s, CO}_2\text{CH}_3\text{)}, \quad 3.75 \, \text{(s, 6-OMe)}, \quad 3.81 \, \text{(s, 3-OMe)}, \quad 5.57 \, \text{(d, J 1 Hz, 5-H)}, \quad 5.79 \, \text{(d, J 8 Hz, 19-H)}, \quad 5.98 \, \text{(dd, J 1 and 18 Hz)}, \quad 6.52 \, \text{(d, J 8 Hz, 1-H)}, \quad \text{and} \quad 6.63 \, \text{(d, J 8 Hz, 2-H)}; \quad \text{(Found: m/z 415.1437. C}_{22}\text{H}_{25}\text{NO}_5\text{S requires M, 415.1454).} \\

8\alpha\text{-Methoxycarbonyl-6,7,8,14-tetrahydro-7-thia-6α,14α-ethenothebaine (128) (R}_f \text{ 0.67) (0.134 g, 6%), had m.p. 138-140°C (from propan-2-ol) (Found: C, 63.48; H, 6.18; N, 3.12; S, 7.69. C}_{22}\text{H}_{25}\text{NO}_5\text{S requires C, 63.61; H, 6.02; N, 3.37; S, 7.71%); } \nu_{\text{max.}} \text{(KBr)} \quad 2940 \, \text{m}, \quad 2840, \quad 2800, \quad 1738, \quad 1633, \quad 1605, \quad 1508, \quad 1455, \quad 1379, \quad 1335, \quad \text{and} \quad 1288 \, \text{cm}^{-1}; \quad \delta_{\text{H}} \text{(CDCl}_3\text{)} \quad 2.34 \, \text{(s, NMe)}, \quad 3.59 \, \text{(s, CO}_2\text{CH}_3\text{)}, \quad 3.68 \, \text{(s, 6-OMe)}, \quad 3.80 \, \text{(s, 3-OMe)}, \quad 4.95 \, \text{(d, J 1.5 Hz, 5-H)}, \quad 5.25 \, \text{(s, 8-H)}, \quad 5.71 \, \text{(d, J 9.5 Hz, 19-H)}, \quad 6.19 \, \text{(d, J 9.5 Hz, 18-H)}, \quad 6.56 \, \text{(d, J 8.1 Hz, 1-H)}, \quad \text{and} \quad 6.62 \, \text{(d, J 8.1 Hz, 2-H)}; \quad \text{(Found: m/z 415.1448. C}_{22}\text{H}_{25}\text{NO}_5\text{S requires M, 415.1454).} \\

Methyl 7,8-didehydro-3,6β-dimethoxy-17-methyl-4,6α-epoxy-5β,14β-thiaethanomorphinan-(19R)-carboxylate (135) 

The cycloadduct (128) (0.145 g, 0.35 mmol) was heated in refluxing toluene for 25 h. Evaporation of the solvent yielded a 2:8 mixture of (128) and (135) which was separated by t.l.c. [neutral Merck 60\text{GF254 Al}_2\text{O}_3 \text{ using ether-light petroleum (55:45)]. The R}_f \text{ values for isomers (128) and (135) were 0.65 and 0.52 respectively. The minor isomer (128), (21 mg 15%), eluted from the plates with CHCl}_3 \text{ had m.p. 138-140°C (from propan-2-ol) (expected 138-140°C). The acetal (135) (95 mg, 65%), eluted with CH}_2\text{Cl}_2 \text{ was a colourless resin which did not crystallise: } \nu_{\text{max.}} \text{(KBr)} \quad 2919 \, \text{(m), 1735, 1490, 1438, 1378, and 1278 cm}^{-1}; \quad \delta_{\text{H}} \text{(CDCl}_3\text{)} \quad 2.38 \, \text{(s, NMe)}, \quad $
3.58 (s, CO₂Me), 3.50 (d, J 1.5 Hz, 5-H), 3.67 (s, 6-OMe), 3.80 (s, 3-OMe), 5.25 (dd, J 10 and 1.5 Hz, 7-H), 6.04 (d, J 10 Hz, 8-H), and 6.60 (s, 1- and 2-H); (Found: m/z 415.1453. C₂₂H₂⁵NO₄S requires M, 415.1454).

7α-Acetyl-6,7,8,14-tetrahydro-8-thia-6α,14α-ethenothebaine, 8-thiathevinone (139)

Method A

Redistilled triethylamine (151 mg, 1.49 mmol) was added with stirring at room temperature to calcium chloride dihydrate (219 mg, 1.49 mmol), the Bunte salt, sodium S-(2-oxopropyl) thiosulphate (137) (366 mg, 1.49 mmol), and thebaine (309 mg, 0.99 mmol) in ethanol-benzene (1:1) (15 ml). After 8 h, the same quantities of triethylamine, calcium chloride and Bunte salt (137) were again added to the reaction mixture. After a further 25 h, the mixture was diluted with chloroform (50 ml) and then filtered through celite. The filtrate was washed twice with distilled water, dried then evaporated, and the residue chromatographed on silica plates developed with ether. The cycloadduct (139) (Rᶠ ca. 0.39) was obtained as a yellow resin (166 mg, 42%) (Found: m/z 399.1502. C₂₂H₂⁵NO₄S requires M, 399.1504); ν max (CHBr₃) 1690 cm⁻¹; δH (CDCl₃) 2.09 (s, Ac), 2.47 (s, NMe), 3.22 (d, J 19 Hz, 10B-H), 3.40 (d, J 8 Hz, 9-H), 3.56 (s, 6-OMe), 3.79 (s, 3-OMe), 3.90 (s, 7-H), 4.51 (s, 5-H), 5.79 (s, 18- and 19-H), 6.45 (d, J 8 Hz, 1-H), and 6.54 (d, J 8 Hz, 2-H).

Method B

The thiosulphonate ester (140) (17.0 g, 69.7 mmol) was dissolved in benzene (100 ml). Calcium chloride dihydrate (10.24 g, 69.7 mmol) was dissolved in ethanol (280 ml) and mixed with the
ester solution. Thebaine (7.23 g, 23.2 mmol) in benzene (220 ml) was added with stirring. Triethylamine (7.05 g, 69.7 mmol) in benzene (800 ml) was then added over 15 min to the mixture. Stirring was continued at room temperature for 120 h. The mixture was filtered through celite. The filtrate was washed with distilled water (5 x 200 ml), to remove triethylamine hydrochloride and residual calcium p-toluene thiosulphonate, dried and evaporated to yield a yellow oil. This was purified on a silica column (Merck No. 7734, 500 g) using dichloromethane-methanol (98:2). The cycloadduct (139) was obtained as a yellow oil (6.9, 75%).

Method C

Redistilled triethylamine (0.03 g, 0.3 mmol) was added with stirring at room temperature to calcium chloride dihydrate (0.443 g, 0.3 mmol) α-tosyldisulphide (141) (0.1 g, 0.3 mmol) and thebaine (0.187 g, 0.6 mmol) in benzene-ethanol (1:1) (12 ml). Stirring was continued for 12 h. The mixture was diluted with chloroform (15 ml) and filtered through celite. The filtrate was washed with distilled water, dried, and evaporated. $^1$H n.m.r. spectroscopy indicated a composition for the mixture: cycloadduct (139): thebaine: α-tosyldisulphide (141), 29:63:8.

8α-Acetyl-6,7,8,14-tetrahydro-7-thia-6α,14α-ethenothebaine (142)

The 7α-8-thia cycloadduct (139) (122 mg, 0.3 mmol) was heated under reflux in redistilled toluene (10 ml) for 5 h. The solution was evaporated to yield a semi-crystalline residue, which was chromatographed on silica plates using ether. The band with $R_f$ 0.66 contained the 7-thia isomer (142) (42 mg, 35%), m.p. 150-151°C (from ethanol) (Found: C, 66.11; H, 6.15; N, 3.33; S, 8.2.
C\textsubscript{22}H\textsubscript{25}NO\textsubscript{4}S requires C, 66.16; H, 6.27, N, 3.51; S, 8.02%; \(\nu\)\textsubscript{max.} (KBr) 2925, 2830, 2795, 1710, 1630, 1600, and 1500 cm\textsuperscript{-1}; \(\delta\)\textsubscript{H} (CDCl\textsubscript{3}) 2.10 (s, Ac), 2.30 (s, NMe), 3.20 (d, \(J\) 18 Hz, 10\textsuperscript{B}-H), 3.58 (s, 6-OMe), 3.79 (s, 3-OMe), 4.97 (s, 5-H), 5.28 (s, 8-H), 5.72 (d, \(J\) 9 Hz, 19-H), 6.09 (d, \(J\) 9 Hz, 18H), 6.52 (d, \(J\) 8 Hz, 1-H), 6.62 (d, \(J\) 8 Hz, 2-H) (Found: m/z 399.1513. C\textsubscript{22}H\textsubscript{25}NO\textsubscript{4}S requires M, 399.1504).

3.4 Secondary Alcohols

Reduction of 8-thiathevinone (139)

8-Thiathevinone (139) (370 mg, 0.93 mmol) was heated under reflux in methanol with sodium borohydride (36 mg, 0.93 mmol) for 1 h. The methanol was evaporated to yield a brown residue. This was dissolved in chloroform and the solution was washed with distilled water, dried, and evaporated. The residue was separated into two components by preparative t.l.c. (neutral Merck 60\textsubscript{Gf}254 Al\textsubscript{2}O\textsubscript{3} using butanone, multiple elutions). The band with \(R_F\) 0.74 gave the (20S) secondary alcohol (148) as a yellow oil which could not be crystallised (152 mg, 41%); \(\nu\)\textsubscript{max.} (CCl\textsubscript{4}) 3520, 2930 (m), 2840, 2800, 1630, 1600, 1500, 1440, and 1110 cm\textsuperscript{-1}; \(\delta\)\textsubscript{H} (CDCl\textsubscript{3}) 1.06 [d, \(J\) 6 Hz, CH(OH)Me], 1.88 (s, OH, exch. with D\textsubscript{2}O), 2.43 (s, NMe), 3.27 (d, \(J\) 19 Hz, 10\textsuperscript{B}-H), 3.65 (s, 6-OMe), 3.82 (s, 3-OMe), 4.21 (br q, 20-H), 4.52 (s, 5-H), 5.69 (d, \(J\) 9 Hz, 19-H), 5.83 (ABq, \(J\) 9 Hz, 18- and 19-H), and 6.63 (d, \(J\) 8 Hz, 2-H) (Found: m/z 401.1658. C\textsubscript{22}H\textsubscript{27}NO\textsubscript{4}S requires M, 401.1661). The band with \(R_F\) 0.66 contained the (20R) secondary alcohol (149) (55 mg, 15%), m.p. 183.5-185°C (from ethanol) (Found: C, 66.52; H, 6.68; N, 3.03; S, 7.78. C\textsubscript{22}H\textsubscript{27}NO\textsubscript{4}S requires C, 65.83; H, 6.73; N, 3.49; S, 7.98%).
\( \nu_{\text{max.}} (\text{CCl}_4) 3500, 2940 \text{ (m), 2840, 2800, 1630, 1598, 1550, and 1500} \text{ cm}^{-1}; \delta_H (\text{CDCl}_3) 1.11 \text{ [d, J 7 Hz, CH(OH)Me]}, 4.65 \text{ (s, OH, exch. with D}_2\text{O), 2.37 \text{ (s, NMe), 3.72 \text{ (s, 6-OE), 3.82 \text{ (s, 3-OE), 4.56 \text{ (s, 5-H), 5.79 \text{ (s, 18- and 19-H), 6.53 (d, J 8 Hz, 1-H, and 6.63 (d, J 8 Hz, 2-H} (\text{Found: } \text{m/z} 401.1666. \text{ C}_{22}\text{H}_{27}\text{NO}_{4}\text{S requires } \text{M, 401.1661).}}

**Determination of Absolute Stereochemistry in the Secondary Alcohols (148) and (149) by a Modification of Horeau's Method**

Gas chromatography was carried out on a Perkin-Elmer F11 gas chromatograph using a hydrogen flame ionisation detector. A silanised glass column of length 3 m and internal diameter 3.5 mm packed with 1% OV-17 on Gas ChromQ, 100-120 mesh size, was used. The nitrogen flow rate was 40 ml min\(^{-1}\). The column temperature was 100°C. Racemic 1-phenylbutyric anhydride (4 \(\mu\)l) was added to each of the secondary alcohols (143), (144), (148), and (149) (1 mg) in dry pyridine (7 \(\mu\)l) and the mixtures were heated at 45°C for 50 min in an aluminium block. (+)-(1\(R\))-Phenylethylamine (6 \(\mu\)l) was added to the mixtures. The amide which precipitated was then redissolved by the addition of Nanograde ethyl acetate (100 \(\mu\)l). The solution was heated gently at 100°C. After 6 min further Nanograde ethyl acetate (400 \(\mu\)l) was added and a 1 \(\mu\)l sample immediately injected into the gas chromatograph. The same procedure was carried out for cyclohexanol. Areas under each curve were calculated using \((\text{peak height } \times \text{retention time}) \div 2\). That for the \((R,S)\)-amide from the reaction with cyclohexanol was subtracted from the area for the \((R,S)\)-amide obtained from the chiral secondary alcohol. A similar correction was made for the area under the \((R,R)\)-amide curve.
the (R,R)-area exceeded the (R,S)-area that alcohol was assigned the (S)-stereochemistry. When the inverse was true, it was assigned the (R)-stereochemistry.

3.5 Reactions of 8-Thiathevinone

Treatment of 8-Thiathevinone (139) with Grignard Reagents: the Formation of Tertiary Alcohols

7α-(1-Hydroxy-1-methylethyl)-6,7,8,14-tetrahydro-8-thia-6α,14α-ethenothebaine (147a)

8-Thiathevinone (139) (400 mg, 1 mmol) in benzene (20 ml) was added to a vigorously refluxing solution of methylmagnesium iodide (439 mg, 2.65 mmol) prepared in dry ether (5 ml). The solution was heated under reflux for 4 h during which time it became dark orange. After cooling, saturated ammonium chloride (10 ml) was added. The organic layer which formed was separated off, dried, and evaporated to yield a yellow oil. This was purified on silica plates developed with ether. The band with RF 0.33 contained methylthiathevinol (147a) (71 mg, 17%), m.p. 162-164°C (from ethanol) (Found: C, 66.68; H, 6.75; N, 3.24; S, 7.45. C_{23}H_{29}NO_4S requires C, 66.51; H, 6.99; N, 3.37; S, 7.71%). ν_max. (KBr) 3505, 2930 (m), 2830, 2970, 1630, 1600, and 1500 cm^{-1}; ν_max. (CCl_4) 3510, 2922 (m), 2850, 2810, and 1505 cm^{-1}; δ_H (CDCl_3) 1.09 (s, CMe2), 2.40 (s, NMe), 3.24 (d, J = 19 Hz, 19-H), 3.36 (s, 7-H), 3.79 (s, 6-OMe), 3.82 (s, 3-OMe), 4.45 (s, OH, exch. with D_2O), 4.52 (s, 5-H), 5.76 (d, J = 9 Hz, 19-H), 5.88 (d, J = 9 Hz, 18-H), 6.51 (d, J = 8 Hz, 1-H), 6.61 (d, J = 8 Hz, 2-H) (Found: m/z 415.1796. C_{23}H_{29}NO_4S requires M, 415.1817).
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8-Thiathevinone (139) (3.99 g, 10 mmol) in sodium-dried toluene (25 ml) was added to a refluxing solution of ethyl magnesium bromide in dry ether. The residue, obtained by the work up described for (147a), was purified by column chromatography [Florisil using dichloromethane-methanol (97:3)]. The early fractions were purified using the Harrison Chromatotron (2 mm SiO₂ plates, ether-light petroleum (25:75)]. Later fractions were passed through a second Florisil column prior to purification on the chromatotron. Separation using the Chromatotron was monitored by t.l.c. (SiO₂ plates developed with ether). The band with Rₚ 0.44 contained the (20R)-ethylthiathevinol (147b) (429 mg, 10%), m.p. 129-130°C (from ethanol) (Found: C, 66.74; H, 7.33; N, 3.15. C₂₄H₃₁NO₄S requires C, 67.10; H, 7.27; N, 3.26%; v max. (CHBr₃) 3430, 3290 (m), 2820, 2790, 1630, 1600, 1500, 1450, and 1370 cm⁻¹; δH (CDCl₃) 0.95 (t, J 7 Hz, CH₂CH₃), 1.08 (5H, br s), 2.41 (s, NMe), 3.81 (s, 6-OMe), 3.83 (s, 3-OMe), 4.55 (s, OH, exch. with D₂O), 4.55 (d, J 1 Hz, 5-H), 5.77 (d, J 9 Hz, 19-H), 5.92 (d, J 9 Hz, 18-H), 6.55 (d, J 8 Hz, 1-H), and 6.65 (d, J 8 Hz, 2-H) (Found: m/z 429.1977. C₂₄H₃₁NO₄S requires M, 429.1974). The band with Rₚ 0.31 contained the (20S)-ethylthiathevinol (147c) (381 mg, 9%), m.p. 169-171°C (from ethanol) (Found: C, 66.80; H, 7.19; N, 3.13. C₂₄H₃₁NO₄S requires C, 67.10; H, 7.27; N, 3.26%; v max. (CHBr₃) 3460, 2900 (m), 2840, 2800, 1630, 1600, 1500, and 1450 cm⁻¹; v max. (CCl₄) 3518, 2950 (m), 2850, 2810, 1635, 1604, 1508, 1450, and 1112 cm⁻¹; δH (CDCl₃) 0.86 (t, J 8 H, CH₂CH₃), 1.03 [s, C(OH)Me], 2.39 (s, NMe), 3.26 (d, J 20 Hz, 10β-H), 3.45 (s, 7-H), 3.79 (s, 6-OMe),
3.83 (s, 3-OMe), 4.05 (s, OH, exch. with D₂O), 4.53 (s, 5-H), 5.76 (d, J 9 Hz, 19-H), 5.87 (d, J 9 Hz, 18-H), 6.52 (d, J 8 Hz, 1-H), and 6.62 (d, J 8 Hz, 2-H). (Found: m/z 429.1916. C₂₄H₃₁NO₄S requires M, 429.1974).

7α-(1-Hydroxy-1-methylbutyl)6,7,8,14-tetrahydro-8-thia-6α,14α-ethenothebaines (147d) and (147e)

8-Thiathievinone (139) (3.99 g, 10 mmol) in sodium-dried toluene (25 ml) was added to a refluxing solution of propylmagnesium bromide (8.82 g, 60 mmol) prepared in dry ether (25 ml). The solution was heated under reflux for 2 h. The residue, obtained as before was purified by column chromatography [SiO₂, Merck (60) No. 7734, 300 g] using dichloromethane-methanol (98:2). Earlier fractions were purified using the Chromatotron [2 mm SiO₂ plates, ether-light petroleum (25:75)]. Later fractions were passed through a second silica column prior to purification on the Chromatotron. The separation was monitored by t.l.c. (SiO₂ plates developed with ether). The band with Rₚ 0.62 contained the (20R)-propylthiathevinol (147d) (272 mg, 6%), m.p. 178.5-179.5°C (from ethanol) (Found: C, 67.60; H, 7.23; N, 3.15. C₂₅H₃₃NO₄S requires C, 67.72; H, 7.45; N, 3.16%); v_max (KBr) 3445, 2930 (m), 2830, 2790, 1630, 1595, and 1500 v_max. (CCl₄) 3510, 2940 (m), 2845, 2800, 1635, and 1502 cm⁻¹; v_max. (CHBr₃) 3450 cm⁻¹; δ_H (CDCl₃) 0.86 (t, J, 6.7 Hz, CH₂CH₂), 1.08 [s, C(OH)Me], 2.42 (s, NMe), 3.26 d, J 18 Hz, 108-H), 3.39 (s, 7-H), 3.81 (s, 6-OMe), 3.83 (s, 3-OMe), 4.54 (s, OH, exch. with D₂O), 4.55 (s, 5-H), 5.77 (d, J 9 Hz, 19-H), 5.91 (d, J 9 Hz, 18-H), 6.55 (d, J 8 Hz, 1-H), and 6.66 (d, J 8 Hz, 2-H) (Found: m/z 443.2143. C₂₅H₃₃NO₄S requires M, 443.2130). The band with Rₚ 0.56 contained the
(20S)-propylthiathevinol (147e) (351 mg, 8%), m.p. 118-120°C (from ethanol) (Found: C, 67.49; H, 7.33; N, 3.17. \( C_{25}H_{33}NO_4S \) requires C, 67.72; H, 7.45; N, 3.16%); \( \nu_{\text{max.}} \) (CHBr\(_3\)) 3450, 2950 (m); \( \nu_{\text{max.}} \) (CCl\(_4\)) 3500, 2930 (m), 1630, 1600, 1500, 1440, and 1108 cm\(^{-1}\); \( \delta_H \) (CDCl\(_3\)) 0.86 (t, J 7 Hz, CH\(_2\)Me), 1.08 [s, C(OH)Me], 2.42 (s, NMe), 3.42 (s, 2-H), 3.80 (s, 6-OMe), 3.83 (s, 3-OMe), 4.13 (s, OH, exch. with D\(_2\)O), 4.54 (d, J 1 Hz, 5-H), 5.77 (d, J 9 Hz, 19-H), 5.91 (d, J 9 Hz, 18-H), 6.54 (d, J 8 Hz, 1-H), and 6.64 (d, J 8 Hz, 2-H) (Found: m/z 443.2128. \( C_{25}H_{33}NO_4S \) requires \( M \), 443.2130).

7α-(1-Hydroxy-1-methylpentyl)6,7,8,14-tetrahydro-8-thia-6a,14a-ethanothebaines (147f) and (147g)

8-Thiaethevinone (139) (3.99 g, 10 mmol) in dry benzene (25 ml) was added to a refluxing solution of butylmagnesium bromide (1.61 g, 100 mmol) prepared in dry ether (25 ml). The solution was heated under reflux for 2 h. The residue, obtained as before, was purified by column chromatography [SiO\(_2\), Merck (60) No. 7734, 500 g] using dichloromethane-methanol (98:2). As before, earlier fractions were purified using the Chromatotron [2 mm SiO\(_2\) plates, ether-light petroleum (25:75)]. Later fractions were passed through a second silica column prior to purification on the Chromatotron. The separation was monitored by t.l.c. (SiO\(_2\) plates developed with ether). The band with \( R_F \) 0.71 contained the

(20R)-butylthiathevinol (147f) (548 mg, 12%), m.p. 173-174°C (from ethanol) (Found: C, 68.41; H, 8.07; N, 3.00. \( C_{26}H_{35}NO_4S \) requires C, 68.24; H, 7.71; N, 3.06%); \( \nu_{\text{max.}} \) (CHBr\(_3\)) 3460, 2960 (m), 1660, 1620, 1530, 1485, and 1400 cm\(^{-1}\); \( \delta_H \) (CDCl\(_3\)) 0.89 (t, J 6 Hz, CH\(_2\)CH\(_3\)), 1.08 [br s, (CH\(_2\))\(_3\) and 20-Me], 2.42 (s, NMe), 3.81 (s, 6-OMe), 3.83 (s, 3-OMe), 4.54 (d, J 1.5 Hz, 5-H), 4.56 (s, OH, exch.
with D₂O), 5.77 (d, J 9 Hz, 19-H), 5.90 (d, J 9 Hz, 18-H), 6.54 (d, J 8 Hz, 1-H), and 6.65 (d, J 8 Hz, 2-H) (Found: m/z 457.2293. C₂₆H₃₅N₀₄S requires M, 457.2287). The band with Rᶠ 0.59 contained the (20S)-butythiathievinol (147 g) (327 mg, 7%), m.p. 125-126°C (from ethanol) (Found: C, 68.32; H, 7.69; N, 3.03. C₂₆H₃₅N₀₄S requires C, 68.24; H, 7.71; N, 3.06%). ν max (CHBr₃) 3460, 2950 (m), 1630, 1600, 1500, and 1450 cm⁻¹: δ H (CDCl₃) 0.87 (t, J 6 Hz, CH₂CH₃), 1.09 (br s, (CH₃)₃ and 20-Me), 3.79 (s, 6-OMe), 3.83 (s, 3-OMe), 4.13 (s, OH, exch. with D₂O), 4.54 (d, J 1.5 Hz, 5-H), 5.76 (d, J 9 Hz, 19-H), 5.87 (d, J 9 Hz, 18-H), 6.54 (d, J 8 Hz, 1-H), and 6.64 (d, J 8 Hz, 2-H) (Found: m/z 457.2289. C₂₆H₃₅N₀₄S requires M, 457.2287).

7α-(1-Hydroxy-1-methylhexyl)6,7,8,14-tetrahydro-8-thia-6α,14α-ethenothebaines (147h) and (147i)

8-Thiathevinone (139) (1.39 g, 3.5 mmol) in sodium-dried benzene (10 ml) was added to a refluxing solution of n-pentyl-magnesium bromide (6.13 g, 35 mmol) prepared in dry ether (10 ml). The solution was heated under reflux for 2 h. The residue, obtained as before, was purified first by column chromatography [Florisil using dichloromethane-methanol (99:1)]. Selected fractions were then purified on silica plates developed with ether-light petroleum (80:20). The band with Rᶠ 0.74 contained the (20R)-pentythiathievinol (147h) (223 mg, 13.5%) obtained as a yellow oil; ν max (CHCl₃) 3460, 2940 (m), 1635, 1600, and 1505 cm⁻¹; ν max. (CHBr₃) 3460 cm⁻¹; δ H (CDCl₃) 0.89 (t, J 7.5 Hz, CH₂CH₃), 1.08 (s, 20-Me), 1.31 [m, (CH₃)₄CH₃], 2.41 (s, NMe), 3.82 (s, 6-OMe), 3.84 (s, 3-OMe), 4.55 (s, 5-H), 4.58 (s, OH, exch. with
D₂O), 5.77 (d, J 9 Hz, 19-H), 5.91 (d, J 9 Hz, 18-H), 6.55 (d, J 9 Hz, 1-H), and 6.64 (d, J 9 Hz, 2-H) (Found: m/z 471.2442. C₂₇H₃₇NO₄S requires M, 471.2443). The band with Rₚ 0.62 contained the (20S)-pentylthiathevinol (147i) (166 mg, 10%), m.p. 148°C (from ethanol) (Found: C, 68.58; H, 7.89; N, 3.01. C₂₇H₃₇NO₄S requires C, 68.79; H, 7.86; N, 2.97%); νmax. (CHCl₃) 3480, 2940 (m), 1632, 1600, 1502, and 1108 cm⁻¹; νmax. (CHBr₃) 3480 cm⁻¹; δH (CDCl₃) 0.87 (m, CH₂CH₂), 1.09 (s, 20-Me), 1.24 [br m, (CH₂)₂CH₃], 2.41 (s, NMe) 3.81 (s, 6-OMe), 3.84 (s, 3-OMe), 4.15 (s, OH, exch. with D₂O), 4.55 (s, 5-H), 5.77 (d, J 9 Hz, 19-H), 5.89 (d, J 9 Hz, 18-H), 6.55 (d, J 9 Hz, 1-H), and 6.65 (d, J 9 Hz, 2-H) (Found: m/z 471.2439. C₂₇H₃₇NO₄S requires M, 471.2443).

7α-(1-Hydroxy-1-methylheptyl)6,7,8,14-tetrahydro-8-thia-6α,14α-ethenothebaines (147j) and (147k)

8-Thiathevinone (139) 2 g, 5 mmol) in sodium-dried benzene (15 ml) was added to a refluxing solution of hexylmagnesium bromide (9.45 g, 50 mmol) prepared in dry ether. The solution was heated under reflux for 2 h. The residue, obtained as before, was purified first by column chromatography [Florisil using dichloromethane-methanol (99.5:0.5)]. Selected fractions were then purified on silica plates developed with ether-light petroleum (9:1). The band with Rₚ 0.78 contained the (20R)-hexylthiathevinol (147j) (128 mg, 5%) obtained as a yellow oil; νmax. (CHBr₃) 3470, 2940 (m), 1630, 1600, 1503, and 1454 cm⁻¹; δH (CDCl₃) 0.85 (m, CH₃), 1.05 (s, 20-Me), 1.24 (br m, (CH₃)₂CH₃), 2.39 (s, NMe), 3.22 (d, J 16 Hz, 108-H), 3.36 (s, 7-H), 3.84 (s, 3-OMe), 3.82 (s, 6-OMe), 4.53 (s, OH, exch. with D₂O), 5.76 (d, J 9 Hz, 19-H), 5.88 (d, J 9 Hz, 18-H), and 6.55 (d, J 9 Hz, 1-H), and 6.65 (d, J 9 Hz, 2-H) (Found: m/z 471.2443).
18-H), 6.52 (d, J 8 Hz, 1-H), and 6.62 (d, J 8 Hz, 2-H) (Found: m/z 485.2591. \( \text{C}_{28}\text{H}_{39}\text{N}_{4}\text{S} \text{ requires } M^{+}, 485.2600 \)). The band with \( R_f \), 0.66 contained the (20S)-hexylthiathevinol (147k) (135 mg, 5.5%) m.p. 143-144°C (from ethanol) (Found: C, 69.08; H, 8.21; N, 2.79. \( \text{C}_{28}\text{H}_{39}\text{N}_{4}\text{S} \text{ requires } C, 69.28; H, 8.04; N, 2.89\%); \( \nu_{\text{max}} \) (CHBr \( _3 \)) 3470, 2940 (m), 2850, 2810, 1630, 1600, and 1505 cm\(^{-1}\); \( \delta_H (\text{CDCl}_3) \) 0.83 [m, \((\text{CH}_2)_5\text{CH}_3\)], 1.07 (s, 20-Me), 1.22 [br s, \((\text{CH}_2)_5\text{CH}_3\)], 2.39 (s, NMe), 3.23 (d, J 18 Hz, 10-B-H), 3.42 (s, 7-H), 3.79 (s, 6-OMe), 3.84 (s, 3-OMe), 4.19 (s, OH, exch. with D\(_2\)O), 4.52 (s, 5-H), 5.76 (d, J 9 Hz, 19-H), 5.88 (d, J 9 Hz, 18-H), 6.52 (d, J 8 Hz, 1-H), and 6.62 (d, J 8 Hz, 2-H) (Found: m/z 485.2587. \( \text{C}_{28}\text{H}_{39}\text{N}_{4}\text{S} \text{ requires } M^{+}, 485.2600 \)).

Treatment of 8-Thiathevinone (139) with Alkyl-lithiums: the
Formation of Tertiary Alcohols and the Rearranged Acetal (157)

The epimeric butylthiathevinols (165f) and (165g)

8-Thiathevinone (139) (3.99 g, 10 mmol) in tetrahydrofuran (25 ml) freshly distilled from LiAlH\(_4\)) was cooled to -78°C. butyl-lithium in hexane (20 mmol) was added through a septum from a syringe, with stirring over 10 min. Stirring was contained for 2 h. The solution was warmed to room temperature. Distilled water (20 ml) was added and the mixture extracted with ether. The extracts were evaporated to yield a yellow oil. This was purified by column chromatography [Si\(_2\)O\(_2\) Merck (60) No. 7734, 500 g] using dichloromethane-methanol (98:2). Selected fractions were purified using the Chromatotron [2 mm Si\(_2\)O\(_2\) plates, ether-light petroleum (25:75)]. Separation was monitored by t.l.c. (Si\(_2\)O\(_2\) plates
developed with ether). The band with \( R_F \) 0.70 contained the 
(20R)-butylthiathevinol (147f) (658 mg, 14%), m.p. 173-174°C (from ethanol) (expected 173-174°C). The band with \( R_F \) 0.57 contained the 
(20S)-butylthiathevinol (147g, 100 mg, 2%). This could not be crystallised.

\[(18R)-18\text{-Acetyl-7,8-didehydro-3,6-dimethoxy-17-methyl-4α,6α-epoxy-14β,5β-thiaethanomorphinan (157)}\]

1-Bromopropane (3.1 g, 25 mmol) in dry ether (10 ml) was added with stirring to small pieces of lithium in dry ether (20 ml) under dry argon at -10°C. Addition took place over 20 min. The solution was allowed to reach room temperature. After 1 h it was filtered through glass wool directly into a pressure-equalising dropping funnel. The propyl-lithium solution was then added over a period of 10 min to a stirred solution of 8-thiathevinone (139) (2.3 g, 5.8 mmol) in THF (20 ml), at -78°C, which had been freshly distilled from lithium aluminium hydride. After 1 h cold distilled water (20 ml) and ether (20 ml) were added. The aqueous layer was extracted with chloroform. The combined extracts were evaporated to yield a brown foam. The crude mixture was purified by t.l.c. (SiO\(_2\) plates developed with ether). Plates were eluted with redistilled ethanol. The band with \( R_F \) 0.67 contained the 
(20R)-propylthiathevinol (147d) (37 mg, 3%), m.p. 178-179°C (from ethanol) (expected 178.5-179.5°C). The band with \( R_F \) 0.47 contained the acetal (157) (160 mg, 10%), m.p. 159-163°C (from ethanol) 
(Found: C, 65.97; H, 6.42; N, 3.54; S, 8.12. \( C_{22}H_{25}NO_4S \) requires C, 66.16; H, 6.26; N, 3.51; S, 8.02%); \( \nu_{\text{max}} \) (CHCl\(_3\)) 3008, 2940, 1715, 1600, 1575, and 1490 cm\(^{-1}\); \( \delta_H \) (CDCl\(_3\), 200 MHz)
2.29 (s, 20-Me), 2.42 (s, NMe), 2.59 (d, J 2.7 Hz, 5-H), 3.22 (d, J 5.9 Hz, 9-H), 3.45 (d, J 18.1 Hz, 10β-H), 3.51 (s, 6-OMe), 3.82 (s, 3-OMe), 4.16 (d, J 1.7 Hz, 18-H), 4.99 (dd, J 9.5 and 2.7 Hz, 7-H), 6.11 (dd, J 9.5 and 0.6 Hz, 8-H), 6.61 (d, J 8.3 Hz, 1-H), and 6.64 (d, J 8.3 Hz, 2-H) (Found: m/z 399.1491. C_{22}H_{25}NO_{4}S requires M, 399.1504).

3.6 Preparation of Methyl-7α-thiathevinol (147a) and Methyl-7β-thiathevinol (154) from the Corresponding Ethyl Esters

**Methyl-7α-thiathevinol (147a)**

The ester (119) (215 mg, 0.5 mmol) in sodium-dried benzene (10 ml) was added to a refluxing solution of methylmagnesium iodide (581 mg, 3.5 mmol) prepared in dry ether (10 ml). The solution was heated under reflux for 2 h. After cooling, distilled water (20 ml) then saturated ammonium chloride (20 ml) were added. The organic layer was evaporated to yield a yellow oil. This was purified on silica plates developed with ether. The band with R_f 0.54 contained methylthiathevinol (147a) (133 mg, 64%), m.p. 162-164°C (from ethanol) (expected 161-164°C).

**Methyl-7β-thiathevinol (154)**

The ester (123) (100 mg, 0.23 mmol) in sodium-dried benzene (10 ml) was added to a refluxing solution of methylmagnesium iodide (581 mg, 3.5 mmol) prepared in dry ether (10 ml). The solution was heated under reflux for 2 h. After cooling, distilled water (20 ml) then saturated ammonium chloride (20 ml) were added. The organic layer was dried and evaporated to yield a yellow oil. This was crystallised from ethanol to give 7β-(1-hydroxy-1-methylethyl)-
6,7,8,14-tetrahydro-8-thia-6α,14α-ethenothebaine (154) (112 mg, 54%), m.p. 153-156°C (Found: C, 66.30; H, 6.78; N, 3.40. C_{23}H_{29}NO_3S requires C, 66.51; H, 6.99; N, 3.37%); ν_{max} (CCl₄) 3510, 2940 (m), 2850, 2810, 1720, 1500, and 1109 cm⁻¹; δ_H (CDCl₃) 1.35 [s, C(OH)CH₃], 1.56 [s, C(OH)CH₃], 2.42 (s, NMe), 3.23 (d, J 19 Hz, 10β-H), 3.71 (s, 6-OMe), 3.82 (s, 3-OMe), 4.45 (s, OH, exch. with D₂O), 5.31 (d, J 2 Hz, 5-H), 5.64 (d, J 9 Hz, 19-H), 6.13 (dd, J 9 and 2 Hz, 18-H), 6.53 (d, J 9 Hz, 1-H), and 6.64 (d, J 9 Hz, 2-H) (Found: m/z 415.1811. C_{23}H_{29}NO_3S requires M, 415.1817).

3.7 Reactions of 7-Thiaisothevinone (142)
(19R)-[19-(1-Hydroxy-1-methylethyl]7,8-didehydro-4-hydroxy-3-methoxy-6-methylene-17-methyl-5β,14β-thiaethanomorphinan (168)

7-Thiaisothevinone (142) (500 mg, 1.25 mmol) in sodium-dried benzene (20 ml) was added to a refluxing solution of methylmagnesium iodide (2.07 g, 12.5 mmol) prepared in dry ether (20 ml). The solution was heated under reflux for 2 h. After cooling, distilled water (20 ml) then saturated ammonium chloride (20 ml) were added. The organic layer which formed was separated off, dried, and evaporated to yield a yellow oil. This was purified on silica plates developed with ether. The band with R_F 0.32 contained the exocyclic diene (168) (74 mg, 15%), m.p. 261-264°C (formed needles from 135°C) (from ethanol) (Found: C, 69.23; H, 7.33; N, 3.49. C_{23}H_{29}NO_3S requires C, 69.17; H, 7.27; N, 3.51%); ν_{max} (KBr) 3420, 2960 (m), 1635, 1612, 1585, 1490, 1455, and 1440 cm⁻¹; ν_{max} (CHCl₃) 3540, 3000 (m) 2850, 2810, 1635, 1618, 1590, 1490, 1460, and 1440 cm⁻¹; δ_H (CDCl₃, 200 MHz) 1.22 (s, 20-Me), 1.43 (s, 20-Me), 2.32 (s, NMe), 2.99 (s, 20-OH, exch. with D₂O), 3.06 (d, J 18.2 Hz,
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10β-H), 3.40 (d, J 5.1 Hz, 9-H), 3.79 (s, 3-OMe), 4.57 (d, J 1.5 Hz, 5-H), 4.66 (s, 1 proton, vinylmethylene-H), 4.74 (s, 19-H), 4.80 (s, 1 proton, vinylmethylene-H), 5.68 (s, 4-OH, exch. with D₂O), 5.74 (d, J 9.6 Hz, 8-H), 5.93 (dd, J 9.6 and 1.5 Hz, 7-H), 6.54 (d, J 8.3 Hz, 1-H), 6.61 (d, J 8.3 Hz, 2-H); δC (CDCl₃) 25.13 (10-C), 28.48 [C(OH)CH₃], 29.69 (15-C), 34.21 [C(OH)CH₃], 42.88 (N-C), 46.73 (16-C), 51.63 (13- or 14-C), 51.70 (13- or 14-C), 53.07 (5- or 9-C), 55.92 (O-CH), 57.46 (5- or 9-C), 66.06 (19-C), 71.50 (20-C), 108.3 (2-C), 109.93 (C=CH₂), 117.31 (1-C), 126.47 (11-C), 128.59 (8-C), 130.57 (18-C), 132.48 (7-C), 142.81 (3-C), 144.26 (4-C), and 147.98 (6-C) (Found: m/z 399.1857. C₂₃H₂₉N₅O₃S requires M 399.1868).

19-Acetyl-6,7-didehydro-8,19-dehydro-4-hydroxy-17-methyl-3,6-dimethoxy-5β,14β-thiaethanomorphinan (170)

7-Thiaisothevinone (142) (159 mg, 0.4 mmol) in sodium-dried benzene (10 ml) was added to a refluxing solution of methylmagnesium iodide (199 mg, 1.2 mmol) prepared in dry ether (10 ml). The solution was heated under reflux for 1 min. After cooling, distilled water (10 ml) was added. The mixture turned pale pink. Saturated ammonium chloride (10 ml) was added. The organic layer was separated off, dried, and evaporated to yield a pink oil which solidified on standing. Trituration with cold redistilled ethanol gave the cyclopropyl methyl ketone (170) (71 mg, 45%), m.p. 220-222°C (from ethanol) (Found: C, 66.03; H, 6.49; N, 3.35. C₂₂H₂₅N₅O₄S requires C, 66.16; H, 6.26; N, 3.51%); ν max (CHCl₃) 3540, 2950 (m), 1680, 1635, and 1490 cm⁻¹; δH (CDCl₃) 2.27 (s, 20-Me), 2.45 (s, NMe), 3.14 (d, J 18 Hz, 10β-H), 3.39 (s, 6-OMe), 3.80 (s, 3-OMe), 4.49 (s, J 2.3 Hz, 5-H), 4.61 (dd, J 6.9 and 2.3
Hz, 7-H), 5.90 (s, OH, exch. with D₂O), and 6.61 (s, 1- and 2-H) (Found: m/z 399.1518. C₂₂H₂₅NO₄S requires M, 399.1504).

8α-(1-Hydroxy-1-methylbutyl)6,7,8,14-tetrahydro-7-thia-6α,14α-ethenothebaine (175)

1-Bromopropane (307 mg, 2.5 mmol) in dry ether (5 ml) was added with stirring to small pieces of lithium in dry ether (5 ml) at -10°C under a positive pressure of dry argon. Addition took place over 30 min. After 1 h, the solution was cooled to -78°C and 7-thiaisothevinone (142) (199 mg, 0.5 mmol) in tetrahydrofuran (10 ml) (freshly distilled from LiAlH₄) was added through a septum over 1½ h. The temperature was maintained at -78°C and the solution stirred for a further ½ h. Small pieces of unreacted lithium were removed and ether (10 ml) then distilled water (10 ml) were added. The organic phase was separated, dried, and the residue (217 mg) chromatographed on silica plates developed with ether. The band with Rₚ 0.59 contained the tertiary alcohol (175) (39 mg, 18%), m.p. 145-147°C (from ethanol) (Found: C, 67.55; H, 7.69; N, 3.02. C₂₅H₃₃NO₄S requires C, 67.72; H, 7.45; N, 3.16%); ν max (CHCl₃) 3020 (m), 1635, 1605, 1510, and 1460 cm⁻¹; δH (CDCl₃) 0.92 (t, J 7 Hz, (CH₂)₂CH₃), 1.04 (s, 20-Me), 2.36 (s, NMe), 3.62 (s, 6-OMe), 3.83 (s, 3-OMe), 4.05 (d, J 7 Hz, 9-H), 4.99 (s, 8-H), 4.70 (s, 5-H), 5.49 (d, J 10 Hz, 19-H), 6.19 (d, J 10 Hz, 18-H), 6.58 (d, J 9 Hz, 1-H), and 6.63 (d, J 9 Hz, 2-H) (Found: m/z 443.2132. C₂₅H₃₃NO₄S requires M, 443.2130). The band with Rₚ 0.71 contained the ketone (142) (28 mg 13%), m.p. 148-150°C (from ethanol) (expected 150-151°C).
(20R)- and (20S)-19-(1-Hydroxy-1-methylbutyl)-6,7-didehydro-8,19-dehydro-4-hydroxy-17-methyl-3,6-dimethoxy-5β,14β-thiaethanomorphinans (176)

1-Bromopropane (615 mg, 5 mmol) in dry ether (10 ml) was added with stirring to small lithium pieces (69.4 mg, 10 mmol) in dry ether (10 ml) at -10°C under a positive pressure of dry argon. After 1 h 7-thiaisothevinone (142) (400 mg, 1 mmol) in tetrahydrofuran (20 ml) (freshly distilled from LiAlH₄) was added with stirring over 5 min. The solution was allowed to reach room temperature. After 1½ h small remaining pieces of lithium were removed and ether (10 ml) then distilled water (10 ml) were added. The organic phase was separated and dried. The residue (295 mg) was purified on silica plates developed with ether. The band with Rᵡ 0.88 contained the less polar tertiary alcohol (176) (59 mg, 13%), m.p. 208-210°C (from ethanol) (formed needles from 185°C onwards) (Found: C, 67.69; H, 7.46; N, 3.09. C$_{25}$H$_{33}$NO$_4$S requires C, 67.72; H, 7.45; N, 3.16%; ν$_{max}$ (CHCl$_3$) 3540, 2960 (m), 1660, 1620, 1585, and 1490 cm$^{-1}$; δ$_H$ (CDCl$_3$) 0.92 (t, J 7 Hz, CH$_2$CH$_2$CH$_3$), 1.31 (s, 20-Me), 2.37 (s, N-Me), 3.46 (s, 6-OMe), 3.83 (s, 3-OMe), 4.24 (s, 20-OH, exch. with D$_2$O), 4.28 (dd, J 6.5 and 2 Hz, 7-H), 4.50 (d, J 2 Hz, 5-H), 5.80 (s, Ar-OH, exch. with D$_2$O), and 6.67 (s, 1- and 2-H). (Found: m/z 443.2136. C$_{25}$H$_{33}$NO$_4$S requires M, 443.2130). The band with Rᵡ 0.85 contained the more polar tertiary alcohol (176) (58 mg, 13%), m.p. 212-214°C (from ethanol) (formed needles from 175°C onwards) (Found: C, 67.84; H, 7.53; N, 3.09. C$_{25}$H$_{33}$NO$_4$S requires C, 67.72; H, 7.45, N, 3.16%; ν$_{max}$ 3540, 2960 (m), 1660, 1620, 1585, and 1440 cm$^{-1}$; δ$_H$ (CDCl$_3$), 0.92 (t, J 7 Hz, CH$_2$CH$_2$CH$_3$), 1.31 (s, 20-Me), 2.37 (s, NMe), 3.46
(s, 6-OMe), 3.83 (s, 3-OMe), 4.25 (s, 20-OH, exch. with D₂O), 4.28 (dd, J 6.5 and 2 Hz, 7-H), 4.50 (d, J 2 Hz, 5-H), 5.95 (s, Ar-OH, exch. with D₂O) and 6.66 (s, 1- and 2-H) (Found: m/z 443.2107. C₂₅H₃₃NO₄S requires M, 443.2130). The band with Rf 0.32 contained the cyclopropyl methyl ketone (170) (35 mg, 9%), m.p. 218-220°C (from ethanol) (expected 220-222°C).
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