Synthesis of 20-Alkyl-8-thiathevinols, Opiate Agonists Derived from 8-Thiathevinone, the Cycloadduct of Thebaine and 2-Oxopropanethial

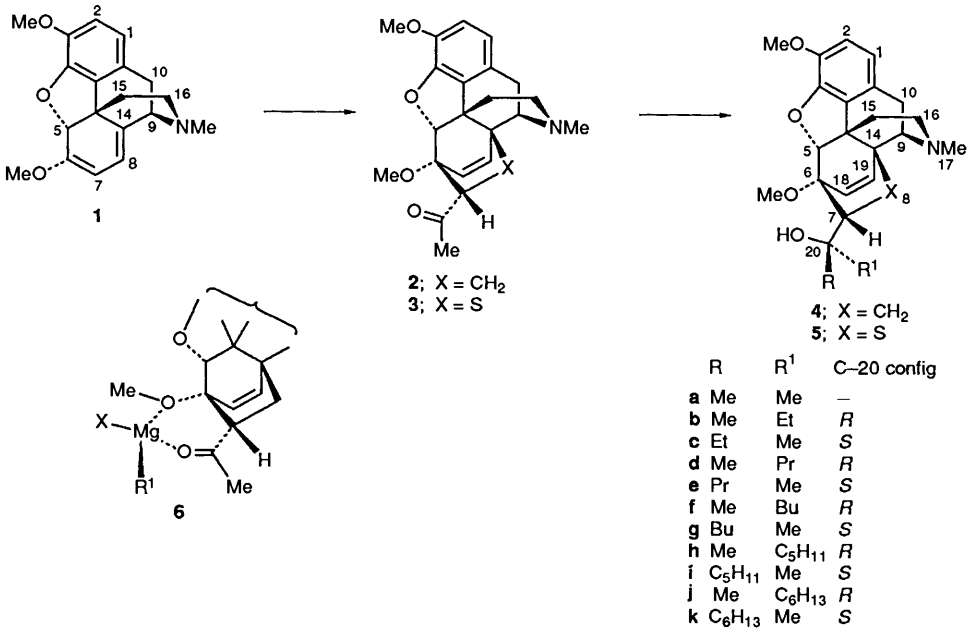
Gordon W. Kirby* and Alastair D. Sclare
Department of Chemistry, University of Glasgow, Glasgow, G12 8QQ, UK

The cycloadduct **7** has been prepared from thebaine **1** and the transient thioaldehyde EtO_2C–CHS formed *in situ* from the Bunte salt EtO_2C–CH_2SSO_3Na. The thermal isomerisation of the adduct **7** to give the regioisomer **8** has been reinvestigated. Prolonged heating gave an equilibrium mixture of the adduct **8** and the major, rearrangement product **9**. Base-catalysed epimerisation of the adduct **7** gave the 7β-isomer **11**, believed to be a transient co-product in the thermal isomerisation of the original adduct **7**. Similarly, thebaine **1** and 2-oxopropanethial **18**, generated from either the Bunte salt $MeCOCH_2SSO_3Na$ or the thiotosylate **16** and triethylamine, gave the cycloadduct 8-thiathevinone **3**, the sulphur analogue of thevinone **2**, the known cycloadduct of thebaine and but-3-en-2-one. 8-Thiathevinone **3** isomerised thermally to give the corresponding, 7-thia regioisomer.

8-Thiathevinone **3** has been converted with Grignard reagents into a series of (20*R*)-and (20*S*)-20-alkyl-8-thiathevinols **5**. The reactions were not stereoselective, unlike those of thevinone **2**, and the tertiary alcohols **5** were accompanied by the secondary alcohols **19** and **20**, products of 'Grignard reduction'. The analgesic potency, in guinea-pig ileum preparations, of the alkylthiathevinols **5** depended upon the C-20 configuration and the alkyl chain length. The (20*R*)-epimers were the more potent, the maximum potency being observed for the (20*R*)-20-pentyl derivative **5h**, which was equipotent with *N*-normorphine. Generally, the thiathevinols were much less potent than the corresponding thevinols. 8-Thiathevinone **3** also reacted with alkyllithium reagents to give (20*R*)-alkylthiathevinols, but the reactions were accompanied by a base-catalysed rearrangement to give the ketoacetal **27**.

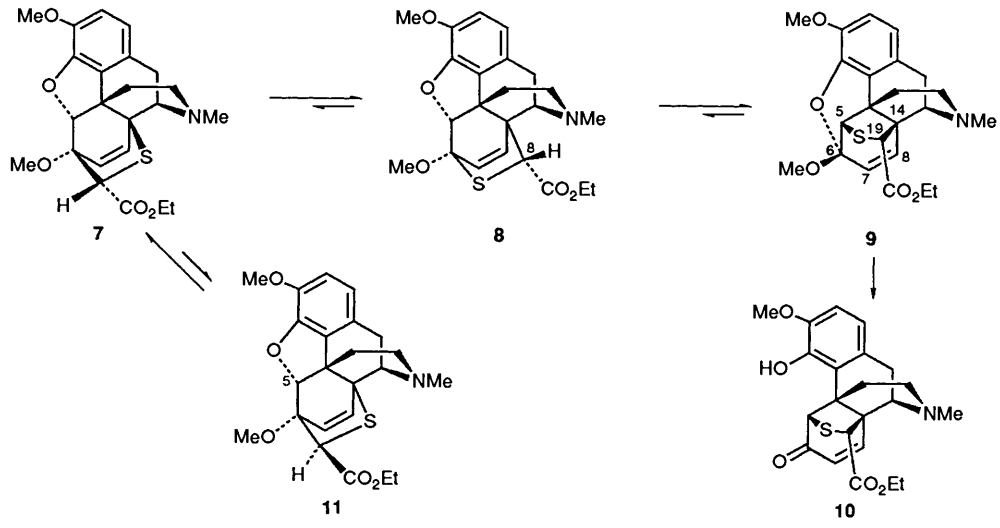
The opium alkaloid thebaine **1** undergoes Diels–Alder cycloadditon with but-3-en-2-one, highly regio- and stereoselectively, to give the *endo* adduct 'thevinone' **2** in high yield (Scheme 1).[1] Bentley *et al.* prepared[2] a series of tertiary alcohols, the 'thevinols' **4**, from thevinone and Grignard reagents and discovered that certain members were remarkably potent analgesics. Generally, the corresponding phenols, 'orvinols', were even more potent.[3] The (20*R*)-propylorvinol, etorphine (**4d**; 3-OH replacing 3-OMe), is used in veterinary medicine, and a structurally modified, (20*R*)-*tert*-butyl derivative, buprenorphine, as a 'safe' analgesic in man. The Grignard reactions were highly stereoselective, giving the 20*R* derivatives (**4**; R = Me, R′ = higher alkyl) in good yield; fortuitously these major products were much more potent than their C-20 epimers. The high stereoselectivity was attributed[2] to co-ordination of magnesium with the ketonic and 6-methoxy group oxygens (see structure **6**) preceding delivery of the alkyl group, R′, from the less-hindered, β face of the ketone.

We have reported[4] that the thioaldehyde ethyl thioxoacetate, EtO_2C–CHS, generated as a reactive intermediate from the appropriate sulphenyl chloride, EtO_2C–CH_2SCl and triethylamine, reacted with thebaine **1** to give the cycloadduct **7**



	R	R^1	C–20 config
a	Me	Me	–
b	Me	Et	*R*
c	Et	Me	*S*
d	Me	Pr	*R*
e	Pr	Me	*S*
f	Me	Bu	*R*
g	Bu	Me	*S*
h	Me	C_5H_{11}	*R*
i	C_5H_{11}	Me	*S*
j	Me	C_6H_{13}	*R*
k	C_6H_{13}	Me	*S*

Scheme 1



Scheme 2

(Scheme 2) in good yield. Further, when heated under reflux in toluene, the 8-thia derivative **7** gave the regioisomer **8** as the major product. We considered that the ketone **3**, '8-thiathevinone', corresponding to the ester **7** should provide a series of sulphur analogues **5** of the potently analgesic thevinols **4**. As a prelude to the synthesis of 8-thiathevinone **3**, a more detailed study was carried out on that of the known ester **7**, and on its thermal rearrangement.

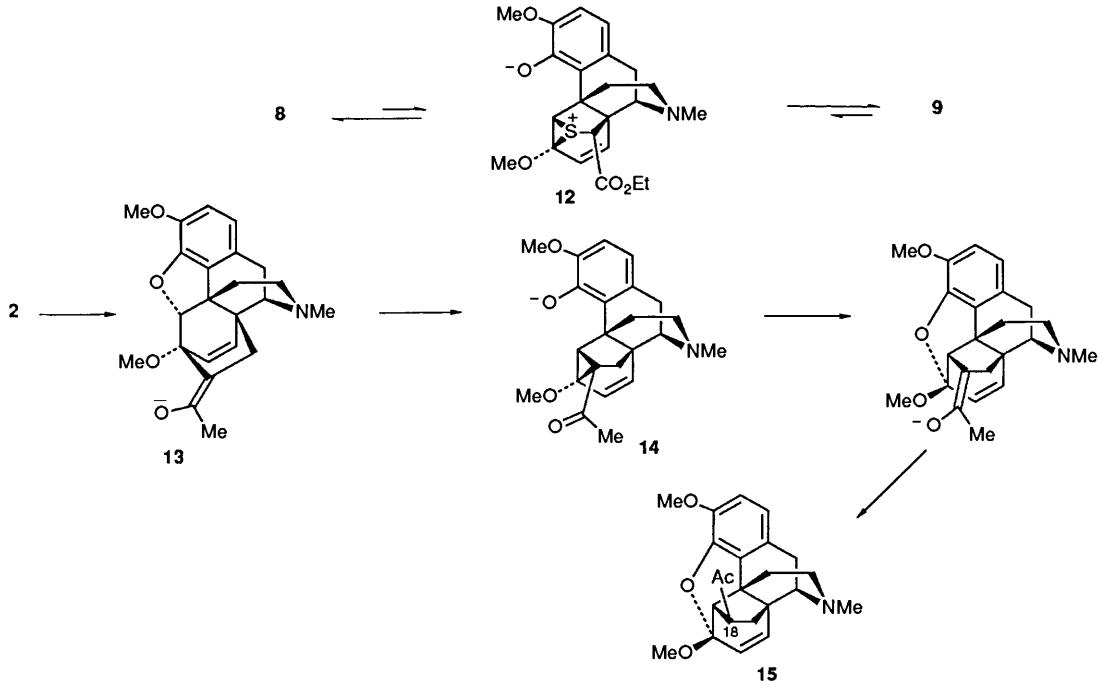
Results and Discussion

In preliminary experiments,[5] 8-thiathevinone **3** had been obtained from thebaine and 2-oxopropanethial **18** generated *in situ* from 2-oxopropanesulphenyl chloride and triethylamine. However, preparation of the sulphenyl chloride, by chlorinolysis of the corresponding disulphide,[6] was inconvenient, as was that of the disulphide. It seemed that the crystalline Bunte salt, $MeCOCH_2SSO_3Na$,[7] might be a better precursor for the thioaldehyde. The synthesis of the ester **7** from the corresponding Bunte salt was therefore investigated first (Scheme 2).

The crystalline salt, $EtO_2C–CH_2SSO_3Na$, readily prepared from ethyl bromoacetate and disodium thiosulphate, undergoes slow elimination of sulphite dianion when treated with triethylamine.[8] The liberated ethyl thioxoacetate may be trapped efficiently *in situ* with reactive dienes, providing that calcium chloride is present to remove the nucleophilic sulphite dianion as its sparingly soluble calcium salt. Hydroxylic solvents are necessary to dissolve the Bunte salt and facilitate elimination, but yields of cycloadducts are highest with low concentrations of water or alcoholic solvents. When thebaine **1** was treated with equimolecular amounts of the Bunte salt, $EtO_2C–CH_2SSO_3Na$, triethylamine, and calcium chloride dihydrate in benzene–ethanol (1:1) for 1 week at room temperature, a mixture of cycloadducts was obtained in good yield (Scheme 2). Chromatography gave the expected[4] adduct **7** (73%), the regioisomer[4] **8** (4%) and a new stereoisomer **11** (5%). The structure and stereochemistry of the isomer **11** was indicated in the ^1H NMR spectrum by the lowfield signal for 5-H, δ 5.55 (d, J 1.5), deshielded relative to the corresponding proton in the epimer **7** (δ 4.57) and regioisomer **8** (δ 4.98) by the ester group. The structure **11** was confirmed, as follows, by base-catalysed epimerisation. When the 7α ester **7** was briefly treated with potassium *tert*-butoxide in *tert*-butyl alcohol at room temperature, a mixture of the epimers **7** and **11** (*ca.* 8:2) was obtained. More prolonged treatment caused rearrangement[9] with opening of the benzofuran ring. The same, *ca.* 8:2, mixture was obtained from the 7β ester **11** under the same conditions. A control experiment showed that the composition of the original mixture of the Diels–Alder reaction products **7**, **8** and **11** was determined directly by the relative rates of the three concurrent cycloadditions, and not by subsequent base-catalysed or 'thermal' isomerisation of the major product **7**. Thus the 7α ester **7** was treated with the Bunte salt, triethylamine and calcium chloride for 1 week under the conditions used in its original preparation. The resulting mixture contained no detectable (TLC and ^1H NMR control) amounts of the isomers **8** and **11**.

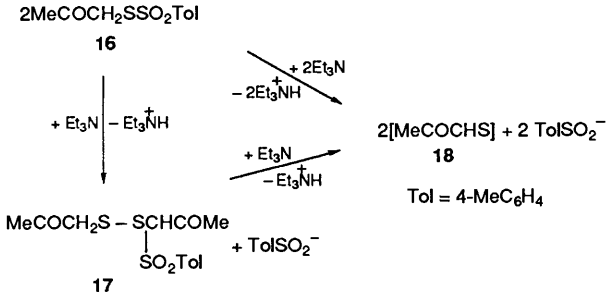
As before,[4] when the 8-thia cycloadduct **7** was heated in toluene under reflux for 8 h, the 7-thia isomer **8** was formed, by dissociation of the cycloadduct **7** and recombination of thebaine and the thioaldehyde, in good yield. When the reaction was monitored by TLC on silica plates, a transient co-product with the R_f value of the epimer **11** was detected. However, the major product **8** was shown by TLC on alumina, but not on silica, plates to be mixed with a small amount of a fourth isomer **9**. The quantity of this acetal **9** increased with further heating until, after 160 h, there was no significant change in the ratio, **8**:**9** = 2:8, of the two components. Further, when the major component **9**, isolated by PLC on alumina, was heated in refluxing toluene, the same, 2:8, mixture resulted, showing that an equilibrium had been established. Thus, the relative stabilities of the 4 isomers are: **9** > **8** ≫ **7** > **11**. The acetal **9**, unlike its isomers, was not obtained in crystalline form, nor was the corresponding methyl ester, obtained in an analogous manner. However, the acetal was readily hydrolysed with acid catalysis to give a crystalline keto phenol **10**. The enone system in the phenol **10** was identified spectroscopically, as was the unique, acetal carbon (C-6, δ_C 106.8) in its progenitor **9**. For preparative purposes, chlorobenzene, b.p. 135 °C, was used as solvent in place of toluene, b.p. 111 °C; essentially the same, equilibrium mixture of the isomers **8** and **9** was obtained in 30 h in refluxing chlorobenzene. The mechanism of the unexpected rearrangement **8** ⇌ **9** is not clear, but the episulphonium phenoxide **12** may be an intermediate (Scheme 3). A corresponding carbocyclic ring system is present in the cyclopropane derivative **14** proposed[1,9] as an intermediate in the base-catalysed rearrangement of thevinone **2**. Not unexpectedly, cyclisation of the enolate anion **13** in a polar solvent is faster than the proposed cyclisation of the sulphides **8** and **9** in toluene.

The synthesis of 8-thiathevinone **3** was initially effected by the Bunte salt method under the conditions optimised for the corresponding ester **7**. The Bunte salt, $AcCH_2SSO_3Na$,[7]



Scheme 3

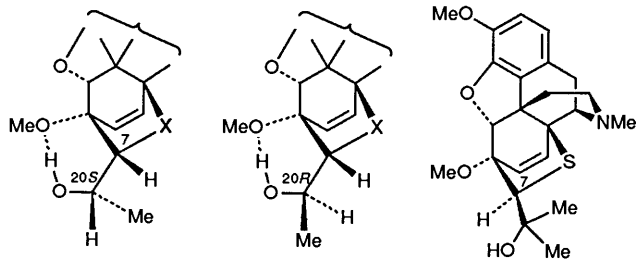
required as a precursor of 2-oxopropanethial **18** was prepared from chloro- or bromo-acetone and disodium thiosulphate in the usual way. Treatment of thebaine **1** with this Bunte salt, triethylamine and calcium chloride gave the oily ketone **3**. But the yield was only 42% and the product was not easily freed from coloured by-products. For these reasons, the toluene-4-thiosulphonate (thiotosylate) **16** and the related α-tosyl disulphide **17** were tested as precursors for the thioaldehyde **18** (Scheme 4). Derivatives of both general types had been shown



Scheme 4

previously[10] to serve as precursors of a variety of thioaldehydes, though not specifically 2-oxopropanethial **18**. Treatment of chloro- or bromo-acetone with an anion-exchange resin charged with thiotosylate[11] gave the derivative **16** together with some of the disulphide **17**. When the mixture was kept on a chromatographic column of silica gel, conversion of the thiotosylate **16** into the disulphide **17** occurred, as expected, but was incomplete. Since both compounds were expected[10] to yield the thioaldehyde, the thiotosylate **16** was employed while still containing some of the disulphide. When thebaine **1** was treated with 3 mol equiv. each of the thiotosylate **16**, triethylamine and calcium chloride dihydrate, in benzene–ethanol at room temperature, 8-thiathevinone **3** was obtained in 74% yield as a yellow oil. The structure of **3** was readily verified spectroscopically by comparison with thevinone **2** and the ester **7**. As expected, when 8-thiathevinone was heated under reflux in toluene, the 7-thia isomer (**8**; Ac replacing CO_2Et) was formed, and was isolated chromatographically in crystalline form. However, the yield was lower than that for the corresponding isomerisation of the ester **7** (Scheme 2). Some polymeric material was formed along with thebaine, implying that the thioaldehyde **18** necessarily liberated transiently during the thermal isomerisation, had polymerised more readily than ethyl thioxoacetate, EtO_2C–CHS.

As planned, 8-thiathevinone **3** was converted with a series of Grignard reagents into the corresponding 8-thiathevinols **5**, under the conditions employed earlier[2] for the parent thevinols **4**. However, the yields of the thiathevinols were generally lower than for the corresponding thevinols and, remarkably, the new reactions lacked the high stereoselectivity characteristic of the old. For example, a solution of 8-thiathevinone **3** in benzene was added to an excess of propylmagnesium bromide in diethyl ether, with heating under reflux. Chromatography of the complex reaction mixture gave the tertiary alcohols **5d** and **5e** in approximately equal amounts, accompanied by smaller amounts of the 'Grignard reduction' products **19** and **20**, the former predominating. Similar results were obtained with the homologous series of Grignard reagents RMgBr (R = C_nH_{2n+1}, n = 2–6). From all reactions, the thiathevinols **5** were isolated in approximately equal yields of *ca.* 10%, together with small amounts of the secondary alcohols **19** and **20** and substantial



19; X = S
21; X = CH_2

20; X = S
22; X = CH_2

23

amounts of polar, unidentified by-products. The parent member of the series **5a** was obtained similarly with methylmagnesium iodide from thiathevinone or, in good yield, the ester **7**. The 7β-dimethylcarbinol **23** was prepared likewise from the corres-

Table 1 Comparative physical data for epimeric pairs of 8-thiathevinols **5** and thevinols **4**

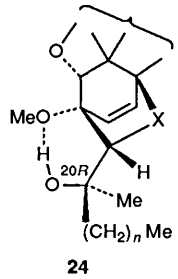
Compound	R	R′	C-20 config.[a]	R_f[a]	δ[b] 20-OH	δ[b] $(CH_2)_nMe$	ν^c_{max}(OH)/cm^{-1}
5b	Me	Et	*R*	0.44	4.55	0.95	3430
5c	Et	Me	*S*	0.31	4.05	0.86	3460
5d	Me	Pr	*R*	0.62	4.54	0.86	3450
5e	Pr	Me	*S*	0.56	4.13	0.86	3450
5f	Me	Bu	*R*	0.71	4.56	0.89	3460
5g	Bu	Me	*S*	0.59	4.13	0.87	3460
5h	Me	C_5H_{11}	*R*	0.74	4.58	0.89	3460
5i	C_5H_{11}	Me	*S*	0.62	4.15	0.87	3480
5j	Me	C_6H_{13}	*R*	0.78	4.53	0.85	3470
5k	C_6H_{13}	Me	*S*	0.66	4.19	0.83	3470
4b	Me	Et	*R*	0.40	4.86	0.96	3430
4c	Et	Me	*S*	0.30	4.39	0.87	3450
4d	Me	Pr	*R*	0.58	4.88	0.91	3450
4e	Pr	Me	*S*	0.50	4.49	0.86	3450
4f	Me	Bu	*R*	0.60	4.65	0.97	3450

[a] Merck GF_{254} silica plates in diethyl ether. [b] ^{1}H NMR chemical shift (90 MHz; $CDCl_3$). [c] IR band in $CHBr_3$; frequency independent of concentration.

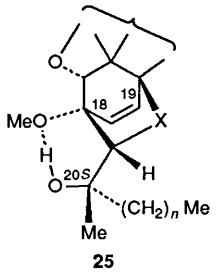
ponding ester **11**. The absence of any substantial stereochemical control (*cf.* structure **6**) in the Grignard reactions with thiathevinone was unexpected, but it may reflect competitive co-ordination of magnesium with sulphur rather than the methoxy oxygen. However, both epimeric series of thiathevinols were thereby conveniently provided for pharmacological comparison.

The determination of the C-20 stereochemistry of the epimeric 8-thiathevinols **5** was not straightforward. However, comparison of the R_f values and certain spectroscopic data belonging to members of the complete series (Table 1) led to assignments that were fully consistent with the subsequent results of pharmacological tests. The corresponding data for thevinols[2] **4b–f** of known stereochemistry provided a firm basis for assigning the configurations of the sulphur-containing analogues. The (20*S*)-derivatives **4c,e** were kindly provided by Reckitt and Colman Pharmaceutical Division (Hull). The (20*R*)-thevinols were prepared,[2] as major products, from thevinone **2** and the appropriate Grignard reagents.

The thiathevinols **5** and thevinols **4** exist in solution, at least in part, in conformations involving hydrogen-bonding between the 20-hydroxy and 6-methoxy groups (see structures **24** and



24



25

25).[2,12] The strength of this hydrogen-bond, and the population of hydrogen-bonded conformations, will depend upon the C-20 stereochemistry, and might reasonably be expected to affect the physical properties listed in Table 1. The existence of intramolecular hydrogen-bonding is indicated by the IR band at *ca.* 3450 cm^{-1} shown by all the tertiary alcohols in dilute solutions. However, only within three pairs of epimers, the ethyl- and pentyl-thiathevinols and the ethylthevinols, is this frequency significantly different. But, in each pair, the (20*R*)-epimer shows a lower frequency, corresponding to stronger hydrogen-bonding. This is understandable, because the larger alkyl group is less hindered (see structure **24**) in these epimers. The ^{1}H NMR chemical shifts of the 20-hydroxy protons also reflect differences in hydrogen-bonding. The effects are large and consistent; in each pair of epimers the hydroxy proton of the (20*R*)-isomer resonates downfield ($\Delta\delta$ 0.39–0.50 ppm) from that of its epimer. Separation of the epimeric thiathevinols depended upon their distinctly different R_f values on silica TLC plates. These values too show a consistent pattern; the (20*R*)-isomers run faster than their epimers. The same effect is shown by the two pairs of thevinols, **4b,c** and **4d,e**, that were available for comparison. Finally, in the hydrogen-bonded conformations **25** of the (20*S*)-thiathevinols and -thevinols, the terminal methyl group of the alkyl chain may come close to the $\Delta_{18,19}$ π bond. This may account for the higher field resonance of this group in all but one of the pairs of epimers. The only exceptions are the propylthiathevinols **5d,e**, which give identical values, δ 0.86, for the terminal methyl group.

The secondary alcohols **19** and **20** were formed generally as by-products from the Grignard reactions of 8-thiathevinone **5**; the (20*S*)-isomer **19** was the major component (*ca.* 80%) of the mixtures. 'Grignard reduction' was also observed earlier[2] with thevinone **4**. The same alcohols were obtained, in approximately equal amounts, by reduction of 8-thiathevinone with sodium borohydride. The relative configuration of the secondary alcohols was again determined by physical data, aided by comparison with the known[2] secondary alcohols **21** and **22** derived from thevinone **2**. An independent determination of their absolute configurations confirmed these conclusions (see below). The relevant physical data are collected in Table 2. As expected, effects attributable to differences in intramolecular hydrogen-bonding are larger than for the tertiary alcohols **4** and **5**, since they depend upon the relative sizes of a methyl group and a hydrogen atom, rather than another alkyl group. The relatively hindered, (20*S*)-epimers **19** and **21** showed IR hydroxy bands at 3520 and 3540 cm^{-1}, whereas their epimers **20** and **22** showed bands at 3500 and 3490 cm^{-1}, respectively, indicative of stronger hydrogen-bonding. Uniquely, the derivative **21** showed a sharp band at 3605 cm^{-1} attributable to a π-bonded hydroxy group, in agreement with the literature.[2] Large differences were evident in the chemical shifts of the 20-hydroxy protons. As expected, higher δ values correlated within each pair with lower hydroxy frequencies. The small differences in chemical shifts for the 20-methyl groups

Table 2 Comparative physical data for the secondary alcohols **19** and **20** derived from 8-thiathevinone **3**, and **21** and **22** from thevinone **2**

Compound	C-20 config.[n]	R_f[a]	δ[b] 20-OH	δ[b] 20-Me	ν^c_{max}(OH)/cm^{-1}
19	*S*	0.74	1.88	1.06	3520
20	*R*	0.66	4.65	1.11	3500
21	*S*	0.73	2.03	1.07	3540, 3605[d]
22	*R*	0.64	4.95	1.11	3490

[a] Merck alumina plates in butanone. [b] ^{1}H NMR chemical shift (90 MHz; $CDCl_3$). [c] IR band in CCl_4; frequency independent of concentration. [d] The relative intensities of the sharp, 3605 cm^{-1} and the broad, 3540 cm^{-1} bands were independent of concentration.

Table 3 Modified Horeau determination of the C-20 configurations of the secondary alcohols **19–22**

Compound	Configuration	Amounts[a] of amides (*R*,*R*)[b]	Amounts[a] of amides (*R*,*S*)[b]
19	20*S*	76	31
20	20*R*	243	262
21	20*S*	201	160
22	20*R*	370	383
(+)-Menthol	1*S*	311	255
(−)-Menthol	1*R*	223	247

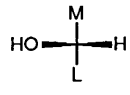
[a] Areas of GLC traces after subtraction of cyclohexanol controls. [b] *N*-[(*R*)-1-Phenylethyl]-(*R*)-2-phenylbutanamide and its (*R*,*S*)-diastereoisomer.

Table 4 Analgesic potency of 8-thiathevinols **5**, the 7β-methylthiathevinol **23** and thevinols **4** in guinea-pig ileum tissue. Agonist potencies (by wt.) (rp) are recorded relative to *N*-normorphine.

	R	R′	C-20 config.[n]	rp
5a	Me	Me		0.00
5b	Me	Et	*R*	0.01
5c	Et	Me	*S*	0.0035
5d	Me	Pr	*R*	<0.01
5e	Pr	Me	*S*	0.0035
5f	Me	Bu	*R*	0.40
5g	Bu	Me	*S*	0.02
5h	Me	C_5H_{11}	*R*	1.0
5i	C_5H_{11}	Me	*S*	0.05
5j	Me	C_6H_{13}	*R*	0.52
5k	C_6H_{13}	Me	*S*	0.037
23				0.025
4d	Me	Pr	*R*	200
4f	Me	Bu	*R*	61
4h	Me	C_5H_{11}	*R*	80
4j	Me	C_6H_{13}	*R*	36

were also consistent with the proposed stereochemistry; in the (20*S*)-epimers this group would be shielded relatively by the $\Delta_{18,19}$ π bond. The (20*R*)-epimer of each pair had the lower R_f value, on alumina plates.

The absolute stereochemistry of all four secondary alcohols **19–22** was determined by a modification[13] of the Horeau method suitable for small samples (*ca.* 1 mg). Each alcohol was separately esterified with an excess of racemic 2-phenylbutanoic anhydride. (+)-(*R*)-1-Phenylethylamine was then added to the remaining anhydride to form a mixture of diastereoisomeric amides, which was analysed by GLC. For each determination, cyclohexanol was treated similarly in parallel to provide a standard mixture of amides. The amounts (integrated areas of the gas chromatogram) of the standards were subtracted from those from the secondary alcohols before the latter were compared. As an independent check on the results (Table 3), the enantiomers of menthol were subjected to the same procedure. According to the method,[13] alcohols with the absolute configuration **26** (M and L represent groups having medium



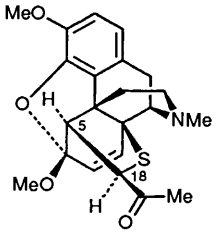
26

and large relative sizes) produce an excess of *N*-[(*R*)-1-phenylethyl]-(*S*)-2-phenylbutanamide over the other diastereoisomer. The analyses for all four alcohols confirm the assigned configurations **19–22**, providing that the groups M and L in structure **26** are taken to be methyl and the C-7 bridge. This confirmation of the assignments made on physical data (Table 2) reinforces the validity of those made similarly (Table 1) for the tertiary alcohols.

In their seminal studies on analgesics derived from thevinone **2**, Bentley *et al.* tested a wide range of thevinols[2] **4** and the related phenols[3] (orvinols). They reported relative molar potencies (rmp) using morphine as their standard in the rat tail pressure test. The secondary alcohols **21** and **22** were approximately equipotent with morphine, and the thevinol **4a** was somewhat more potent (rmp 2.7). Along the series of (20*R*)-thevinol derivatives with alkyl groups R′ (R = Me), the potency initially increased then later decreased with increasing chain length. Thus, for **4a**, **b**, **d**, **f**, **h** and **j** the relative potencies were successively 2.7, 20, 96, 24, 15 and 2. Significantly, in all cases, tertiary alcohols with the (20*S*)-configuration are much less potent than their epimers. In the present study the thiathevinols **5** and the single 7β derivative **23** were tested by Dr. C. F. C. Smith and his colleagues (Reckitt and Colman Ltd.), who used a more recent method[14] employing electrically stimulated, guinea-pig ileum tissue. As is usual, *N*-normorphine was used as the standard (this derivative cannot be used in intact animals since it does not penetrate the blood–brain barrier effectively). The results of assays with isolated tissue are easier to interpret since they are free from the dependence upon rates of absorption, transport, metabolism, and excretion characteristic of tests with intact animals. The results are collected in Table 4 along with values for several (20*R*)-thevinols for comparison. It was soon apparent that the agonist potencies of the new, sulphur-containing derivatives were some two orders of magnitude lower than those of the classical thevinols. As with the latter, the series showed a rise then fall of activity with increasing alkyl chain length, although the peak was reached later, at the pentyl derivative **5h** rather than the propyl derivative **4d**. The potencies of earlier members of the series **5** were too small to allow reliable comparison between (20*R*)- and (20*S*)-derivatives. However, for the later pairs **5f**,**g**, **5h**,**i** and **5j**,**k** it is clear that the (20*R*)-epimers are much more potent, a feature characteristic of the thevinols **4**. The shift in the chain length for maximum activity between the old and new series is not unexpected when account is taken of the changes in

bond lengths and angles caused by the replacement of a methylene group by sulphur. However, the striking fall in overall potency is remarkable since the high potency of the thevinols **4** must depend upon the binding of a flexible alkyl group to the opiate receptor. The point of attachment (C-7) of this group will be displaced only slightly by the introduction of sulphur, and this displacement should easily be accommodated by a compensating change in alkyl chain length. Moreover, comparisons between the potencies of thevinols and thiathevinols in tissue preparations would not normally be expected to be complicated by secondary effects of absorption or metabolism, *e.g.* S-oxidation. For the present, this major difference between the two series remains unexplained. The (20*R*)-pentyl-8-thiathevinol **5h** is equipotent with normorphine. The corresponding phenol (a thiaorvinol) would be expected to be substantially more potent as an analgesic agonist, however plans to investigate the corresponding series of phenols were abandoned in the light of the properties of the codeine derivatives **5**.

Grignard reagents rather than alkyllithium reagents were used routinely to prepare thevinols in the original studies.[2] Generally, alkyllithium reagents were less stereoselective and complications arising from base-catalysed rearrangements[1,9] (see Scheme 3) of thevinone were observed. However, formation of the secondary alcohols **21** and **22** did not occur and, for this reason, the occasional use of alkyllithium reagents was recommended.[2,15] Since the Grignard reactions of 8-thiathevinone **3** were neither high-yielding nor stereoselective, the reactions with alkyllithium reagents were briefly studied. Addition of butyllithium to 8-thiathevinone **3** gave a mixture of the butylthiathevinols **5f,g**. Curiously, the reaction was more stereoselective than the corresponding Grignard reaction, but the yields of purified products were still low, 14 and 2% for the (20*R*)- **5f** and (20*S*)-epimer **5g**, respectively. As expected, none of the secondary alcohols **19** and **20** was observed. The corresponding reaction with propyllithium was complicated by rearrangement of the thiathevinone **3**. Apart from a small quantity of (20*R*)-20-propyl-8-thiathevinone **5d**, the only identified product was the acetal **27**. Comparison of the ^{1}H NMR spectrum of the rearranged product **27** with those of the ester **9** and the acetal **15** derived from thevinone aided the determination of the structure **27**. In particular, the small coupling (*J* 1.7 Hz) between 5-H and 18-H, is that expected for an 18β-configuration with a torsion angle of *ca.* 90° between these two protons. No doubt, the acetal **27** arises by base-catalysed rearrangement of 8-thiathevinone **3** by a mechanism[1,9] strictly analogous to that shown in Scheme 3 for thevinone **2**. Presumably protonation of a rearranged enolate ultimately gives the thermodynamically more stable 18β-epimer **27**, as occurs in the formation of the acetal **15**. Very



27

likely, 8-thiathevinone **3** is more susceptible to base-catalysed rearrangement than is thevinone **2**, on account of the increased acidity of the proton, 7-H, α to sulphur. However, when propyllithium was added slowly to 8-thiathevinone **3** at −78 °C, rearrangement was suppressed and the (20*R*)-propylthiathevinol **5d** was obtained in 38% yield. It appears therefore, that, with further investigation of reaction conditions, alkyllithium reagents might prove to be superior to Grignard reagents for the preparation of (20*R*)-alkylthiathevinols.

Experiments are in progress[16] on the reductive desulphurisation of the adduct **8** and its rearrangement product **10**, and of similar 7-thia derivatives, as a route to 14-substituted morphinans. Revesz *et al.*[17] have recently reported related studies, leading from the cycloadducts of *N*-cyclopropylmethyl-*N*-northebaine with thiobenzaldehyde and various alkanethials, to 14-benzyl- and 14-alkyl-morphinans.

Experimental

General.—M.p.s were determined on a Kofler, hot-stage apparatus. IR spectra were recorded on either a Perkin-Elmer 580 or 953 spectrometer. ^{1}H NMR spectra were obtained, except where otherwise stated, for solutions in deuteriochloroform at 90 MHz with a Perkin-Elmer R34 or JEOL 90 FT spectrometer. *J* Values are in Hz. ^{13}C NMR spectra were obtained likewise, but at 50.3 MHz with a Bruker WP 200 SY spectrometer, along with the corresponding ^{1}H spectra at 200 MHz. Mass spectra were obtained by EI at 70 eV with AEI MS12 and MS9 spectrometers. Layer chromatography generally employed Merck GF_{254} silica gel on glass plates, or on the rotor of a Harrison Chromatotron under nitrogen. Column chromatography[18] was carried out with Merck HF_{254} silica gel, the flow being assisted with a water pump. Compounds were detected by UV light or iodine vapour. Solutions in organic solvents were dried over magnesium sulphate and evaporated with a Büchi Rotavapor. Light petroleum refers to the fraction with b.p. 40–60 °C.

Preparation of Bunte Salts.—The following salts were prepared, as precursors of thioaldehydes, in the usual way from aq. sodium thiosulphate and ethyl bromoacetate in ethanol, methyl chloroacetate in methanol and bromo- or chloroacetone in ethanol. Generally, the bromo derivatives required only brief heating with thiosulphate to effect complete reaction. Sodium *S*-ethoxycarbonylmethyl thiosulphate had m.p. 152–161 °C (decomp.) (from ethanol) (lit.,[19] 155 °C) (Found: C, 21.4; H, 3.0; S, 28.7. Calc. for $C_4H_7NaO_5S_2$: C, 21.6; H, 3.2; S, 28.8%); ν_{max}(KBr)/cm^{-1} 1716; δ_H(D_2O; internal standard Bu^{t}OH, δ 1.29) 1.31 (t, *J* 7, Me), 3.90 (s, SCH_2) and 4.25 (q, *J* 7, OCH_2). Sodium *S*-methoxycarbonylmethyl thiosulphate had m.p. 150 °C (decomp.) (the lit.[20] reports a wide m.p. beginning at 150 °C) (Found: C, 17.4; H, 2.4; S, 30.7. Calc. for $C_3H_5NaO_5S_2$: C, 17.3; H, 2.4; S, 30.8%); ν_{max}(KBr)/cm^{-1} 1715; δ_H(D_2O; internal standard Bu^{t}OH, δ 1.29) 3.82 (s, Me) and 3.96 (s, CH_2). *Sodium* S-(2-*oxopropyl*)*thiosulphate* had m.p. 215 °C (decomp.) (Found: C, 18.6; H, 2.6; S, 33.7. $C_3H_5NaO_4S_2$ requires C, 18.8; H, 2.6; S, 33.3%); ν_{max}(KBr)/cm^{-1} 1710; δ_H(D_2O internal standard Bu^{t}OH, δ 1.29) 2.41 (s, Me) and 4.08 (s, CH_2). Baker and Barkenbus[7] reported the salt as a trihydrate.

The Toluene-p-*thiosulphonate* **16** *and the Derived Disulphide* **17**.—Mixtures of the precursors **16** and **17** of 2-oxopropanethial **18** were obtained as follows.[10,11] 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 cm^3) overnight at room temperature. The resin was collected and washed with water (4 × 25 cm^3) and then acetone (4 × 25 cm^3). The resulting resin was stirred in benzene (7 cm^3) with chloroacetone (0.69 g, 7.5 mmol) overnight at room temperature. The resin was filtered off and washed with chloroform–benzene (1:1) (50 cm^3), and the combined filtrate and washings were evaporated to yield an oily mixture (1.72 g) of the derivatives **16**

and **17**. The proportions of **16** (*ca.* 78%) and **17** (*ca.* 22%) were determined by ^{1}H NMR spectroscopy. *S*-(2-Oxopropyl) toluene-*p*-thiosulphonate **16** gave δ_H 2.24 (s, Ar*Me*), 2.47 (s, Ac), 3.89 (s, CH_2), and 7.39 and 7.82 (2 × d, *J* 9, C_6H_4). 2-Oxopropyl 1-(*p*-tolylsulphonyl)-2-oxopropyl disulphide **17** gave δ_H 2.24 (s, Ar*Me*), 2.47 (s, 2 × Ac), 3.79 (s, CH_2), 5.18 (s, CH), and 7.38 and 7.81 (2 × d, *J* 9, C_6H_4). The proportion of the disulphide **17** was increased to 61% when the mixture was adsorped onto silica gel (Merck 60, 'flash' chromatography grade) then eluted with chloroform after 48 h at room temperature.

The Cycloadducts **7**, **8** *and* **11** *of Thebaine and Ethyl Thioxoacetate.*—Triethylamine (0.56 g, 5.5 mmol) was added to a stirred mixture of calcium chloride dihydrate (0.81 g, 5.5 mmol), sodium *S*-ethoxycarbonylmethyl thiosulphate (1.22 g, 5.5 mmol) and thebaine (1.56 g, 5.0 mmol) in ethanol–benzene (1:1) (25 cm^3) at room temperature. Stirring was continued for 160 h and then the mixture was diluted with chloroform (100 cm^3) and filtered through Celite. The filtrate was evaporated and the residue was chromatographed on a column of silica gel. Elution of the products with mixtures of chloroform and diethyl ether was monitored with silica TLC plates developed with diethyl ether. Typical R_f values were 0.54, 0.61 and 0.72 for the cycloadducts **7**, **11** and **8**, respectively. The 7α-8-thia cycloadduct **7** (1.58 g, 74%) had m.p. 116–118 °C (from propan-2-ol) (lit.,[4] 116–118 °C), the 8α-7-thia cycloadduct **8** (0.11 g, 5%) had m.p. 126–128 °C (from propan-2-ol) (lit.,[4] 125–128 °C) and *ethyl* 6,7,8,14-*tetrahydro*-8-*thia*-6α,14α-*ethenothebaine*-7β-*carboxylate* **11** (0.087 g, 4%) had m.p. 139–142 °C (from propan-2-ol) (Found: C, 64.5; H, 6.5; N, 3.2; S, 7.5%; *m/z* 429.1614. $C_{23}H_{27}NO_5S$ requires C, 64.3; H, 6.3; N, 3.3; S, 7.5%; *M*, 429.1610); ν_{max}(KBr)/cm^{-1} 1730; δ_H(200 MHz) 1.32 (t, *J* 7.1, OCH_2Me), 1.78 (ddd, *J* 13.1, 3.5 and 1.0, 15_{eq}-H), 2.41 (s, NMe), 3.25 (td, *J* 12.8 and 5.7, 15_{ax}-H), 3.30 (d, *J* 18.7, 10β-H), 3.38 (d, *J* 6.6, 9-H), 3.60 (s, 6-OMe), 3.77 (s, 7-H), 3.82 (s, 3-OMe), 4.23 (m, OCH_2), 5.55 (d, *J* 1.6, 5-H), 5.81 (d, *J* 9.0, 19-H), 6.00 (dd, *J* 9.0 and 1.7, 18-H), 6.54 (br d, *J* 8.2, 1-H) and 6.64 (d, *J* 8.2, 2-H); δ_C(50.3 MHz) 14.1 (OCH_2Me), 23.1 (C-10), 30.9 (C-15), 43.4 (NMe), 45.7 (C-16), 49.6 (C-13 or -14), 52.9 (C-14 or -13), 53.2 (OMe), 56.8 (OMe), 60.2 (C-9), 61.7 (OCH_2), 80.7 (C-6), 89.9 (C-5), 114.2 (C-2), 119.3 (C-1), 125.8 (C-17 or -18), 126.7 (C-11 or -12), 134.3 (C-12 or -11), 136.2 (C-18 or -17), 142.3 (C-3), 147.4 (C-4) and 170.8 (C=O).

Base-catalysed Epimerisation of the Esters **7** *and* **11**.—Potassium *tert*-butoxide (0.6 mmol) in *tert*-butyl alcohol (3 cm^3) was added to the 7α-ester **7** (284 mg, 0.66 mmol) in *tert*-butyl alcohol (2 cm^3). The mixture was stirred at room temperature for 30 min, during which time the colour changed to dark orange. Saturated aq. ammonium chloride (6 cm^3) and dichloromethane (10 cm^3) were added. Evaporation of the organic layer gave a yellow oil containing the esters **7** and **11** in the ratio 85:15, as determined by ^{1}H NMR spectroscopy. Preparative TLC gave the 7α-ester **7** (21%) and the 7β-ester **11** (25%). The latter was treated with potassium *tert*-butoxide under the foregoing conditions to give a mixture of the epimers **7** and **11**, ratio 8:2.

The Cycloadducts of Thebaine and Methyl Thioxoacetate.—The foregoing experiment was repeated, but with sodium *S*-methoxycarbonylmethyl thiosulphate in place of the ethoxy carbonyl salt and with methanol in place of ethanol. Chromatography of the reaction mixture, as before, gave the methyl esters corresponding to the ethyl esters **7**, **11** and **8**. *Methyl* 6,7,8,14-*tetrahydro*-8-*thia*-6α,14α-*ethenothebaine*-7α-*carboxylate* (**7**; Me replacing Et) (73%) (R_f 0.59) had m.p. 142–144 °C (from propan-2-ol) (Found: C, 63.5; H, 5.9; N, 3.2; S, 7.6%; *m/z* 415.1460. $C_{22}H_{25}NO_5S$ requires C, 63.6; H, 6.0; N, 3.4; S, 7.7%; *M*, 415.1545); ν_{max}(KBr)/cm^{-1} 1750 and 1725w; δ_H 2.37 (s, NMe), 3.22 (d, *J* 19, 10β-H), 3.40 (d, *J* 7, 9-H), 3.63 (s, 6-OMe), 3.68 (s, CO_2Me), 3.81 (s, 3-OMe), 4.54 (s, 5-H), 5.86 (br s, 18- and 19-H), 6.57 (d, *J* 8, 1-H), 6.63 (d, *J* 8, 2-H). *Methyl* 6,7,8,14-*tetrahydro*-8-*thia*-6α,14α-*ethenothebaine*-7β-*carboxylate* (**11**; Me replacing Et) (4%) (R_f 0.62) had m.p. 154–156 °C (from propan-2-ol) (Found: C, 63.6; H, 6.0; N, 3.1; S, 8.0%; *m/z* 415.1437. $C_{22}H_{25}NO_5S$ requires C, 63.6; H, 6.0; N, 3.4; S, 7.7%; *M*, 415.1454); ν_{max}(KBr)/cm^{-1} 1735; δ_H 2.39 (NMe), 3.22 (d, *J* 19, 10β-H), 3.40 (d, *J* 7, 9-H), 3.59 (s, CO_2Me), 3.75 (s, 6-OMe), 3.81 (s, 3-OMe), 5.57 (d, *J ca.* 1, 5-H), 5.79 (d, *J* 8, 19-H), 5.98 (dd, *J* 8 and *ca.* 1, 18-H), 6.52 (d, *J* 8, 1-H) and 6.63 (d, *J* 8, 2-H). *Methyl* 6,7,8,14-*tetrahydro*-7-*thia*-6α,14α-*ethenothebaine*-8α-*carboxylate* (**8**; Me replacing Et) (6%) (R_f 0.67) had m.p. 138–140 °C (from propan-2-ol) (Found: C, 63.5; H, 6.2; N, 3.1; S, 7.7%; *m/z* 415.1448. $C_{22}H_{25}NO_5S$ requires C, 63.6; H, 6.0; N, 3.4; S, 7.7%; *M*, 415.1454); ν_{max}(KBr)/cm^{-1} 1738; δ_H 2.34 (s, NMe), 3.59 (s, CO_2Me), 3.68 (s, 6-OMe), 3.80 (s, 3-OMe), 4.95 (d, *J* 1.5, 5-H), 5.25 (s, 8-H), 5.71 (d, *J* 9.5, 19-H), 6.19 (d, *J* 9.5, 18-H), 6.56 (d, *J* 8.1, 1-H) and 6.62 (d, *J* 8.1, 2-H).

(19R)-*Ethyl* 7,8-*Didehydro*-3,6β-*dimethoxy*-17-*methyl*-4,6α-*epoxy*-5β,14β-*thiaethanomorphinan*-19-*carboxylate* **9**.—The 7-thia ester[4] **8** (200 mg, 0.46 mmol) was heated under reflux in chlorobenzene (25 cm^3) for 30 h. Evaporation of the mixture gave the ester **8** (*ca.* 20%) and the acetal **9** (*ca.* 80%), which were separated chromatographically on neutral, Merck 60 GF_{254}, alumina (silica gel was ineffective) plates developed with diethyl ether-light petroleum (65:35). The starting material **8** (R_f *ca.* 0.7) (33 mg, 16%) was identified by its m.p. and mixed m.p. 126–128 °C. The *acetal* **9** (R_f *ca.* 0.6) (127 mg, 64%) was obtained as an oil [Found: *m/z* 429.1620 and 310.1432. $C_{23}H_{27}NO_5S$ requires *M*, 429.1610 and (*M* − $C_4H_7O_2S$), 310.1444]; ν_{max}-(KBr)/cm^{-1} 1728; δ_H (200 MHz) 1.24 (t, *J* 7.1, OCH_2Me), 2.38 (s, NMe), 3.38 (d, *J* 19.0, 10β-H), 3.49 (d, *J* 2.4, 5-H), 3.50 (d, *J* 6.0, 9-H), 3.59 (s, 6-OMe), 3.80 (s, 3-OMe), 4.12 (m, OCH_2), 5.24 (dd, *J* 10.0 and 2.4, 7-H), 5.52 (s, 19-H), 6.05 (dd, *J* 10.0 and 0.6, 8-H) and 6.62 (s, 1- and 2-H); δ_C(50.3 MHz) 14.1 (OCH_2Me), 25.5 (C-10), 30.6 (C-15), 43.2 (NMe), 44.8 (C-16), 49.6 (C-13 or -14), 50.9 (6-OMe), 51.5 (C-19), 52.1 (C-14 or -13), 54.3 (C-9), 56.3 (3-OMe), 57.1 (C-5), 61.2 (OCH_2), 106.8 (C-6), 109.9 (C-2), 118.5 (C-1), 124.8 (C-7 or -8), 128.6 (C-11 or -12), 130.7 (C-12 or -11), 138.0 (C-8 or -7), 143.0 (C-3), 146.6 (C-4) and 170.1 (C=O). The same mixture of the isomers **8** and **9** (*ca.* 2:8) was obtained by prolonged heating of either the 8-thia derivative **7** or the acetal **9**.

(19R)-*Methyl* 7,8-*Didehydro*-3,6β-*dimethoxy*-17-*methyl*-4,6α-*epoxy*-5β,14β-*thiaethanomorphinan*-19-*carboxylate* (**9**; Me replacing Et).—The foregoing methyl ester (**8**; Me replacing Et) was heated under reflux in toluene for 25 h to afford a mixture of the starting material (*ca.* 20%) and the acetal (**9**; Me replacing Et) (*ca.* 8·%). Chromatography on alumina plates, as described for the corresponding ethyl esters, gave the 7-thia ester (**8**; Et = Me) (15%) and the *methyl ester acetal* (**9**; Et = Me) (65%) as a resin (Found: *m/z* 415.1453. $C_{22}H_{25}NO_5S$ requires *M*, 415.1454); ν_{max}(KBr)/cm^{-1} 1735; δ_H 2.38 (s, NMe), 3.50 (d, *J* 1.5, 5-H), 3.58 (s, CO_2Me), 3.67 (s, 6-OMe), 3.80 (s, 3-OMe), 5.25 (dd, *J* 10 and 1.5, 7-H), 5.55 (s, 19-H), 6.04 (d, *J* 10, 8-H) and 6.60 (s, 1- and 2-H).

(19R)-*Ethyl* 7,8-*Didehydro*-4-*hydroxy*-3-*methoxy*-17-*methyl*-6-*oxo*-5β,14β-*thiaethanomorphinan*-19-*carboxylate* **10**.—The acetal **9** (75 mg) was heated in hydrochloric acid (2 mol dm^{-3}; 15 cm^3) at 100 °C for 5 min. The mixture was treated with a slight excess of sodium hydrogen carbonate and then extracted with chloroform to yield the *ketone* **10** (49 mg), m.p. 173–174 °C

(from aq. ethanol) (Found: C, 63.5; H, 5.9; N, 3.0%; *m/z* 415.1471. $C_{22}H_{25}NO_5S$ requires C, 63.6; H, 6.0; N, 3.4%; *M*, 415.1453); ν_{max}(KBr)/cm^{-1} 3420 br, 1733 and 1685; ν_{max}(CCl_4)/cm^{-1} 3530, 1729 and 1690; δ_H (200 MHz) 1.24 (t, *J* 7.1, OCH_2Me), 2.36 (s, NMe), 2.74 (dd, *J* 18.7 and 5.8, 10α-H), 3.17 (d, *J* 18.7, 10β-H), 3.68 (d, *J* 5.0, 9-H), 3.75 (s, 3-OMe), 4.13 (q, *J* 7.1, OCH_2), 4.66 (dd, *J* 1.7 and 0.8, 5-H), 5.38 (s, 19-H), 5.85 (s, OH, exch. with D_2O), 5.92 (dd, *J* 10.0 and 1.7, 7-H), 6.57 (d, *J* 8.5, 1-H), 6.60 (d, *J* 8.5, 2-H) and 6.76 (dd, *J* 10.0 and 0.4, 8-H); δ_C(50.3 MHz) 14.1 (OCH_2Me), 25.2 (C-10), 30.0 (C-15), 42.8 (NMe), 45.5 (C-17), 52.2 (C-13 or -14), 53.2 (C-5 or -19), 53.5 (C-14 or -13), 55.6 (C-19 or -5), 55.9 (3-OMe), 59.1 (C-9), 61.4 (OCH_2), 108.9 (C-2), 118.0 (C-1), 124.2 (C-11), 129.8 (C-12), 130.2 (C-7), 142.7 (C-3), 144.7 (C-4), 148.8 (C-8), 169.8 (CO_2Et) and 194.2 (C-6).

7α-Acetyl-6,7,8,14-tetrahydro-8-thia-6α,14α-ethenothebaine (8-Thiathevinone) **3**.—The cycloadduct **3** was obtained in 42% yield from thebaine and sodium *S*-(2-oxopropyl) thiosulphate, as described for the preparation of the ester **7**. Alternatively, solutions of the thiosulphonate **16** (17.0 g, 69.7 mmol) (containing some of the disulphide **17**) in benzene (100 cm^3), calcium chloride dihydrate (10.25 g, 69.7 mmol) in ethanol (280 cm^3) and thebaine (7.23 g, 23.2 mmol) in benzene (220 cm^3) were mixed at room temperature. Triethylamine (7.04 g, 69.7 mmol) in benzene (80 cm^3) was added during 15 min to the stirred mixture. Stirring was continued for 120 h. The mixture was filtered through Celite and the filtrate was washed with water (5 × 200 cm^3) and then dried and evaporated to give a yellow oil. Chromatography on a column of silica gel gave 8-*thiathevinone* **3** as a resin (6.9 g, 75%) (Found: *m/z* 399.1502. $C_{22}H_{25}NO_4S$ requires *M*, 399.1504); ν_{max}($CHBr_3$)/cm^{-1} 1690; δ_H 2.09 (s, Ac), 2.47 (s, NMe), 3.22 (d, *J* 19, 10β-H), 3.40 (d, *J* 7, 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, 1-H) and 6.54 (d, *J* 8, 2-H). The ^{1}H NMR spectrum was strikingly similar to that of the ester[4] **7**, apart from the signals for acetyl and ester groups.

8α-Acetyl-6,7,8,14-tetrahydro-7-thia-6α,14α-ethenothebaine (**8a**; Ac replacing CO_2Et).—8-Thiathevinone **3** (122 mg) was heated under reflux in toluene (10 cm^3) for 5 h. The mixture was evaporated to yield a semi-crystalline residue, which was chromatographed on silica gel plates developed with diethyl ether. The *7-thia isomer* (**8**; Ac replacing CO_2Et) (42 mg, 34%) had m.p. 150–151 °C (from ethanol) (Found: C, 66.1; H, 6.2; N, 3.3; S, 8.2%; *m/z* 339.1513. $C_{22}H_{25}NO_4S$ requires C, 66.2; H, 6.3; N, 3.5; S, 8.0%; *M*, 339.1504); ν_{max}(KBr)/cm^{-1} 1710; δ_H 2.10 (s, Ac), 2.30 (s, NMe), 3.20 (d, *J* 18, 10β-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, 19-H), 6.09 (d, *J* 9, 18-H), 6.52 (d, *J* 8, 1-H) and 6.62 (d, *J* 8, 2-H). The ^{1}H NMR spectrum was strikingly similar to that of the ester[4] **8**, apart from the signals for acetyl and ester groups.

Reduction of 8-Thiathevinone **3**, *the Secondary Thiathevinols* **19** *and* **20**.—8-Thiathevinone **3** (370 mg, 0.93 mmol) was heated under reflux with sodium borohydride (36 mg, 0.95 mmol) in methanol for 1 h. The mixture was evaporated and the residue shaken with chloroform and water. The chloroform layer was dried and then evaporated to give a mixture of the alcohols **19** and **20** which was separated by TLC on neutral, Merck 60 GF_{254} alumina plates, developed by multiple elution with butan-2-one. The band with R_f 0.74 gave (20S)-8-*thiathevinol* **19** as an oil (152 mg, 41%) (Found: *m/z* 401.1658. $C_{22}H_{27}NO_4S$ requires *M*, 401.1661); ν_{max}(CCl_4)/cm^{-1} 3520; δ_H 1.06 (d, *J* 6, 20-Me), 1.88 (s, OH, exch. with D_2O), 2.43 (s, NMe), 3.27 (d, *J* 19, 10β-H), 3.38 (s, 7-H), 3.65 (s, 6-OMe), 3.82 (s, 3-OMe), 4.21 (m, 20-H), 4.51 (s, 5-H), 5.67 (d, *J* 9, 19-H), 5.82 (d, *J* 9, 18-H), 6.52 (d, *J* 9, 1-H) and 6.62 (d, *J* 9, 2-H). The band with R_f 0.66 gave (20R)-8-*thiathevinol* **20** (55 mg, 15%), m.p. 183.5–185 °C (from ethanol) (Found: C, 66.5; H, 6.7; N, 3.1; S, 7.8%; *m/z* 401.1666. $C_{22}H_{27}NO_4S$ requires C, 65.8; H, 6.7; N, 3.5; S, 8.0%; *M*, 401.1661); ν_{max}(CCl_4)/cm^{-1} 3500; δ_H 1.11 (d, *J* 7, 20-Me), 2.37 (s, NMe), 3.72 (s, 6-OMe), 3.82 (s, 3-OMe), 4.56 (s, 5-H), 4.65 (s, OH, exch. with D_2O), 5.79 (s, 18- and 19-H), 6.53 (d, *J* 8, 1-H) and 6.63 (d, *J* 8, 2-H).

Determination of the Absolute Configuration of the Secondary 8-Thiathevinols **19** *and* **20**.—A modification[13] of Horeau's method, employing gas chromatographic separation of diastereoisomeric amides, was employed. GLC was carried out with a Perkin-Elmer F11 instrument using a hydrogen, flame-ionisation detector and a silanised glass column (3 m × 3.5 mm) packed with 1% OV-17 stationary phase on Gas Chrom Q (100–120 mesh), with nitrogen as carrier gas (flow rate 40 cm^3 min^{-1}) and at a column temperature of 100 °C. Racemic 2-phenylbutanoic anhydride (4 mm^3) was added to each of the secondary alcohols **19**–**22** (1 mg), each in dry pyridine (7 mm^3), and the mixtures were heated to 45 °C for 50 min. (+)-(1*R*)-1-Phenylethylamine (6 mm^3) was added to each of the mixtures, followed by ethyl acetate (100 mm^3) to dissolve the amides that precipitated. The solutions were heated at 100 °C for 6 min and then were diluted with ethyl acetate (400 mm^3). The resulting mixtures were immediately analysed by GLC (1 mm^3 aliquots). The same procedure was carried out with cyclohexanol to provide GLC, peak-area standards for *N*-[(*R*)-1-phenylethyl]-(*S*)-2-phenylbutanamide and the corresponding (*R*,*R*)-amide. Control experiments were carried out with the enantiomers of menthol. See the main text and ref. 13 for the method of calculation, and Table 3 for the results.

Preparation of 20-Methyl-8-thiathevinol **5a** *and Its 7β-Epimer* **23** *from the Esters* **7** *and* **11**.—The ester **7** (215 mg, 0.50 mmol) in benzene (10 cm^3) was added to a solution of methylmagnesium iodide (3.5 mmol) in diethyl ether (10 cm^3) with heating under reflux. After 2 h, the mixture was cooled and then treated successively with water and aq. ammonium chloride. The organic layer was dried and evaporated and the residue was chromatographed on silica plates developed with diethyl ether. *20-Methyl-8-thiathevinol* **5a** (133 mg, 64%) had m.p. 162–164 °C (from ethanol) (Found: C, 66.7; H, 6.8; N, 3.2%; *m/z* 415.1796. $C_{23}H_{29}NO_4S$ requires C, 66.5; H, 7.0; N, 3.4%; *M* 415.1817); ν_{max}(KBr)/cm^{-1} 3505; ν_{max}(CCl_4)/cm^{-1} 3510; δ_H 1.09 (s, CMe_2), 2.40 (s, NMe), 3.24 (d, *J* 19, 10β-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, 19-H), 5.88 (d, *J* 9, 18-H), 6.51 (d, *J* 8, 1-H) and 6.61 (d, *J* 8, 2-H). The alcohol **5a** was obtained in the same way from 8-thiathevinone **3**, but in lower yield.

Similarly, the 7β-ester **11** gave *20-methyl-7β-8-thiathevinol* **23** (54%), m.p. 153–156 °C (from ethanol) (Found: C, 66.3; H, 6.8; N, 3.4%; *m/z* 415.1811. $C_{23}H_{29}NO_4S$ requires C, 66.5; H, 7.0; N, 3.4%; *M*, 415.1817); ν_{max}(CCl_4)/cm^{-1} 3510; δ_H 1.35 (s, 19-Me), 1.56 (s, 19-Me), 2.42 (s, NMe), 3.23 (d, *J* 19, 10β-H), 3.71 (s, 6-OMe), 3.82 (s, 3-OMe), 4.45 (s, OH. exch. with D_2O), 5.31 (d, *J* 2, 5-H), 5.64 (d, *J* 9, 19-H), 6.13 (dd, *J* 9 and 2, 18-H), 6.53 (d, *J* 9, 1-H) and 6.64 (d, *J* 9, 2-H).

Preparation of the 20-Alkyl-8-thiathevinols **5** *from 8-Thiathevinone* **3** *and Grignard Reagents*.—In general, 8-thiathevinone **3** in benzene or toluene was added to a solution of the appropriate alkylmagnesium bromide (3–10 mol equiv.) in diethyl ether, with heating under reflux, as described in the foregoing preparation of the methylthiathevinols **5a** and **23** (see also ref. 2). As before, the reaction mixtures were decomposed with water and aq. ammonium chloride. Generally, the reaction mixtures contained the epimeric tertiary alcohols **5**, which were

Table 5 M.p.s and analytical data for the 20-alkyl-8-thiathevinols **5** (data for **5a** are recorded in the main text)

Compound	M.p. (°C) (from EtOH)	Molecular formula	Found: C; H; N%	Requires: C; H; N%	Found: *m/z*	Requires: *M*
5b	129–130	$C_{24}H_{31}NO_4S$	66.7; 7.3; 3.2	67.1; 7.2; 3.3	429.1977	429.1974
5c	169–171	$C_{24}H_{31}NO_4S$	66.8; 7.2; 3.1	67.1; 7.2; 3.3	429.1976	429.1974
5d	178.5–179.5	$C_{25}H_{33}NO_4S$	67.6; 7.2; 3.2	67.7; 7.4; 3.2	443.2143	443.2130
5e	118–120	$C_{25}H_{33}NO_4S$	67.5; 7.3; 3.2	67.7; 7.4; 3.2	443.2128	443.2130
5f	173–174	$C_{26}H_{35}NO_4S$	68.4; 8.1; 3.0	68.2; 7.7; 3.1	457.2293	457.2287
5g	125–126	$C_{26}H_{35}NO_4S$	68.3; 7.7; 3.0	68.2; 7.7; 3.1	457.2289	457.2287
5h	*a*	$C_{27}H_{37}NO_4S$			471.2442	471.2443
5i	148	$C_{27}H_{37}NO_4S$	68.6; 7.9; 3.0	68.8; 7.9; 3.0	471.2439	471.2443
5j	*a*	$C_{28}H_{39}NO_4S$			485.2591	485.2600
5k	143–144	$C_{28}H_{39}NO_4S$	69.1; 8.2; 2.8	69.2; 8.0; 2.9	485.2587	485.2600

[a] Obtained as an oil.

isolated in yields of typically 10% each after purification, lesser amounts of the secondary alcohols **19** and **20**, and substantial quantities of more-polar, amorphous material that was not identified. Chromatographic separation was effected initially on silica gel or Florisil columns, further separation being then achieved with a Chromatotron. R_f Values and selected IR and NMR data are recorded in Table 1. Apart from signals for the 20-alkyl and -hydroxy groups (Table 1), the ^{1}H NMR spectra of the tertiary alcohols **5** were, as expected, virtually indistinguishable from that recorded above of the methylthiathevinol **5a**; generally, chemical shifts differed by only ±0.05 ppm, with the exception of those for 7-H which lay in the range δ 3.36–3.45 (*cf.* δ 3.36 for **5a**). Since these differences barely exceed the reproducibility of the spectrometer (90 MHz), individual spectra are not listed. M.p.s and analytical data are given in Table 5. None of the compounds had been described before in the literature.

Reaction of 8-Thiathevinone **3** *with Butyllithium.*—8-Thiathevinone **3** (3.99 g, 10 mmol) in freshly dried tetrahydrofuran (THF) (25 cm^3) was cooled in an acetone–solid carbon dioxide bath (−78 °C). Butyllithium (20 mmol) in a mixture of hexanes was added dropwise to the stirred solution during 10 min. Stirring was continued for 2 h and the solution was then allowed to warm to room temperature. Water was added to the mixture, which was then extracted with diethyl ether. Chromatography of the extracts in the manner described for the preparation of the alcohols **5** gave the 20-butyl-8-thiathevinols **5f** (14%) and **5g** (2%).

Reactions of 8-Thiathevinone **3** *with Propyllithium; Formation of the Ketoacetal* **27** *and the 20-Propylthiathevinol* **5d**.—Propyllithium was prepared in diethyl ether (10 cm^3) from lithium and 1-bromopropane (3.1 g, 25 mmol) in the usual way. This solution was filtered through glass wool and then added to a stirred solution of 8-thiathevinone **3** (2.3 g, 5.8 mmol) in freshly dried THF (20 cm^3) at −78 °C (bath temperature). After 1 h, the mixture was quenched with water (20 cm^3) and ether (20 cm^3). The organic products were extracted with chloroform and separated by TLC on silica plates developed with diethyl ether. A small quantity (*ca.* 3%) of the (20*R*)-20-propylthiathevinol **5d** was isolated. The major product was the *ketoacetal* **27** (10%), m.p. 159–163 °C (from ethanol) (Found: C, 66.0; H, 6.4; N, 3.5; S, 8.1%; *m/z* 399.1491. $C_{22}H_{25}NO_4S$ requires C, 66.2; H, 6.3; N, 3.5; S, 8.0%; *M*, 399.1504); $\nu_{max}(CHCl_3)/cm^{-1}$ 1715; δ_H(200 MHz) 2.29 (s, Ac), 2.42 (s, NMe), 2.59 (br d, *J* 2.7, 5-H), 3.22 (d, *J* 5.9, 9-H), 3.45 (d, *J* 18.1, 10β-H), 3.51 (s, 6-OMe), 3.82 (s, 3-OMe), 4.16 (d, *J* 1.7, 18-H), 4.99 (dd, *J* 9.5 and 2.7, 7-H), 6.11 (dd, *J* 9.5 and 0.6, 8-H), 6.61 (d, *J* 8.3, 1-H) and 6.64 (d, *J* 8.3, 2-H).

In a second experiment propyllithium (45 mmol) in ether (35 cm^3) was added during 40 min to a stirred solution of 8-thiathevinone **3** (3.52 g, 8.8 mmol) in THF (30 cm^3) at −78 °C under dry argon. Work-up, as before, and chromatography on a silica column then silica plates gave the (20*R*)-propylthiathevinol **5d** (1.49 g, 38%).

Pharmacological Testing.—The analgesic potencies of the 8-thiathevinols **5** and 7β-methylthiathevinol **23**, with a selection of thevinols **4** for comparison, were determined by Dr. C. F. C. Smith and his colleagues at Reckitt and Colman Pharmaceutical Division (now Reckitt and Colman Products) in Hull. The results are recorded in Table 4 with kind permission of Dr. Smith and Dr. J. W. Lewis. Potencies were determined *in vitro* with electrically stimulated, guinea-pig ileum preparations by the method of Kosterlitz and Watt.[14] The procedure was modified so that agonist dose–response curves were obtained by cumulative dosing. Standard, dose–response curves for *N*-normorphine were obtained before and after those for each compound under test.

Acknowledgements

We thank the SERC and Reckitt and Colman Ltd. (Hull) for financial support, Dr. C. F. C. Smith (Reckitt and Colman) for pharmacological tests, Drs. J. W. Lewis and C. P. Chapleo (Reckitt and Colman) for their interest in the research, Professor C. J. W. Brooks and Dr. W. J. Cole (Glasgow) for advice on GLC[13] and Dr. D. S. Rycroft (Glasgow) for NMR spectra.

References

1 K. W. Bentley and D. G. Hardy, *J. Am. Chem. Soc.*, 1967, **89**, 3267.
2 K. W. Bentley, D. G. Hardy and B. Meek, *J. Am. Chem. Soc.*, 1967, **89**, 3273.
3 K. W. Bentley and D. G. Hardy, *J. Am. Chem. Soc.*, 1967, **89**, 3281.
4 C. M. Bladon, I. E. G. Ferguson, G. W. Kirby, A. W. Lochead and D. C. McDougall, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1541.
5 G. W. Kirby and C. J. McCorkindale, unpublished work.
6 F. Asinger, W. Schäfer, G. Baumgarte and P. F. Müting, *Liebigs Ann. Chem.*, 1963, **661**, 95.
7 R. H. Baker and C. Barkenbus, *J. Am. Chem. Soc.*, 1936, **58**, 262.
8 G. W. Kirby, A. W. Lochhead and G. N. Sheldrake, *J. Chem. Soc., Chem. Commun.*, 1984, 922.
9 K. W. Bentley, D. G. Hardy, H. P. Crocker, D. I. Haddlesey and P. A. Mayor, *J. Am. Chem. Soc.*, 1967, **89**, 3312.
10 G. W. Kirby, A. W. Lochead and G. N. Sheldrake, *J. Chem. Soc., Chem. Commun.*, 1984, 1469.
11 S. Takano, K. Hiroya and K. Ogasawara, *Chem. Lett.*, 1983, 255.
12 W. Fulmor, J. E. Lancaster, G. O. Morton, J. J. Brown, C. F. Howell, C. T. Nora and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, 1967, **89**, 3322.
13 C. J. W. Brooks and J. D. Gilbert, *J. Chem. Soc., Chem. Commun.*, 1973, 194; A. Horeau and H. B. Kagan, *Tetrahedron*, 1964, **20**, 2431.

14 H. W. Kosterlitz and A. J. Watt, *Br. J. Pharmacol. and Chemotherapy*, 1968, **33**, 266.
15 See also, L. L. Knipmeyer and H. Rapoport, *J. Med. Chem.*, 1985, **28**, 461.
16 G. W. Kirby and J. T. McQuillan, unpublished work.
17 L. Revesz, R. A. Siegel, H.-H. Buescher, M. Marko, R. Maurer and H. Meigel, *Helv. Chim. Acta*, 1990, **73**, 326.
18 L. M. Harwood, *Aldrichimica Acta*, 1985, **18**, 25.
19 B. Milligan and J. M. Swan, *J. Chem. Soc.*, 1961, 1194.
20 C. C. Price and W. G. Jackson, *J. Am. Chem. Soc.*, 1947, **69**, 1065.

Paper 1/022357H
Received 20*th May* 1991
Accepted 28*th May* 1991