Isovanillyl Sweeteners. Synthesis and Sweet Taste of Sulfur Heterocycles

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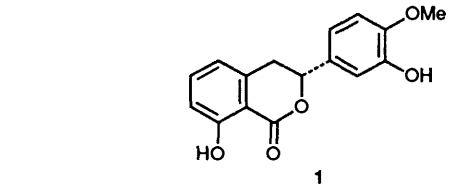
As part of an investigation into the structure–sweetness relationship in isovanillyl sweeteners, 15 compounds containing sulfur atoms either in the heterocyclic or the isovanillyl ring have been synthesised and tasted. In general the replacement of oxygen by sulfur maintained or improved the sweetness potency when the heteroatom is in the heterocyclic ring, while the same change in the OH or OMe groups eliminated the sweetness. The most effective structure for generating sweetness is that with a sulfur atom occupying position 1 and an oxygen atom position 3 of a chain, in which the isovanillyl ring is linked to C-2. 2-(3-Hydroxy-4-methoxyphenyl)-4*H*-3,1-benzoxathiane **10b** (sweet potency 9000) is the sweetest isovanillyl sweetener synthesised until now.

Some very sweet compounds contain sulfur atoms: examples among intensive sweeteners are sulfonamides or sulfamates, *e.g.* saccharin, cyclamates and acesulfame-K, and the sulfide alitame.[1] However the sweetness of these compounds is attributed to complex interactions of the molecules with the receptor rather than to a specific effect of sulfur atoms. In other cases, modifications of known sweet molecules by the replacement of carbon or oxygen atoms by sulfur led to an increase in sweetness potency (for a discussion see the recent review by Roy[2]). Thus, thiophenesaccharin[3] is about 15 times sweeter than the parent compound, the thiourea analogue[4] of the urea Suosan is about 3.5 times sweeter than Suosan, and a positive effect of the replacement of oxygen by sulfur atoms in the alkyl substituent of sulfamates was observed.[5] Among sugars, 5-thio-β-D-glucose and 6-thio-β-D-fructopyranose[6] were found to be about 1.25 fold sweeter than the corresponding sugar. No rationale was given for these modifications, which were made on a purely empirical basis. Lindley and Shallenberger[6] attempted to explain the effect in the case of 5-thio-β-D-glucose and 6-thio-β-D-fructopyranose in two ways. The angle C–S–C is 105 ± 3° while the angle C–O–C is 111 ± 3°: this difference could provoke a change in the molecule interatomic distances that induces a better fit of the taste entity (anomeric OH and CH_2OH) at the receptor. A second reason for the enhancement in sweet-taste potency could be that sulfur increases the access and/or the binding of the molecule to the receptor. More recently, Woods *et al.*,[7] using *ab initio* quantum-mechanical calculations, tried to understand more thoroughly why sulfur has a positive effect on the sweet taste of these thiosugars, without, however, obtaining conclusive results.

In previous papers[8,9] we have presented the synthesis and a study of the sweet-taste–structure relationship of a series of oxygen heterocycles belonging to the class of the isovanillyl sweeteners,[10] *i.e.* analogues of the natural compound phyllodulcin[11] **1** and of the semisynthetic sweetener neohesperidin-dihydrochalcone (NHDC).[12] In this class of sweet compounds, the 4-methoxy and 3-hydroxy substituents in the aromatic ring are considered to be involved in the binding of the tastant molecule with an A-H/B system present in the sweet taste receptor, according to the classical model of Shallenberger and Acree,[13] modified by Kier,[14] and included in the more recent hypotheses of Temussi and co-workers[15] and Tinti and Nofre[16] on the shape of the sweet taste receptor.

As a part of an investigation of the structural features responsible for the sweetness of this class, we have modified the number and the position of the oxygen atoms and the size of the heterocyclic ring. In this paper we report on the effect on the sweet taste of a systematic replacement of oxygen by sulfur atoms both in the heterocyclic ring and in the two important polar groups. Only a few of these compounds had been investigated previously. Thus Yamato *et al.*[17] prepared compounds **2** and **3**, whose sweet potencies are 300 and 150 with respect to sucrose, while the oxygen derivatives **4** and **5** are 'tasteless' and 'very sweet', respectively[18] (the parent compound phyllodulcin was reported to be 400[17] or 600–800[19] times sweeter than sucrose). Recently Unterhalt and Dabringhaus[20] reported 1-(3-hydroxy-4-methoxyphenyl)-2-thienylethane, a thiophene derivative of 1-(3-hydroxy-4-methoxyphenyl)-2-phenylethane (350 times sweeter than sucrose),[21] to be sweet, although quantitative assessment was not reported.



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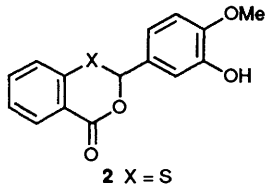

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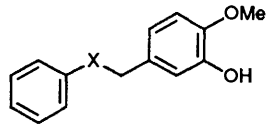
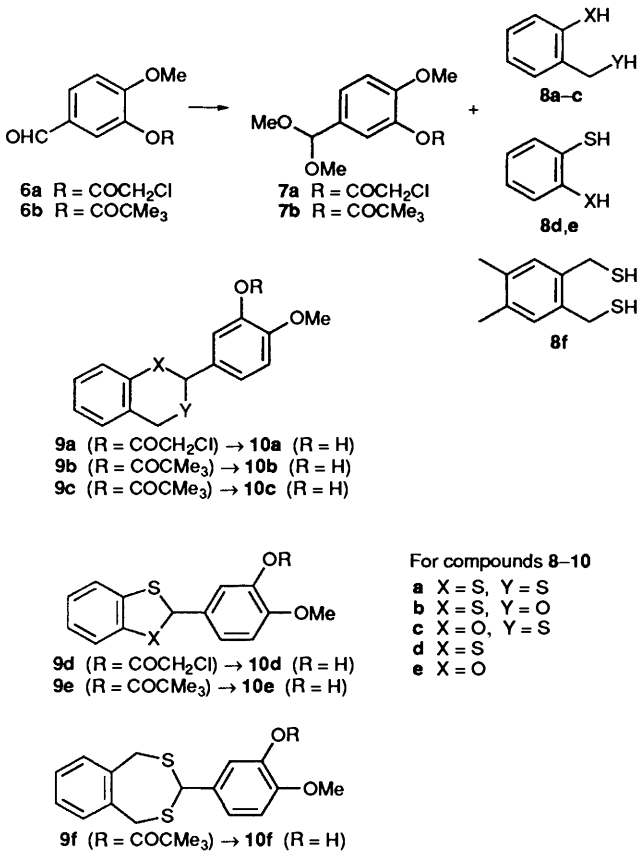
4 X = O



3 X = S
5 X = O

Results

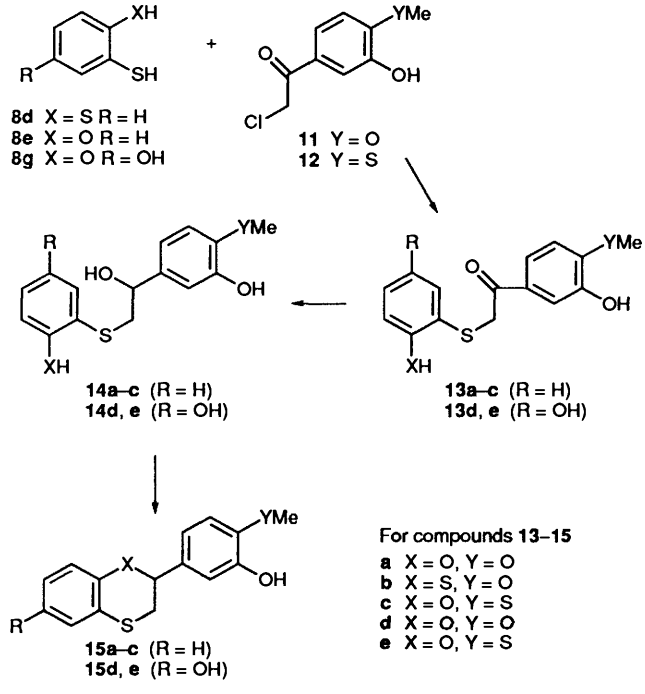
The cyclic thioketals or dithioketals **10a–c** and **10d–f** were synthesised by transketalisation of the dimethyl acetal of protected isovanillin **7** with the suitable dithiol or hydroxythiol **8** (Scheme 1). 2-Mercaptomethylphenol **8c** was prepared from 2-methylphenol in an overall 76% yield, by a sequence of acetylation, bromination of the benzylic position with *N*-bromosuccinimide, reaction under phase-transfer conditions with sodium hydrogen sulfide to give 2-acetoxyphenylmethanethiol (and in part the already deprotected 2-hydroxy derivative) and hydrolysis with aqueous sodium hydroxide. Isovanillin was protected as 2-chloroacetate **7a** for the synthesis of compounds **10a** and **10d**, and as 2,2-dimethylpropionate **7b** for compounds **10b, c, e** and **f**, the latter protection ensuring



Scheme 1

increased stability of the compound during the deprotection, which was accomplished with lithium aluminium hydride.

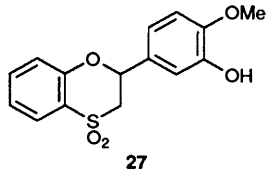
For the synthesis of compound **15a** 2-mercaptophenol[22] **8e** (obtained from 2-aminophenol through reduction of the xanthate with lithium aluminium hydride) was condensed with 3-hydroxy-4-methoxy-α-chloroacetophenone[8] **11** under basic conditions (Scheme 2). The structure of compound **13a** was



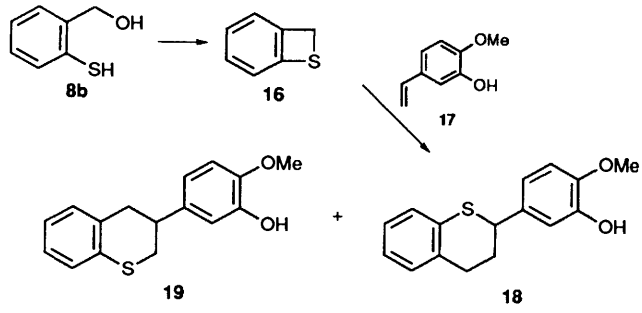
Scheme 2

assigned on the basis of NMR spectroscopy and mass spectra. The higher nucleophilicity of sulfur with respect to oxygen allowed a complete selectivity in the substitution in agreement with literature precedent.[23,24] Reduction of the ketone **13a** with $NaBH_4$ and cyclisation with Amberlyst acid ion exchanger in toluene gave the expected 2,3-dihydro-1,4-benzoxathiine **15a**.

Compound **15d** was obtained from 2-mercaptohydroquinone **8g** by a similar sequence of reactions. In this case using K_2CO_3 in dioxane, as a base it was not necessary to protect the phenolic groups of the thiol in the condensation with ketone **11**. The synthesis of compound **15b** was accomplished by the same procedure starting from benzene-1,2-dithiol **8d**. Sulfone **27** was obtained from compound **15a** by oxidation with 1 equivalent of *meta*-chloroperbenzoic acid in dichloromethane, in the presence of $NaHCO_3$.



Compounds **18** and **19** were synthesized by a recently developed procedure[25] based on the cycloaddition between benzothiete **16** and substituted styrene **17** (Scheme 3). The

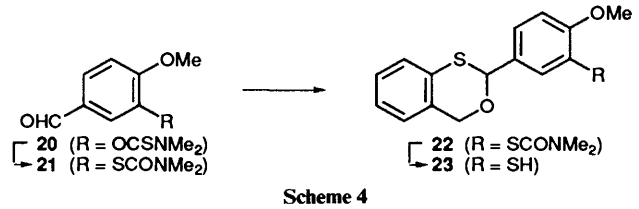


Scheme 3

former reagent can be obtained by flash vacuum pyrolysis[26] of 2-mercaptophenylmethanol **8a**. The cycloaddition produced a 4:3 mixture of the two compounds which were separated by careful chromatography.

Compounds **15c** and **15e** were prepared by the sequence depicted in Scheme 2. In this case the condensation was accomplished on 2-chloro-1-(3-hydroxy-4-methylthiophenyl)-ethanone **12**. This ketone was prepared from 2-methylthiophenol, by a sequence involving esterification by 2-choroacetyl chloride and pyridine in dichloromethane, Friedel–Craft acylation by 2-chloroacetyl chloride and $AlCl_3$ in dichloromethane and hydrolysis. The substitution on the aromatic ring was verified by NOE experiments.

Compound **23** was prepared as shown in Scheme 4 from 3-



Scheme 4

mercapto-4-methoxybenzaldehyde protected as dimethylcarbamate **21**: reaction of the potassium salt of isovanillin with dimethylthiocarbamoyl chloride in dioxane gave the dimethyl-

Table 1 Sweetness potency[a] of the compounds prepared

Compd.	Potency
10a	5000
10b	9000
10c	500
10d	200
10e	300
10f	Tasteless
15a	250
15b	500
15d	500
18	200
19	Tasteless
27	50

[a] Compared with a 3% (w/v) aqueous solution of sucrose.

Table 2 Sweetness potency[a] of the compounds prepared

Compd.	Potency
15c	Tasteless
15e	Tasteless
23	50

[a] Compared with a 3% (w/v) aqueous solution of sucrose.

thiocarbamate **20** which was rearranged to the carbamate of the thiophenol **21** by heating in diphenyl ether.[27] This protecting group was stable during the ketalisation and was hydrolysed only after the ring formation.

The compounds were tasted only once by an untrained panel, with the 'sip and spit' technique in comparison with a 3% solution of sucrose. As they are not soluble enough in distilled water, they had first to be dissolved in a small amount of ethanol, then diluted with water to the desired concentrations. In the case of **18** and **19**, the suspensions thus obtained were sonicated immediately before tasting to ensure as far as possible a homogeneous dispersion of the compounds: sweetness data for these compounds must be considered approximate. Compounds **10d** and **23** are scarcely stable, becoming red within 2 h after column chromatography, even if kept under nitrogen at −20 °C. They were tasted immediately after the purification. Compounds **15c** and **15e** are unstable at room temp., but remain unchanged for some months at −20 °C under nitrogen.

Relative taste potencies based on mass were determined from the ratios of the concentrations which gave the same sweet sensation of the 3% sucrose solution in the same solvent mixture. The results obtained are shown in Tables 1 and 2.

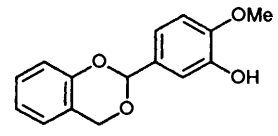
Discussion

Replacement of oxygen by sulfur maintained in many cases and even improved in others the sweetness potency when the heteroatom was in the heterocyclic ring (Table 1). However, the same change in the OH or OMe groups of the isovanillyl ring, deemed necessary for the interaction with the receptor, according to the Shallenberger–Acree model,[13] eliminated the sweetness (compounds **15c, 15e, 23**, Table 2). An explanation for this effect may be the decrease in hydrogen bonding donor or acceptor strength of the SH *vs.* OH and of the SMe *vs.* OMe group, respectively, which could be insufficient to induce the primary interaction with the receptor sites. This result confirms the previous observations[28] on the very few possibilities of modifications in the corresponding ring of dihydrochalcones.

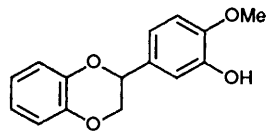
Changing the dimensions of the heterocyclic ring provoked the same trend of effect already observed[9] in the oxygen series, *i.e.* the five-membered ring compounds were less sweet than the six-membered analogues, and the 7-membered analogue was tasteless (Table 1). This could support the rationalisation proposed in the case of the oxygen series[9] for the dependence of the taste potency on the geometry of the compounds.

Considering the 6-membered compounds, in the mono-substituted derivatives **18** and **19** a decrease of potency (200, 0) was observed with respect to the corresponding oxygen derivatives (350, 200 respectively), although the low solubility of the sulfur analogues (see above) might have influenced the result.

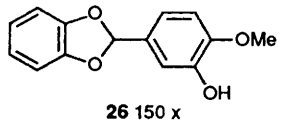
When the heteroatoms are in positions 1 and 4 (compounds **15a** and **b**) the potency is maintained at a degree similar to that in the corresponding 2,3-dihydro-1,4-benzodioxine **25**.[9] Unfortunately, difficulties in the synthesis have so far prevented the preparation of the 2,3-dihydro-4,1-benzoxathiine isomer. An attempt to increase the solubility of **15a** by introducing the hydrophilic OH group in position 6, [compound **15d**, partition coefficients (log *P*) 2.27 *cf.* 3.42 for **15a**], a region deemed not to interact with specific sites of the receptor, gave in fact a two-fold increase of potency. A similar modification in the more sensitive position 1, by preparation of the sulfone **27** (log *P* 1.87), reduced the sweetness almost to nil.



24 3000 x



25 450 x



26 150 x

The most interesting results were, however, achieved with the preparation of the 1,3-derivatives. The 4*H*-1,3-benzodioxine **24**[29] is the sweetest compound (3000) among the 6-membered compounds in the oxygen series. Introduction of sulfur in position 1 gave a sharp increase in sweetness: compound **10b** (9000) is indeed the sweetest so far prepared in the isovanillyl series. The reverse placement (1-O, 3-S) of the atoms in compound **10c** induces a decrease (500), whereas in compound **10a** with two sulfur atoms there is some increase (5000), although smaller than for **10b**. Considering the trend also observed in the 5-membered ring compounds (**10e**, 300; **10d**, 200; **26**, 150) it appears that the most effective structure in generating sweetness in this series is when a sulfur atom occupies position 1 and an oxygen atom position 3 of a chain, in which the isovanillyl ring is linked to C-2.

The difference in potency between the compounds with 6- or 5-atom rings might be a consequence of the spatial requirements of the receptor. In fact, assuming that the primary interaction with the active site of the receptor is due to the OH and OMe groups of the isovanillyl ring, the hydrophobic group, also necessary to develop the sweet response and represented here by the benzene ring, occupies different positions in the two series (Fig. 1).

It can be noticed that the 6-membered ring compounds fit quite well in the receptor map proposed by Temussi.[15] It is difficult to explain why the 1-S, 3-O arrangement is preferred. The change in geometry due to the different bond lengths and angles is probably too small to justify the sharp difference in potency between compounds **10b** and **10c**, which also have approximately the same lipophilicity. Therefore, it is possible that the localised interaction of the tastant with the receptor in the two sites corresponding to the positions 1 and 3 of our

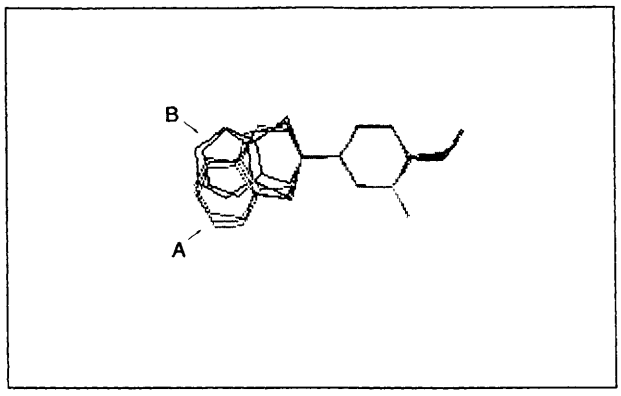


Fig. 1 Superimposition of the structures of compounds **10a–c** (A: 6-membered ring) and **10d** and **e** (B: 5-membered ring). Minimised structures were obtained by molecular mechanics calculations with the MMPMI(85) program.[9]

compounds depends on some particular feature of the two kind of atoms, *e.g.* electronegativity, or polarisability, or the size itself, which interacts specifically with a similar property of the corresponding site.[2] Work is in progress to obtain a quantitative structure–activity relationship in the whole series of oxygen and sulfur compounds.

The high sweetness potency of compound **10b** led us to investigate some of the features that might be connected with its possible use as a sweetener. First of all, the compound has a very low acute toxicity, its LD_{50} being $\geqslant$ 8000 mg kg^{-1} in the mouse by oral dose, and is not mutagenic (Ames test). Moreover, as expected, compound **10b** being a thioketal rather than a ketal, it is more stable than the corresponding 4*H*-1,3-benzodioxine **24** in aqueous solution. Monitoring the formation of isovanillin in a solution in D_2O and [$^2H_6$]DMSO by NMR spectroscopy showed that after 3 h at room temperature 20% of **24** was decomposed (*cf.* lit.[29]), whereas after 23 h no isovanillin was formed from **10b**. In acidic aqueous–alcoholic solution, **10b** appears unaltered (as shown by TLC) after 24 h at room temperature at pH 1, after 1 h at reflux at pH 4, and only traces of aldehyde appear after 1 h at pH 2 at reflux.

Experimental

Melting points are uncorrected. NMR spectra were recorded on a Bruker WP80 at 80 MHz in $CDCl_3$ using tetramethylsilane as internal standard and are expressed in ppm (δ). *J* Values are given in Hz. Mass spectra were recorded on a Finnigan TSQ70 equipped with an ICIS data system.

Flash column chromatography was performed on silica gel 60 (Merck, 0.040–0.063 mm). Toluene, dichloromethane and acetonitrile were dried by refluxing and distillation from phosphorus pentoxide. Tetrahydrofuran (THF) and ether were distilled from sodium–benzophenone immediately before use.

Benzene-1,2-dithiol **8d**, durenedithiol **8f** and 2-methylthiophenol were purchased from Fluka. 2-Mercaptophenylmethanethiol[30] **8a** and 2-mercaptophenylmethanol[31] **8b** were obtained by reduction with lithium aluminium hydride of 1,2-benzodithiole-3-thione and 2-mercaptobenzoic acid respectively. 2-Mercaptohydroquinone **8g**[32] was obtained in two steps[33] from *p*-benzoquinone. 4-Methoxy-3-(2,2-dimethylpropionyloxy)benzaldehyde **6b** was obtained by treating isovanillin with 2,2-dimethylpropionyl chloride and pyridine at 0 °C in chloroform (55%, yield, m.p. 60 °C).

2-Mercaptomethylphenol **8c**.—2-Methylphenyl acetate (7 g, 46.7 mmol), *N*-bromosuccinimide (9.13 g, 51 mmol) and benzoyl peroxide (0.35 g) in tetrachloromethane (110 cm^3) were warmed at reflux for 10 h with stirring in a flask equipped with a $CaCl_2$ valve. The mixture was filtered and the solid was washed with dichloromethane. The combined solvents were concentrated under reduced pressure and the oily residue was purified by column chromatography (hexane–ethyl acetate 97:3). 2-Bromomethylphenyl acetate was obtained as a reddish oil (9.14 g, 86%) and used without further purification, $\delta_H(CDCl_3)$ 2.38 (3 H, s, $OCOCH_3$), 4.43 (2 H, s, CH_2Br) and 7.0–7.5 (4 H, arom). This compound (4.14 g, 18 mmol) in acetonitrile (52 cm^3) was treated with sodium hydrogen sulfide (NaHS) (2.48 g, 44 mmol) and tetrabutylammonium bromide (0.4 g) under nitrogen with vigorous stirring for 4 h at room temp. The solvent was concentrated under reduced pressure and the residue was treated with dichloromethane (30 cm^3) and an aqueous solution of HCl 0.3 mol dm^{-3}; 30 cm^3. The layers were separated and the aqueous phase extracted with dichloromethane (2 × 20 cm^3). After drying, the solvent was concentrated under reduced pressure to give a crude oil (3.36 g) showing by TLC the expected 2-mercaptomethylphenyl acetate and hydrolysed 2-mercaptomethylphenol **8c**. Without further purification the oil was dissolved in ethanol (30 cm^3) under nitrogen and treated with 5% NaOH (10.5 cm^3) at room temp. for 4 h. The solvent was concentrated under reduced pressure and the residue was taken up in dichloromethane and acidified with an aqueous solution of HCl (0.3 mol dm^{-3}) to pH 5. The layers were separated and the aqueous phase was extracted with dichloromethane (2 × 20 cm^3). The dried organic solution was concentrated under reduced pressure to give 2-mercaptomethylphenol **8c** as a white solid which was crystallised from toluene (2.40 g, 95%), m.p. 96–98 °C (Found: C, 60.25; H, 5.6; S, 22.7. C_7H_8OS requires C, 60.00; H, 5.71, S. 22.86%); $\delta_H(CDCl_3)$ 1.65 (1 H, br, SH), 3.70 (2 H, s, CH_2), 5.5 (1 H, br, OH) and 6.75–7.25 (4 H, arom).

2-(3-Hydroxy-4-methoxyphenyl)-4H-1,3-benzodithiine **10a**.—In a flask equipped with a Soxhlet containing 3 Å molecular sieves, 3-chloroacetoxy-4-methoxybenzaldehyde **6a** (1.52 g, 6.7 mmol), trimethyl orthoformate (1.64 g, 15 mmol, 1.7 cm^3), toluene-*p*-sulfonic acid (0.25 g, 1.3 mmol) and toluene (45 cm^3) were heated at reflux, and the formation of the dimethyl acetal **7a** was monitored by TLC. 2-Mercaptophenylmethanethiol[30] **8a** (1.04 g, 6.7 mmol) in toluene (5 cm^3) was added and the mixture was refluxed for 3 h. After cooling, a 2% aqueous solution of pyridine was added until the solution became neutral. The aqueous solution was extracted with ethyl acetate (3 × 20 cm^3). The organic solvents were dried and concentrated under reduced pressure. The residue was purified by column chromatography (hexane–ethyl acetate 9:1). 2-(3-Chloroacetoxy-4-methoxyphenyl)-4*H*-1,3-benzodithiine **9a** was obtained as a white solid (0.76 g, 31%), m.p. 98–100 °C. This compound (0.76 g, 2.1 mmol) was dissolved in a mixture of methanol (23 cm^3), acetone (7.6 cm^3) and a saturated aqueous solution of sodium hydrogen carbonate. The mixture was stirred for 3 h at room temp., then acidified with HCl (0.2 mol dm^{-3}) to pH 5, and the solvents were concentrated in part. The aqueous solution was extracted with ethyl acetate (3 × 20 cm^3). The solvents were evaporated under reduced pressure and the solid residue crystallized from cyclohexane. The title compound **10a** was obtained as a white solid (0.5 g, 86%), m.p. 104 °C (Found: C, 62.1; H, 4.9. $C_{15}H_{14}O_2S_2$ requires C, 62.06; H, 4.86%); $\delta_H(CDCl_3)$ 3.88 (3 H, s, OCH_3), 3.98 (2 H, s, CH_2), 5.43 (OH), 5.59 (1 H, s, 2-H) and 6.7–7.4 (7 H, arom); ν_{max}/cm^{-1} 3450, 1275, 1120 and 1025.

2-(3-Hydroxy-4-methoxyphenyl)-4H-1,3-benzodithiole **10d**.—Following a procedure similar to that described above, 3-chloroacetoxy-4-methoxybenzaldehyde **6a** (0.74 g, 3.2 mmol), trimethyl orthoformate (0.6 cm^3) and toluene-*p*-sulfonic acid (0.1 g, 0.5 mmol) in toluene (18 cm^3) afforded dimethyl acetal

7a which without isolation, was treated with benzene-1,2-dithiol **8d** (0.53 g, 3.2 mmol). 2-(3-Chloroacetoxy-4-methoxyphenyl)-1,3-benzodithiole **9d** was obtained as a white solid (0.68 g, 46%), m.p. 45 °C; $\delta_H(CDCl_3)$ 3.80 (3 H, s, OCH_3), 4.28 (2 H, s, CH_2Cl), 6.15 (1 H, s, 2-H) and 6.8–7.5 (7 H, arom). This compound decomposes easily and was kept in a freezer under nitrogen. After hydrolysis of the protecting group as described above, the title compound **10d** was obtained as a reddish oil (0.25 g, 47%); $\delta_H(CDCl_3)$ 3.85 (3 H, s, OCH_3), 5.58 (1 H, s, OH), 6.10 (1 H, s, H-2) and 6.7–7.3 (7 H, arom). The compound obtained was pure by TLC. But it decomposed easily even under nitrogen. It was impossible to obtain satisfactory elemental analysis and it was tasted immediately after purification.

2-(3-*Hydroxy*-4-*methoxyphenyl*)-4H-3,1-*benzoxathiine* **10b**.—A solution of 2,2-dimethylpropionyloxy-4-methoxybenzaldehyde **6b** (4 g, 17 mmol), trimethyl orthoformate (2.4 cm^3, 22.3 mmol), and toluene-*p*-sulfonic acid (0.11 g, 0.55 mmol) was refluxed for 10 h in toluene (160 cm^3) in a flask equipped with a Soxhlet containing 3 Å molecular sieves. The mixture was cooled and washed with 2% aqueous pyridine. The aqueous solution was extracted with ethyl acetate (3 × 10 cm^3). The combined organic layers were dried and concentrated under reduced pressure. The oily residue was purified by column chromatography (hexane–ethyl acetate 85:15) to obtain the dimethyl acetal **7b** (4.4 g, 92%) as a colourless oil; $\delta_H(CDCl_3)$ 1.38 (9 H, s, CH_3), 3.25 (6 H, s, OCH_3), 3.90 (3 H, s, $ArOCH_3$), 5.33 (1 H, s, CH), 6.69 (1 H, d, J = 8, 5-H), 7.10 (1 H, d, J = 2, 2-H) and 7.23 (1 H, dd, J = 8 and 2, 6-H). This acetal (4.1 g, 16 mmol) was refluxed for 4 h with 2-mercaptophenylmethanol [31] **8b** (2.2 g, 1.1 mmol) and toluene-*p*-sulfonic acid (0.22 g, 1.1 mmol) in toluene (180 cm^3) in an apparatus similar to that described above. After cooling the mixture was washed with 2% aqueous pyridine (50 cm^3). The organic solvent was dried and concentrated under reduced pressure. The residue was purified by column chromatography (hexane–ethyl acetate 8:2) and crystallised from cyclohexane. 2-[3-(2,2-Dimethylpropionyloxy)-4-methoxyphenyl]-4*H*-3,1-benzoxathiine **9b** was obtained as a white solid (3.72 g, 68%), m.p. 134 °C; $\delta_H(CDCl_3)$ 1.35 (9 H, s, CH_3), 3.80 (3 H, s, OCH_3), 5.06 (2 H, s, 4-H), 6.04 (1 H, s, 2-H) and 6.9–7.3 (7 H, arom). This compound (3.72 g, 10.4 mmol) in anhydrous THF (10 cm^3) was added slowly under nitrogen to a slurry of lithium aluminium hydride (LAH) (0.7 g, 38 mmol) in THF (140 cm^3). After stirring for 4 h at room temp., ethyl acetate and 10% H_2SO_4 were added. The salts were filtered and the solvents concentrated under reduced pressure. The residue was dissolved in water (50 cm^3) and extracted with dichloromethane (3 × 50 cm^3). The organic layer was washed with brine, dried and concentrated under reduced pressure. The solid residue was crystallised from cyclohexane. The title compound **10b** was obtained as a white solid (2.72 g, 95%), m.p. 104 °C (Found: C, 65.9; H, 5.0. $C_{15}H_{14}O_3S$ requires C, 65.69; H, 5.15%); $\delta_H([^2H_6]DMSO–D_2O)$ 3.83 (3 H, s, OCH_3), 5.08 (2 H, s, CH_2), 5.60 (OH), 6.14 (1 H, s, CH), 7.03 (3 H, s, arom) and 7.18 (4 H, s, arom); ν_{max}/cm^{-1} 3380, 1210, 1125 and 1015.

2-(3-*Hydroxy*-4-*methoxyphenyl*)-4H-1,3-*benzoxathiine* **10c**.—Following a procedure similar to that described above, the dimethyl acetal **7b** (1 g, 3.6 mmol) and 2-mercaptomethylphenol **8c** (0.52 g, 3.6 mmol) afforded 2-[3-(2,2-dimethylpropionyloxy)-4-methoxyphenyl]-4*H*-1,3-benzoxathiine **9c** (0.3 g, 23%), m.p. 122 °C (cyclohexane); $\delta_H(CDCl_3)$ 1.53 (9 H, s, CH_3), 3.83 (3 H, s, OCH_3), 3.70 and 4.30 (2 H, AB, J 16, 4-H_2), 5.65 (OH), 6.10 (1 H, s, 2-H) and 6.85–7.45 (7 H, arom). Reduction with LAH (0.1 g, 2.6 mmol) of this compound (0.28 g, 0.78 mmol) in THF (13 cm^3) afforded 2-(3-hydroxy-4-methoxyphenyl)-4*H*-1,3-benzoxathiine **10c** as a white solid (0.18 g, 82%), m.p. 142 °C (cyclohexane) (Found: C, 69.9; H, 5.5. $C_{15}H_{14}O_2S$ requires C, 69.74; H, 5.46%; $\delta_H(CDCl_3)$ 3.63 and 4.23 (2 H, AB, J 16, 4-H_2), 3.83 (3 H, s, OCH_3), 5.55 (1 H, br, OH), 6.00 (1 H, s, 2-H) and 6.8–7.25 (7 H, arom).

2-(3-*Hydroxy*-4-*methoxyphenyl*)-1,3-*benzoxathiole* **10e**.—Following the above procedure, the dimethyl acetal **7b** (1.6 g, 5.7 mmol), 2-mercaptophenol [22] **8e** (0.72 g, 5.7 mmol) and toluene-*p*-sulfonic acid (90 mg, 0.47 mmol) afforded compound **9e** (0.6 g, 30%), m.p. 75 °C (isopropyl alcohol) (Found: C, 66.3; H, 5.8. $C_{19}H_{20}O_4S$ requires C, 66.27; H, 5.85%); $\delta_H(CDCl_3)$ 1.35 (9 H, s, CMe_3), 3.8 (3 H, s, OMe) and 6.8–7.5 (8 H, arom. and CH); m/z (%) 344 (100), 259 (39) and 137 (20).

This compound was hydrolysed to give compound **10e** as an oil (62%) (Found: C, 64.35; H, 4.5. $C_{14}H_{12}O_3S$ requires C, 64.61; H, 4.61%); $\delta_H(CDCl_3)$ 3.9 (3 H, s, OMe), 4.3 (1 H, br, OH) and 6.7–7.3 (8 H, m, arom. and CH); m/z (%) 260 (100) and 137 (31).

7,8-*Dimethyl*-3-(3-*hydroxy*-4-*methoxyphenyl*)-1,5-*dihydro*-2,4-*benzodithiepine* **10f**.—Following the procedure described above, the dimethyl acetal **7b** (1 g, mmol), durenedithiol **8f** (0.48 g, 2 mmol) and toluene-*p*-sulfonic acid (40 mg, 0.2 mmol) afforded 7,8-dimethyl-3-[3-(2,2-dimethylpropionyloxy)-4-methoxyphenyl]-1,5-dihydro-2,4-benzodithiepine **9f** (0.26 g, 25%); m.p. 180 °C (cyclohexane); $\delta_H(CDCl_3)$ 1.33 (9 H, s, CH_3), 2.23 (6 H, s, $ArCH_3$), 3.75 (3 H, s, OCH_3) 3.98 (4 H, AB, J 14, CH_2S), 5.16 (1 H, s, CH), 6.83 (1 H, d, J 8, 5′-H), 6.95 (2 H, s, 6-H), 7.03 (1 H, d, J 2, 2′-H) and 7.18 (1 H, dd, J 8 and 2, 6′-H). Reduction with LAH (0.1 g, 3 mmol) gave the title compound **10f** (0.13, 65%), m.p. 213 °C (cyclohexane) (Found: C, 64.65; H, 6.0. $C_{18}H_{20}O_2S_2$ requires C, 65.05; H, 6.07%); $\delta_H(CDCl_3)$ 2.23 (6 H, s, $ArCH_3$), 3.84 (3 H, s, OCH_3), 3.98 (4 H, AB, J 14, CH_2), 5.15 (1 H, s, CH), 5.51 (OH) and 6.6–7.0 (5 H, arom).

2-(3-*Hydroxy*-4-*methoxyphenyl*)-2,3-*dihydro*-1,4-*benzoxathiine* **15a**.—Sodium hydride (80% in paraffin oil; 0.045 g, 1.5 mmol) was suspended in anhydrous toluene (10 cm^3). 2-Mercaptophenol [22] **8e** (0.188 g, 1.5 mmol) was added and the mixture was heated at reflux with stirring. After 15 min a solution of 3-hydroxy-4-methoxy-α-chloroacetophenone **11** (0.3 g, 1.5 mmol) in toluene (3 cm^3) was added dropwise. The mixture was refluxed for 7 h, then acidified with HCl (6 mol dm^{-3}). After extraction with ethyl acetate (3 × 10 cm^3) and washing with saturated aqueous sodium hydrogen carbonate, the solvent was dried and concentrated under reduced pressure. Chromatography (hexane–ethyl acetate 1:1) and crystallisation (methanol) gave 1-(3-hydroxy-4-methoxyphenyl)-2-(2-hydroxyphenylithio)ethanone **13a** as a pale yellow solid (0.2 g, 46%), m.p. 128 °C; $\delta_H(CDCl_3)$ 3.95 (3 H, s, OCH_3), 4.2 (2 H, s, CH_2), 4.6 (1 H, OH) and 6.8–7.95 (7 H, m); m/z (%) 290 (44), 152 (9), 151 (100), 137 (6), 123 (9), 108 (6) and 65 (6). This ketone (0.04 g, 0.138 mmol) was dissolved in anhydrous ethanol (1 cm^3) and sodium borohydride (5 mg, 0.138 mmol) was added, with stirring for 10 min. The solvent was concentrated, the solid residues dissolved in water, neutralised with dilute HCl and extracted with ethyl acetate (2 × 2 cm^3). After drying, concentration and crystallisation from chloroform 1-(3-hydroxy-4-methoxyphenyl)-2-(2-hydroxyphenylthio)ethanol **14a** was obtained as a solid (0.04 g, 100%); $\delta_H([^2H_6]acetone)$ 2.8 (3 H, br, OH), 3.0–3.2 (2 H, AB of ABX, CH_2), 3.9 (3 H, s, OCH_3), 4.5–5.0 (1 H, X of ABX, CH) and 6.8–7.6 (7 H, arom); m/z (%) 292 (6), 274 (26), 214 (100), 164 (8), 153 (30), 140 (44), 125 (17), 121 (16), 109 (40), 108 (25), 107 (58) and 105 (27). This compound (40 mg, 0.138 mmol) and Amberlyst 15 (20 mg) were heated at reflux for 2 h in toluene. The mixture was filtered and the solvent was evaporated. The residue was purified by column chromatography (hexane–ethyl acetate 6:4). After crystallisation (cyclohexane) the title compound **15a** was obtained as a

white solid (40 mg, 100%), m.p. 92–93 °C (Found: C, 65.65; H, 5.2. $C_{15}H_{14}O_3S$ requires C, 65.69; H, 5.15%); $\delta_H(CDCl_3)$ 2.9–3.4 (2 H, AB of ABX, CH_2), 3.90 (3 H, s, OCH_3), 5.1 (1 H, X of ABX, 2-H), 5.65 (1 H, s, OH) and 6.8–7.2 (7 H, arom); *m/z* (%) 274 (100), 241 (15), 213 (11), 150 (35), 135 (17), 107 (45), 105 (26) and 104 (45).

2-(3-*Hydroxy*-4-*methoxyphenyl*)-2,3-*dihydro*-1,4-*benzoxathiin*-6-*ol* **15d**.—Following a similar procedure, 2-mercaptohydroquinone[32] **8g** (0.3 g, 2.11 mmol), and 3-hydroxy-4-methoxy-α-chloroacetophenone **11** (0.423 g, 2.11 mmol) were heated under nitrogen in dioxane (20 cm^3) in the presence of potassium carbonate (0.39 g, 2.11 mmol), affording 1-(3-hydroxy-4-methoxyphenyl)-2-(2,5-dihydroxyphenylthio)ethanone **13d** as a yellowish oil, which crystallised slowly (0.7 g, 91%), m.p. 118 °C; ν_{max}/cm^{-1} 3400, 2800–3000 and 1650; $\delta_H([^2H_6]acetone)$ 2.9 (3 H, OH), 3.95 (3 H, s, OCH_3), 4.35 (H, s, CH_2) and 6.7–8.05 (6 H, arom); *m/z* (%): 306 (5), 166 (7) and 151 (100). This compound (0.59 g, 1.93 mmol) in ethanol was reduced with sodium borohydride (73 mg, 1.93 mmol) and cyclised without isolation of the intermediate triol **14d** by addition of conc. HCl and heating at reflux for 15 min to give 2-(3-hydroxy-4-methoxyphenyl)-2,3-dihydro-1,4-benzoxathiin-6-ol **15d** as a white solid (0.21 g, 38%), m.p. 136 °C (cyclohexane–ethyl acetate) (Found: C, 62.1; H, 4.8. $C_{15}H_{14}O_4S$ requires C, 62.07; H, 4.83%); $\delta_H(CDCl_3)$ 2.8 (2 H, br, OH), 3.0–3.4 (2 H, AB of ABX, CH_2), 3.8 (3 H, s, OCH_3), 5.0 (1 H, X of ABX, 2-H) and 6.5–7.0 (6 H, arom); *m/z* (%) 290 (47), 150 (100), 135 (50), 112 (13) and 107 (19).

2-(3-*Hydroxy*-4-*methoxyphenyl*)-2,3-*dihydro*-1,4-*benzodithiine* **15b**.—Following the above procedure, benzene-1,2-dithiol **8d** (1 g, 7 mmol), potassium carbonate (0.972 g, 7 mmol) and 3-hydroxy-4-methoxy-α-chloroacetophenone **11** (0.41 g, 7 mmol) in dioxane (30 cm^3) gave 1-(3-hydroxy-4-methoxyphenyl)-2-(2-mercaptophenylthio)ethanone **13b** (0.24 g, 11%) as a yellow oil; $\delta_H(CDCl_3)$ 3.9 and 3.85 (3 H, two s, OCH_3, open and ring-closed tautomers), 3.1 and 3.5 (2 H, AB, CH_2, ring-closed), 4.2 (2 H, s, CH_2, open form) and 6.7–7.6 (7 H, arom); *m/z* (%): 306 (8), 166 (19), 153 (12), 151 (100), 123 (97) and 108 (8). This compound (0.24 g, 0.78 mmol) was reduced with sodium borohydride (30 mg, 0.78 mmol) to give 1-(3-hydroxy-4-methoxyphenyl)-2-(2-mercaptophenylthio)ethanol **14b** (0.16 g, 66.4%) as a yellowish oil, which was cyclised directly using Amberlyst 15 (80 mg) in toluene to give 2-(3-hydroxy-4-methoxyphenyl)-2,3-dihydro-1,4-benzodithiine **15b** as a white solid (100 mg, 66.6%), m.p. 95 °C (cyclohexane) (Found: C, 61.8; H, 4.8. $C_{15}H_{14}O_2S_2$ requires: C, 62.07; H, 4.83%); $\delta_H(CDCl_3)$ 3.25–3.5 (2 H, AB of ABX, CH_2), 3.85 (3 H, s, OCH_3), 4.5 (1 H, X of ABX, CH), 5.6 (1 H, s, OH) and 6.8–7.25 (7 H, arom); *m/z* (%) 290 (34), 153 (100), 135 (50) and 107 (14).

2-(3-*Hydroxy*-4-*methoxyphenyl*)-2,3-*dihydro*-1,4-*benzoxathiine S,S-Dioxide* **27**.—2-(3-Hydroxy-4-methoxyphenyl)-2,3-dihydro-1,4-benzoxathiine **15a** (0.1 g, 0.36 mmol) was dissolved in anhydrous CH_2Cl_2 (30 cm^3). Sodium hydrogen carbonate (0.165 g, 0.2 mmol) was added and a solution of 3-chloroperbenzoic acid (85%, 75 mg, 0.36 mmol) in CH_2Cl_2 (10 cm^3) was added dropwise. The mixture was stirred at room temp. for 5 h, then poured into saturated aqueous sodium hydrogen carbonate, extracted with CH_2Cl_2 (2 × 4 cm^3), dried and concentrated. The crude residue was purified by column chromatography (hexane–ethyl acetate 4:5) to produce a colourless oil which was recrystallised from ethyl acetate–cyclohexane (40 mg, 36%), m.p. 135 °C (Found: C, 58.6; H, 4.6. $C_{15}H_{14}O_5S$ requires: C, 58.82; H, 4.58%); $\delta_H(CDCl_3)$ 3.9 (3 H, s, OCH_3), 3.4–4.2 (2 H, AB of ABX, CH_2), 5.6–5.9 (1 H, X of ABX, CH), 5.8 (1 H, OH) and 6.9–8.0 (7 H, arom); *m/z* (%) 306 (38), 150 (100), 135 (48) and 111 (86).

2-(3-*Hydroxy*-4-*methoxyphenyl*)-3,4-*dihydro*-2H-1-*benzothiopyran* **18** and 3-(3-*Hydroxy*-4-*methoxyphenyl*)-3,4-*dihydro*-2H-1-*benzothiopyran* **19**.—A solution of benzothiete[26] **16** (0.6 g, 5 mmol) and 3-hydroxy-4-methoxystyrene **17** (1.1 g, 7.4 mmol) in anhydrous toluene (10 cm^3) was refluxed for 8 h in a flask equipped with a Dean–Stark apparatus. The solvent was then evaporated under reduced pressure and the crude residue was chromatographed on a column of silica gel (hexane–ethyl acetate 98:2). Separation of the resultant mixture of the two isomers **18** and **19** (4:3 by NMR spectroscopy, 35% total yield), was achieved by further column chromatography (toluene–hexane 7:3) and eventually by preparative TLC with the same eluent.

Compound **18** m.p. 83–85 °C (Found: C, 70.4; H, 6.0. $C_{16}H_{16}O_2S$ requires C, 70.57; H, 5.92%); $\delta_H(CDCl_3)$ 2.15 (1 H, m, 3-H), 2.32 (1 H, m, 3-H), 2.91 (2 H, m, 4-H), 3.82 (3 H, s, OCH_3), 4.33 (1 H, dd, *J* 8 and 2.5, 2-H), 5.73 (OH) and 6.7–7.2 (7 H, arom).

Compound **19** m.p. 77–78 °C (Found: 70.2; H, 5.95. $C_{16}H_{16}O_2S$ requires C, 70.57; H, 5.92%); $\delta_H(CDCl_3)$ 2.8–3.2 (5 H, m, 2-H, 3-H, 4-H), 3.88 (3 H, s, OCH_3), 6.85 (OH) and 6.8–7.2 (7 H, arom).

2-*Chloro*-1-(3-*hydroxy*-4-*methylthiophenyl*)*ethanone* **12**.—A solution of 2-methylthiophenol (1 g, 7.1 mmol) and pyridine (0.72 cm^3, 14.3 mmol) in dichloromethane (8 cm^3) was treated dropwise with chloroacetyl chloride (0.57 cm^3, 7.1 mmol) at 0 °C. The mixture was stirred for 3 h at room temperature, 10% HCl was added and the two layers separated. The aqueous phase was extracted with dichloromethane (2 × 20 cm^3). The mixed organic phase was washed with a 10% solution of HCl (20 cm^3), 4% NaOH (20 cm^3) and water. After drying and evaporation the 2-methylthiophenyl chloroacetate was obtained as a crystalline solid (1.44 g, 93%), m.p. 91 °C (diethyl ether) (Found: C, 49.9; H, 4.6. $C_9H_9ClO_2S$ requires C, 49.89; H, 4.16%); ν_{max}/cm^{-1} 1770; $\delta_H(CDCl_3)$ 2.45 (3 H, s, SCH_3), 4.35 (2 H, s, CH_2) and 7.0–7.4 (4 H, arom); *m/z* (%) 218 (4), 216 (3) and 140 (100).

Aluminium trichloride (1.23 g, 9.2 mmol) was added to a solution of chloroacetyl chloride (0.52 g, 4.6 mmol) in dichloromethane (20 cm^3). The mixture was cooled at 0 °C and treated dropwise with a solution of 2-methylthiophenyl chloroacetate (1 g, 4.6 mmol) in dichloromethane (10 cm^3). The mixture was stirred at reflux for 4 h and then poured in saturated aqueous sodium hydrogen carbonate. After separation, the aqueous layer was extracted with dichloromethane (2 × 20 cm^3). The combined organic phase was washed with water, dried and concentrated to give 2-chloro-1-[3-(2-chloroacetoxy)-4-methylthiophenyl]ethanone as a white solid (1.16 g, 86%), m.p. 94 °C (cyclohexane–ethyl acetate 3:1); ν_{max}/cm^{-1} 1699 (ketone) and 1765 (ester); $\delta_H(CDCl_3)$ 2.5 (3 H, s, SCH_3), 4.32 (2 H, s, CH_2), 4.6 (2 H, s, CH_2), 7.3 (1 H, d, *J* 10, 5-H), 7.68 (1 H, d, *J* 2, 2-H) and 7.78 (1 H, dd, *J* 10 and 2, 6-H); *m/z* (%) 294 (21), 292 (30), 216 (41) and 167 (100). This compound (0.1 g, 0.34 mmol) was dissolved in methanol (3 cm^3) under nitrogen. Sodium hydroxide (1 mol dm^{-3}, 2 cm^3) was added and the mixture was stirred for 5 h at room temp., then acidified with HCl and concentrated to a low volume. The mixture was extracted with dichloromethane (3 × 5 cm^3), dried and concentrated to give a residue which was purified by column chromatography (hexane–ethyl acetate, 1:3) giving 2-chloro-1-(3-hydroxy-4-methylthiophenyl)ethanone **12** as a white solid (70 mg, 94%), m.p. 140 °C (cyclohexane–ethyl acetate) (Found: C, 49.95; H, 4.2. $C_9H_9ClO_2S$ requires: C, 49.88; H, 4.19%); ν_{max}/cm^{-1} 1690 (ketone); $\delta_H(CDCl_3)$ 2.4 (3 H,

s, SCH_3), 4.6 (2 H, s, CH_2), 6.4 (1 H, br, OH) and 7.45 (3 H, s, arom); *m/z* 216 (25) and 167 (100).

2-(3-*Hydroxy*-4-*methylthiophenyl*)-2,3-*dihydro*-1,4-*benzoxathiine* **15c**.—A solution of 2-mercaptophenol **8e** (0.233 g, 1.85 mmol) in toluene (1 cm^3) was added dropwise to a slurry of sodium hydride (50 mg, 1.85 mmol, 80% in paraffin oil) in toluene (10 cm^3) under nitrogen. The mixture was heated at reflux for 15 min, then cooled and treated dropwise with 2-chloro-1-(3-hydroxy-4-methylthiophenyl)ethanone **12** (0.4 g, 1.85 mmol) in toluene (2 cm^3). The mixture was heated at reflux for 17 h, cooled, poured in 5% HCl and extracted with ethyl acetate (3 × 5 cm^3). The organic layer was washed with a saturated solution of sodium hydrogen carbonate, brine, dried and concentrated under reduced pressure. Purification by column chromatography (hexane–ethyl acetate 6:4) gave 1-(3-hydroxy-4-methylthiophenyl)-2-(2-hydroxyphenylthio)ethanone **13c** (0.5 g, 90%), m.p. 136 °C; $\delta_H(CDCl_3)$ 2.4 (3 H, s, SCH_3), 4.15 (2 H, s, CH_2), 6.3 (1 H, s, OH) and 6.7–7.7 (7 H, m, arom); *m/z* (%) 306 (13) and 167 (100). This compound (0.78 g, 2.55 mmol) was dissolved in ethanol (5 cm^3) and treated with sodium borohydride (94 mg, 2.55 mmol). The mixture was stirred for 30 min, concentrated, taken up with dilute HCl and extracted with ethyl acetate (3 × 5 cm^3). After drying and concentration 1-(3-hydroxy-4-methylthiophenyl)-2-(2-hydroxyphenylthio)ethanol **14c** was obtained as an oil (0.72 g, 92%), $\delta_H(CDCl_3)$ 2.3 (3 H, s, SCH_3), 2.6–3.3 (2 H, AB of ABX, CH_2), 4.5–4.8 (1 H, X of ABX, CH) and 6.5–7.5 (10 H, m, arom. and 3 OH); *m/z* (%) 308 (4), 169 (48) and 140 (100).

Without further purification this compound (0.34 g, 1.1 mmol) was heated at reflux for 2 h in anhydrous toluene (5 cm^3) in the presence of Amberlyst 15 (0.2 g). The mixture was then filtered, evaporated and purified by column chromatography (hexane–ethyl acetate 7:3) to give 2-(3-hydroxy-4-methylthiophenyl)-2,3-dihydro-1,4-benzoxathiine **15c** as a viscous oil (128 mg, 40%) (Found: C, 61.7; H, 5.1. $C_{15}H_{14}O_2S_2$ requires C, 62.06; H, 4.88%); $\delta_H(CDCl_3)$ 2.3 (3 H, s, SCH_3), 2.9–3.4 (2 H, AB of ABX, CH_2), 4.0–4.3 (1 H, X of ABX, CH), 6.6 1 H, br, OH) and 6.8–7.6 (7 H, m, arom.); *m/z* (%) 290 (100) and 166 (8).

2-(3-*Hydroxy*-4-*methylthiophenyl*)-2,3-*dihydro*-1,4-*benzoxathiin*-6-*ol* **15e**. —Following a similar procedure, 2-mercaptohydroquinone **8g**, 2-chloro-1-(3-hydroxy-4-methylthiophenyl)-ethanone **12** (0.4 g, 1.85 mmol) and potassium carbonate (2.57 g, 1.85 mmol) in dioxane (20 cm^3) afforded 1-(3-hydroxy-4-methylthiophenyl)-2-(2,5-dihydroxyphenylthio)ethanone **13e** as a yellowish solid (0.52 g, 87%); ν_{max}(Nujol)/cm^{-1} 1640; $\delta_H[^2H_6]$(DMSO) 2.4 (3 H, s, SCH_3), 4.3 (2 H, s, CH_2) and 6.4–7.6 (9 H, m, arom. and 3 OH); *m/z* (%) 322 (20) and 167 (100). Reduction of this compound with sodium borohydride in ethanol (15 cm^3) under nitrogen gave the alcohol **14e** which was cyclised by addition of a few drops of concentrated HCl and heating for 25 min. The residue obtained after workup was purified by column chromatography (hexane–ethyl acetate) to give 2-(3-hydroxy-4-methylthiophenyl-2,3-dihydro-1,4-benzoxathiin-6-ol **15e** as an oil (0.148 g, 30%) (Found: C, 58.85; H, 4.4. $C_{15}H_{14}O_3S_2$ requires C, 58.82; H, 4.57%); $\delta_H(CDCl_3)$ 2.3 (3 H, s, SCH_3), 2.8–3.4 (2 H, AB of ABX, CH_2), 4.9–5.1 (1 H, X of ABX, CH) and 6.3–7.5 (8 H, m, arom. and 2 OH); *m/z* (%) 306 (51) and 166 (100).

2-(3-*Mercapto*-4-*methoxyphenyl*)-4H-3,1-*benzoxathiine* **23**.—The potassium salt of 3-hydroxy-4-methoxybenzaldehyde (3.71 g, 19.5 mmol) was dissolved in dioxane (50 cm^3) and treated with dimethylcarbamoyl chloride (2.41 g, 19.5 mmol) in dioxane (10 cm^3). The mixture was heated for 4 h at 80 °C, filtered and concentrated to give unstable 3-(*N*,*N*-dimethylthiocarbamoyloxy)-4-methoxybenzaldehyde **20** which was used in the following reaction without purification (4.88 g); ν_{max}/cm^{-1} 1680, 1600 and 1275; $\delta_H(CDCl_3)$ 3.38 (3 H, s, NCH_3), 3.46 (3 H, s, NCH_3), 3.93 (3 H, s, OCH_3), 7.13 (1 H, d, *J* 9, 5-H), 7.51 (1 H, d, *J* 2, 2-H), 7.85 (1 H, dd, *J* 9 and 2, 6-H) and 9.88 (1 H, s, CHO). This compound (1 g, 4.2 mmol) was heated in diphenyl ether (20 cm^3) at 258 °C for 2 h under nitrogen. The mixture was cooled in an ice-bath and diethyl ether (120 cm^3) was added. 3-(*N*,*N*-Dimethylcarbamoylthio)-4-methoxybenzaldehyde **21** separated as a brownish solid which was filtered and dried (0.36 g, 55%); ν_{max}/cm^{-1} 1690, 1670 and 1260; $\delta_H(CDCl_3)$, 3.5 (6 H, s, NCH_3), 3.95 (3 H, s, OCH_3) and 7.0–7.15 and 7.9–8.0 (4 H, arom. and CHO); *m/z* (%) 239 (100), 167 (3), 125 (3) and 111(9). This aldehyde was heated for 8 h under nitrogen in methanol in the presence of trimethyl orthoformate (0.12 g, 1.1 mmol) and NH_4Cl (0.11 g, 0.2 mmol). After concentration of the solvent the crude dimethyl acetal (0.12 g) was refluxed for 1 h with 2-mercaptophenylmethanol **8b** (84 mg, 0.6 mmol) and toluene-*p*-sulfonic acid (8 mg, 0.04 mmol) in anhydrous toluene (6 cm^3). After work-up as described for compound **9b**, 2-[3-*N*,*N*-[dimethylcarbamoylthio)-4-methoxyphenyl]-4*H*-3,1-benzoxathiine **22** was obtained as a glassy solid (80 mg, 44%); $\delta_H(CDCl_3)$ 3.05 (6 H, s, NCH_3), 3.9 (3 H, s, OCH_3), 5.1 (2 H, s, CH_2), 6.05 (1 H, s, CH) and 6.8–7.6 (7 H, arom.); *m/z* (%) 361 (24), 289 (6), 238 (13), 194 (48), 121 (100).

This compound was dissolved in methanol (2 cm^3), treated with a solution of 10% aqueous NaOH (0.2 cm^3) and heated at reflux for 4 h under nitrogen. The mixture was acidified with diluted HCl and neutralised with sodium carbonate. After extraction with ethyl acetate (2 × 2 cm^3), drying and concentration of the solvent, compound **23** was purified by column chromatography (light petroleum–ethyl acetate 72:25) (60 mg, 94%); $\delta_H(CDCl_3)$ 3.8 (1 H, s, SH), 3.9 (3 H, s, OCH_3), 5.05 (2 H, s, CH_2), 6.0 (1 H, s, CH) and 6.7–7.8 (7 H, arom.); *m/z* (%) 290 (45), 168 (18) and 122 (100).

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