Studies of the Synthesis of 2-Hydroxy- and 2-Acetoxy-6-Methyl-1,4-Oxathiane S-Oxides and Related Compounds[+]

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Summary: The 4R-and 4S-oxides of (2R, 6S) and (2S,6S)-2-acetoxy-6-methyl-1, 4-oxathiane have been prepared by routes involving S-oxidation of the respective 1,4-oxathianes with periodate. In these compounds, an equatorial acetoxy group at C-2 leads to preponderant axial S-oxygenation by periodate, whereas an axial acetoxyl group at C-2 favours equatorial S-oxygenation. Basic hydrolysis of (2R, 4S, 6S)-2-acetoxy-6-methyl-1,4-oxahiane S-oxide provides a convenient route to (4S, 6S)-2-hydroxy-6-methyl-1,4-oxathiane S-oxide. The allyl (and prop-1-enyl) and p-nitrophenyl groups were shown to be unsuitable for the protection of HO-2 during the synthesis of 2-hydroxy-1,4-oxathiane derivatives.

Discussion

In an approach [1,2] to the stereospecific synthesis of naturally occurring asymmetric sulphoxides, it was necessary to prepare stereochemically defined derivatives [e.g (1)] of 2-hydroxy-1,4-oxathiane S-oxide and then remove the protecting group from HO-2. Because sulphoxides are known to be racemised by treatment with acid, the use of protecting groups that could be removed by very mild acid conditions, or by base, has been examined, and we now report on these studies.

The allyl group is conveniently removed by isomerisation to the prop-1-enyl group and subsequent mild hydrolysis with acid, and the use of this procedure for the conversion of allyl glycosides into free sugars has been described [3]. Conventional tritylation of allyl α-D-glucopyranoside with trityl chloride-pyridine gave allyl 6-O-trityl-α-D-glucopyranoside (2). Oxidation of (2) with lead tetraacetate followed by reduction of the resulting dialdehyde with sodium borohydride gave syrupy (2R, 1'S)-2-O- (1'-allyloxy-2'-hydroxyethyl)-1-O-tritylglycerol (3) which was characterised as the di(azobenzene-p-sulphonate) (4). Treatment of (4) with sodium sulphide in ethanol then gave (2S, 6R)-2-allyloxy-6-trityloxymethyl-1,4-oxathiane (5) in 60% yield. However, the oxathiane (5) was resistant to the allyl→prop-1-enyl isomerisation. Thus, conventional [3] treatment of (5) with potassium tert-butoxide in dimethyl sulphoxide at 100° for 2 hours gave only a small proportion (∿7%) of the required 2-(prop-1-enyloxy)-1,4-oxathiane (6) together with 57% of recovered starting-material. Variation in the reaction conditons (longer periods and higher temperatures) did not significantly increase the proportion of (6), and the reasons for the low extent of isomerisation are not understood because complete conversion of allyl

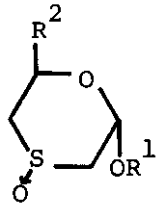
[+] Some of these results have been reported in preliminary from [8,9].

tetra-O-methyl-α-D-glucopyranoside into the prop-1-enyl glycoside occurred rapidly [4] at 100°. Similar treatment of the allyl-diol (3) also resulted in incomplete isomerisation, and chromatographic fractionation of the resulting mixture of diols gave a low yield of the prop-1-enyl-diol which was characterised as the di(azobenzene-p-sulphonate) (7). Treatment of (7) with sodium sulphide in ethanol gave (2S, 6R)-2-(prop-1-enyloxy)-6-trityloxymethyl-1,4-oxathiane (6) in 50% yield.

Optimisation of yields in the preparation of (6) was not attempted because its behaviour on treatment with dilute acid was not straight forward. Thus, the expected rapid loss of the trityl and prop-1-enyl groups, to give (6R)-2-hydroxy-6-hydroxymethyl-1,4-oxathiane (8), was accompanied by the formation (t.l.c. analysis) of a second major product. This unidentified component was also formed when (2S,6R)-2-methoxy-6-trityloxymethyl-1,4-oxathiane (9), the 2-allyloxy derivative (5), and (8) itself were treated under the same acidic conditions. Thus, although acid hydrolysis of detritylated (9) has been used [2] to prepare (8), it is concluded that the fully hydrolysed oxathiane is not stable under acid conditions. Moreover, it was subsequently found [5] that 2-hydroxy-1,4-oxathiane S-oxides cannot be obtained by acid hydrolysis of the 2-alkoxy derivatives, because the latter undergo rapid Pummerer rearrangement [6] in acid, and the use of base-labile p-nitrophenyl [7] and acetyl groups for the protection of HO-2 has therefore been examined.

Sequential application of periodate oxidation, reduction with sodium borohydride, and toluene-p-sulphonylation to p-nitrophenyl L-rhamnopyranoside gave crystalline (2S)-2-[1'-p-nitrophenyloxy-2'-(toluene-p-sulphonyloxy)ethyloxy] propyl toluene-p-sulphonate (10). However, treatment of the disulphonate (10) with a boiling solution of sodium sulphide in methanol resulted in rapid disappearance (5 min, t.l.c.) of the disulphonate, which was accompanied by the formation of a yellow colour and extensive decomposition (at least 13 products, t.l.c.). The yellow colour suggested that the basic conditions (pH 9) caused hydrolysis of the p-nitrophenyl group; on treatment with boiling methanolic sodium sulphide at pH 7, the disulphonate (10) was unchanged after 24 hours. The pattern of decomposition of (10) on treatment with sodium sulphide has not been established, but it is clear that this route cannot be used to prepare 2-(p-nitrophenyloxy)-1, 4-oxathiane derivatives.

In an alternative approach, a satisfactory route to 2-hydroxy-6-methyl-1,4-oxathiane S-oxide has been developed using the acetyl group to protect HO-2. The synthesis of (2R, 6S)-2-acetoxy-6-methyl-1,4-oxathiane has been described [2], together with the assignment [2,8,9] of the diequatorial conformation (11) on the basis of n.m.r. data. S-Oxidation of (11) with sodium metaperiodate has now given a mixture (~ 6:1) of (2R, 4S, 6S)- and (2R, 4R, 6S)-2-acetoxy-6-methyl-1,4-oxathiane S-oxides (12) and (13), from which the pure sulphoxides were isolated by fractional crystallisation and column chromatography. The assignments of the 4S configuration (axial sulphoxide group) to the major product (12) (43% isolated yield) and the 4R configuration (equatorial sulphoxide group) to (13) (5% isolated yield) were made [9] from n.m.r. data. In particular, the H-2 quartet ($J_{2a,3a}$ 9.8 $J_{2a,3e}$ 1.9 Hz) for (12) was at much lower field (6.48) than that (5.74, $J_{2a,3a}$ 10.1, $J_{2a,3e}$ 1.6 Hz) for (13), as a



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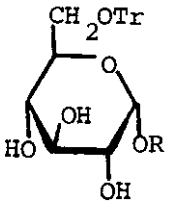
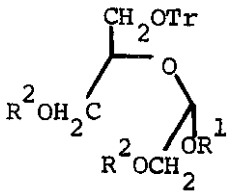


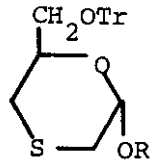
2 R=$CH_2CH=CH_2$



3 R^1=$CH_2CH=CH_2$, R^2=H

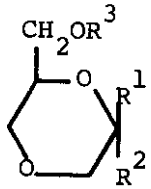
4 R^1=$CH_2CH=CH_2$, R^2=$SO_2C_6H_4N=NC_6H_5$

7 R^1=CH=CH-CH_3, R^2=$SO_2C_6H_4N=NC_6H_5$



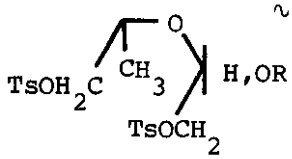
5 R=$CH_2CH=CH_2$

6 R=CH=CH-CH_3

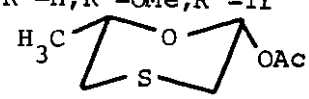


8 R^1,R^2=H,OH, R^3=H

9 R^1=H, R^2=OMe, R^3=Tr



10 R=$C_6H_4NO_2$-p



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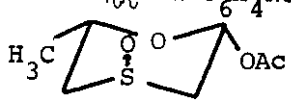

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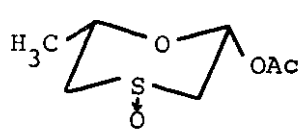

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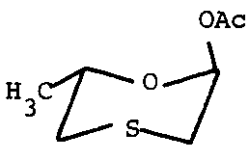

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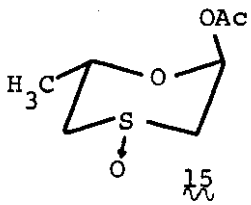

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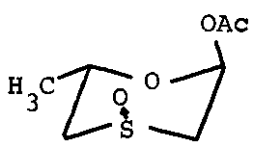

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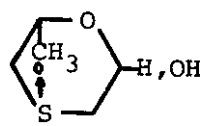

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result [9] of the "syn-axial effect" of the axial S O group in (12). Confirmation that (12) and (13) retained the 2R,6S-configuration was obtained by their separate oxidations with permanganate to give (2R,6S)-2-acetoxy-6-methyl-1,4-oxathiane S,S-dioxide, which was also obtained by similar oxidation of (11). The preponderant formation of the axial sulphoxide (12) on oxidation of (11) with periodate is consistent with the behaviour [10] of other 1,4-oxathianes having an equatorial anomeric substituent at C-2 and with the general preference for axial S-oxygenation of 4-substituted thianes by periodate [11].

In order to obtain a higher yield of a diastereoisomeric equatorial sulphoxide in this series, and also to provide a complete set of compounds for n.m.r. study, the S-oxidation of (2S,6S)-2-acetoxy-6-methyl-1,4-oxathiane (14) was also examined. Oxathiane (14) was obtained in low yield (~ 10%) by fractionation of the ~2:1 mixture of the (2R,6S):(2S,6S) isomers produced [2] by acid-catalysed equilibration of the (2R,6S)-isomer (11). The preponderance in this mixture of isomer (11) having an equatorial acetoxyl group at C-2 is consistent with the behaviour of other 2-substituted 1,4-oxathiane derivatives [2,12] and contrasts with the behavi-

our of tetrahydropyran analogues where operation of the anomeric effect leads to a preference for an axial 2-substituent [13]. The n.m.r. spectrum of (14) showed [9] a triplet for H-2 at δ 6.14 ($J_{2e,3a}$ 2.8 Hz) typical of an equatorial proton equally coupled to the axial and equatorial protons of a vicinal methylene group and consistent with conformation (14).

Oxidation of (14) with periodate gave the equatorial sulphoxide, (2S, 4R,6S)-2-acetoxy-6-methyl-1, 4-oxathiane S-oxide (15), and only a trace (t.l.c.) of the axial sulphoxide (16). This is a situation where axial S-oxidation by periodate is hindered by the axial substituent at C-2 [10], and again illustrates that steric control of the S-oxidation of derivatives of 1,4-oxathianes is best achieved by variation of the configuration at C-2. This observation is important because variation in the oxidant [10] is not a convenient route for the preparation of a pair of diastereoisomeric sulphoxides in the 1,4 oxathiane series. The very small proportion of (16) produced by oxidation of (14) did not permit its direct isolation. However, equilibration of sulphoxide (12) with toluene-p-sulphonic acid in acetic anhydride-acetic acid gave a mixture of sulphoxides (12), (15), and (16) as a result of racemisation at the sulphoxide centre as well as at C-2; sulphoxide (13) was not detected in this mixture. The minor component, (2S,4S,6S) 2-acetoxy-6-methyl-1, 4-oxathiane S-oxide (16) was isolated as a syrup (10% yield) by column chromatography and characterised by oxidation with permanganate to give (2S,6S)-2-acetoxy-6-methyl-1,4-oxathiane S,S-dioxide. The sulphone was also obtained by similar oxidation of (14) and (15), thereby indicating that the (2S,6S) configuration of (14) had been retained in the sulphoxide (15) and (16). The assignments of the 4R and 4S configurations for (15) and (16), respectively, were made [9] from n.m.r. data. Although it was not established that true equilibrium had been reached for the mixture of sulphoxides (12), (15), and (16), it may confidently be concluded that the equatorial sulphoxide (15) is thermodynamically more stable than the axial sulphoxide (16). This contrasts with the greater stability of the axial sulphoxide in thiane derivatives [11], and this difference is attributed to the effect of the axial acetoxyl group at C-2 in the pair of sulphoxides (15) and (16). In agreement with this conclusion, the absence of the equatorial sulphoxide (13) from the equilibrated mixture indicates that the axial isomer (12) is the more stable of the pair of sulphoxides having an equatorial acetoxyl group at C-2.

In the final stage of the synthesis, alkaline hydrolysis of the acetate group in sulphoxide (12) gave crystalline (4S,6S)-2-hydroxy-6-methyl-1,4-oxathiane S-oxide (17) in 62.5% yield. Similarly, alkaline hydrolysis of (13) gave (4R,6S)-2-hydroxy-6-methyl-1,4-oxathiane S-oxide. However, although the use of 2-acetoxy derivatives provides a useful route to the 4S-sulphoxide (17), the method is not convenient for the preparation of the diastereoisomeric 4R-sulphoxide because of the low yields in the stages (11) → (13) and (11) → (14).

Experimental

General methods

Thin-layer chromatography (t.l.c.) was performed on Kieselgel G (Merck) and detection was effected with vanillin-sulphuric acid [14] and/or iodine vapour. N.m.r. spectra were recorded for 5% solutions in $CDCl_3$ (internal Me_4Si) with Varian A-60 (60 MHz)

and JEOL JNM-4H-100 (100 MHz) spectrometers. Pyridine was dried by distillation five times from phosphorus pentaoxide and stored over sodium hydroxide pellets. Light petroleum refers to the fraction having b.p. 60-80°.

Allyl 6-O-trityl-α-D-glucopyranoside (2)

A solution of allyl α-D-glucopyranoside [15] (20 g) and chlorotriphenylmethane (24 g) in dry pyridine (80 ml) was kept at 100° for 1 hour. Water (2 ml) was then added to the cooled solution which, after 30 minutes was poured into an excess of ice-water. The solid obtained by trituration was recrystallised from ethyl acetate-light petroleum to give (2) (30 g), m.p. 95-96°, $[\alpha]_D^{32}$ +59° (c 1, chloroform).

Anal. Calc. for $C_{28}H_{30}O_6$: C, 72.9; H, 6.8. Found: C, 72.9; H, 6.5.

(2R,1'S)-2-O-[1'allyloxy-2'-(azobenzene-p-sulphonyloxy)ethyl]-3-O-(azobenzene-p-sulphonyl)-1-O-tritylglycerol (4)

Lead tetra-acetate (265 g) was added in portions to a solution of allyl 6-O-trityl-α-D-glucopyranoside (145 g) in dry chloroform (1.2 litre). After the mixture had been stirred for 24 hour, saturated aqueous oxalic acid was added to remove the excess of lead ions, and the filtered solution was washed with water, aqueous sodium hydrogen carbonate (10%), and water. The dried ($MgSO_4$) solution was concentrated to give the dialdehyde as a clear syrup (52.4 g) that was dissolved in ethanol (250 ml) and treated with sodium borohydride (11g) at 0°. After storage overnight, excess of water was added to the solution which was then extracted with chloroform (3 x 300 ml). The dried ($MgSO_4$) extract was concentrated under diminished pressure to give the syrupy crude diol (3) (50 g).

The diol (3) (1g) was treated with azobenzene-p-sulphonyl chloride (1.5 g) in dry pyridine (4 ml) at room temperature for 48 hours. After addition of water (0.5 ml) and storage for 30 minutes, the mixture was poured into an excess of ice-water, and the resulting syrup was crystallised from ethanol to give the di(azobenzene-p-sulphonate)$_{23}$(4) (800 mg, 40%), m.p. 65°, $[\alpha]_{5461}^{23}$ - 10.2° (c 2.7, chloroform).

Anal. Calc. for $C_{51}H_{46}N_4O_9S_2$: C, 66.4; H, 5.9; N, 6.1; S, 6.9. Found: C, 66.5, H, 5.3; N, 6.4; S, 7.2.

(2S,6R)-2-allyloxy-6-trityloxymethyl-1,4-oxathiane (5)

A solution of the di(azobenzene-p-sulphonate) (4) (20g) and dried sodium sulphide (4 g) in dry ethanol (100 ml) was boiled under reflux for 2 hour and then concentrated under diminished pressure. Excess of water was then added, the solution was extracted with chloroform (3 x 200 ml), and the combined extracts were filtered through a charcoal pad, dried ($MgSO_4$), and concentrated in vacuc. The syrupy residue (8 g) was purified on a column of silica gel (300 g; hexane-ether, 99:1) and crystallised from ethanol to give oxathiane (5) (6 g, 67%), m.p. 75° $[\alpha]_D^{25}$ +9° (c 1,ethanol). N.m.r. data (CCl_4): 4.85 (t, 1 H, $J_{2e,3a}$ + $J_{2e,3e}$ 6 Hz, H-2) and 7.35 (m, 15 H, trityl).

Anal. Calc.for $C_{27}H_{28}O_3S$: C, 75.0;

H, 6.5; S, 7.4. Found: C, 74.8; H, 6.8; S, 7.55.

(2R, 1'S)-3-O-(azobenzene-p-sulphonyl)-2-O-[2'-azobenzene-p-sulphonyloxy)-1'-(prop-1-enyloxy)ethyl]-1-O-tritylglycerol (7)

Potassium tert-butoxide (1.4 g) was added to a solution of the crude diol (3) (1.4 g) in dimethyl sulphoxide (24 ml), and the mixture was kept at 100° for 2 hours with constant stirring. Most of the dimethyl sulphoxide was evaporated under diminished pressure, and the solution was then neutralised with solid carbon dioxide and extracted with chloroform (100 ml). The extract was concentrated to yield a syrup (0.8 g) that contained two main components [R_f 0.6 (allyl diol) and 0.5 (prop-1-enyl diol)]. The syrup was fractionated on a column of silica gel (Merck 7734, 80 g; ethyl acetate) to give the prop-1-enyl diol as a syrup (220 mg) having ν_{max} 1675 cm^{-1} (prop-1-enyl group).

The crude diol (200 gm) was treated with azobenzene-p-sulphonyl chloride (400 mg) in pyridine (2 ml) as described for the allyl diol (3), to give the di (azobenzene-p-sulphonate) (7) (100 mg), m.p. 70° (from ethanol), $[\alpha]^{23}_{5461}$ - 8.4° (c 2.7, chloroform); ν_{max} 1675 cm^{-1} (prop-1-enyl group). The n.m.r. spectrum ($CDCl_3$) showed a 3-proton doublet at δ1.45 for the terminal methyl group.

Anal. Calc. for $C_{51}H_{46}N_4O_9S_2$: C, 66.4; H, 5.0; N, 6.1; S, 6.9. Found: C, 66.0; H, 5.0; N, 6.2; S, 7.0.

(2S,6R)-2-(Prop-1-enloxy)-6-tritylloxymethyl-1,4-oxathiane (6) - (a)

The 2-allyloxyoxathiane (5) (700 mg) was added to a solution of potassium tert-butoxide (700 mg) in dry dimethyl sulphoxide (35 ml) and the mixture was kept 100° for 2 hours. Chloroform (100 ml) was added to the cooled solution, and the mixture was washed with water (3 x 150 ml), dried ($MgSO_4$), and concentrated under diminished pressure to give a syrup (500 mg) that contained two components [R_f 0.79 and 0.5 (5); t.l.c, benzene]. The product was fractionated on a column of silica gel (Merck 7734, 50 g; hexane-ether, 99:1) to give the starting material (5) (400 mg) and the component having R_f 0.79 (50 mg). The latter component was crystallised from ethanol to give 6 (20 mg), m.p. 88°, $[\alpha]^{29}_{D}$ -61° (c 1, chloroform). N.m.r. data (CCl_4): δ 6.9 (m, 15 H, aromatic), 4.8 (t, 1H, $J_{2e,3a} + J_{2e,3e} \sim 5$ Hz, H-2), and 1.6 (d, 3 H, $CH=CH-CH_3$).

Anal. Calc. for $C_{27}H_{28}O_3S$: C, 75.0; H, 6.5; S, 7.4. Found: C, 75.1; H, 6.3; S, 7.4.

(b) A solution of di(azobenzene-p-sulphonate) (7) (140 mg) and dried sodium sulphide (50 mg) in dry ethanol (15 ml) was boiled under reflux for 2 hours and then concentrated under diminished pressure. Water (5 ml) was added to the residue, and the solution was extractd with chloroform (3 x 10 ml). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo to give a syrupy residue (80 mg) that was purified by chromatography on a column of silica gel (Merck 7734, 20 g; hexane-ether, 99:1) to give (6) as a syrup (30 mg, 45%). After crystallisation from ethanol, the product had m.p. 88° and was indistinguishable from (6) prepared in (a)

Acid hydrolysis of 1,4-oxathiane derivatives

0.05M sulphuric acid (1 ml) was added to a solution of (2S,6R)-2-(prop-1-enyloxy)-6-trityloxymethyl-1,4-oxathiane (6) (50 mg) in ethanol (1 ml), and the mixture was heated at 100° for 15 minutes. Water (3 ml) was added to the cooled solution, the acid was neutralised with solid barium carbonate, and the filtered solution was saturated with sodium chloride and extracted with chloroform (3 x 5 ml). The combined extracts were dried ($MgSO_4$) and concentrated to give a syrup that showed two components in t.l.c. [(ethyl acetate, R_f 0.7 and 0.34) (compound) (8)]; the starting material (6) was not present.

The same products were observed when compounds (5) and (8) were similarly treated with sulphuric acid.

(2S)-2-[1'-p-Nitrophenyloxy-2'-(toluene-p-sulphonyloxy)ethyloxy]propyl toluene-p-sulphonate (10)

A solution containing p-nitrophenyl L-rhamnopyranoside (5 g; m.p. 165°, $[\alpha]_D^{28}$ + 120° in water; prepared by the general method of Shafizadeh and Stacey [16] and sodium metaperiodate (10 g) in aqueous methanol (1:1, 40 ml) was kept at room temperature for 24 hours. Aqueous barium chloride was then added, the precipitated salts were removed by filtration, and the solution was extracted with chloroform (3 x 100 ml). The combined extracts were dried ($MgSO_4$) and concentrated under diminished pressure. The resulting syrup (3 g) was dissolved in ethanol (40 ml), sodium borohydride (1.5 g) was added at 0°, and the mixture was kept at 0° overnight. Water (50 ml) was added and the solution was then extracted with chloroform (3 x 100 ml). The combined extracts were dried ($MgSO_4$) and concentrated under diminished pressured to give a syrup (3.1 g) that showed one component (R_f 0.6) in t.l.c. (benzene-methanol, 9:1).

Toluene-p-sulphonyl chloride (1.5 g) was added to a stirred solution of the foregoing syrup (0.6 g) in dry pyridine (3 ml), and the mixture was kept at 0° overnight. Water (0.2 ml) was then added and, after storage at 0° for 20 minutes, the mixture was poured into ice-water (200 ml). The solid (1 g) produced by trituration was recrystallised from ethanol to give the disulphonate (10) (0.7 g), m.p. 75-80°, $[\alpha]_D^{29}$ + 17.3° (c 1.4, ethanol).

Anal. Calc. for $C_{25}H_{27}NO_{10}S_2$: C, 53.1; H, 4.9; N, 2.5; S, 11.3. Found: C, 52.95; H, 4.9; N, 2.5; S, 11.4.

When a solution of (10) (300 mg) and dried sodium sulphide (100 mg) in dry methanol (10 ml) was boiled under reflux for 5 minutes, it became yellow and t.l.c. (benzene) showed the absence of (10). The solvent was evaporated, water (25 ml) was added, and conventional extraction with chloroform gave a syrup (30 mg) that showed 13 components in t.l.c. (benzene); one component had the same R_f value as (6S)-2-hydroxy-6-methyl-,4-oxathiane.

Oxidation of (2R,6S)-2-acetoxy-6-methyl-1,4-oxathiane (11) with sodium metaperiodate

A solution of (11) [2] (1.4 g) in ethanol was added dropwise, with stirring, to a solution of sodium metaperiodate (2.1 g) in water (22 ml) at 0°, and the mixture was kept at 0° overnight. The filtered solution

was then extracted with chloroform (2 x 25 ml), and the dried ($MgSO_4$) extracts were concentrated under diminished pressure. The resulting residue (1.5 g, ~100%) was recrystallised from ethyl acetate-light petroleum to give a sulphoxide mixture (0.8 g), m.p. 110-135°, $[\alpha]_D^{30}$ + 95.5° (c, 1.7, ethanol), R_f 0.48 and 0.43 (major) (t.l.c.; benzene-methanol, 9:1).

Recrystallisation of the sulphoxide mixture (800 mg) from ethyl acetate-light petroleum gave (2R, 4S,6S)-2-acetoxy-6-methyl-1,4-oxathiane S-oxide (12) (500 mg), m.p. 153°, $[\alpha]_D^{20}$ + 110° (c 0.3, ethanol), R_f 0.43. N.m.r. data ($CDCl_3$): δ 6.48 (q, 1H $J_{2a,3a}$ 9.8, $J_{2a,3e}$ 1.9 Hz, H-2) and 4.80 (bm, 1 H, H-6); for further data, see ref. [9].

Anal. Calc. for $C_7H_{12}O_4S$: C, 43.75; H, 6.3; S, 16.65. Found: C, 43.9; H, 6.1; S, 16.8

The syrup (300 mg) recovered from the mother liquors from the foregoing recrystallisation was fractionated on a column of silica gel (Merck 7734, 40 g) with benzene-metahnol (99:1) to give (a) the minor sulphoxide (R_f 0.48; 80 mg), (b) a mixture (50 mg) of the two sulphoxides, and (c) the major sulphoxide (12) (150 mg). Recrystallisation of (a) from ethyl acetate-light petroleum gave (2R, 4R,6S)-2-acetoxy-6-methyl-1,4-oxathiane S-oxide (13) (50 mg), m.p. 92°, $[\alpha]_D^{27}$ + 8° (c 1, chlorofom), R_f 0.48. N.m.r. data ($CDCl_3$): 5.74 (q, 1H, $J_{2a,3a}$ 10.1, $J_{2a,3e}$ 1.6 Hz, H-2) and 3.80 (bm, 1 H, H-6); for further data, see ref. [9].

Anal. Calc. for $C_7H_{12}O_4S$: C, 43.75; H, 6.3; S, 16.65. Found: C, 43.6; H, 6.2; S, 16.5.

(2R,6S)-2-acetoxy-6-methyl-1,4-oxathiane S, S-dioxide.

Aqueous potassium permanganate (3%, 5 ml) was added dropwise during 3 hours, with stirring, to a solution of the 4S-sulphoxide (12) (50 mg) in acetic acid (0.5 ml). The excess of permanganate was reduced by the addition of aqueous hydrogen peroxide, and the solution was poured into ic-water (10 ml). Conventional extraction with chloroform then gave the title sulphone (30 mg), (55%), m.p. 156° (from ethanol), $[\alpha]_D^{32}$ + 25° (c 1, ethanol).

Anal. Calc. for $C_7H_{12}O_5S$: C, 40.4; H, 5.8; S, 15.4. Found: C, 40.6; H, 6.0; S, 15.25.

Similar oxidation of compounds (11) and (13) gave samples of the sulphone that were indistinguishable from the foregoing product.

(2S,6S)-2-Acetoxy-6-methyl-1,4-oxathiane (14)

A solution of (2R,6S)-2-acetoxy-6-methyl-1,4-oxathiane (11) (2 g) and toluene-p-sulphonic acid (2 mg) in acetic anhydride-acetic acid (1:1, 50 ml) was kept at room temperature for 3 hours. Water (100 ml) was then added and, after 15 minutes, the acid was neutralised with solid sodium hydrogen carbonate and the filtered solution was extracted with chloroform (3 x 100 ml). The dried ($MgSO_4$) extracts were evaporated *in vacuo* to give a syrup (1.8 g) that was fractionated on a column of silica gel (Merck 7734, 200 g) with benzene to give (a) the 2R-isomer (11) (600 mg), R_f 0.33 (t.l.c. benzene), (b)

a mixture of the 2R- and 2S-isomers (600 mg), and (c) the 2S-isomer (14) (200 mg, 10%; R_f 0.26).

Distillation of fraction (c) gave (14), b.p. 80° (bath)/0.2 mmHg, $[\alpha]_D^{27}$ ~0° (c 0.6, ethanol.

Anal. Calc. for $C_7H_{12}O_3S$: C, 47.7; H, 6.8. Found: C, 47.9; H, 6.7.

(2S,6S)-2-Acetoxy-6-methyl-1,4-oxathiane S, S-dioxide

Compound (14) (0.3 g) was oxidised with aqueous potassium permanganate, following the procedure described for the oxidation of (12), to give the title sulphone (66% yield), m.p. 147° (from ethanol), $[\alpha]_D^{29}$ -43.2° (c 0.8, ethanol).

Anal. Calc. for $C_7H_{12}O_5S$; C, 40.4; H, 5.8; S, 15.4. Found: C, 40.45; H, 5.9; S, 15.2

(2S,4R,6S)-2-Acetoxy-6-methyl-1,4-oxathiane S-oxide (15)

The 2S,6S-oxathiane (14) (300 mg) was oxidised with sodium metaperiodate (500 mg), follwoing the procedure described for the 2R,6S-isomer, to give a product that showed two components (R_f 0.21, major; 0.19, trace) in t.l.c. (chlorofom). Fractionation of the product on a column of silica gel (Merck 7734, 20 g;chloroform) gave sulphoxide (15) (200 mg), m.p. 77-78°, $[\alpha]_D^{32}$ - 90° (c 1, ethanol). N.m.r. data ($CDCl_3$):δ 6.42 (t, 1 H, $J_{2e,3a}$ + $J_{2e,3e}$ ~4.8 Hz, H-2) and 4.15 (m, 1H, H-6); for further data, see ref. [9].
Anal. Calc. for $C_7H_{12}O_4S$: C, 43.75; H, 6.3; S, 16.65. Found: C, 43.85; H, 6.5; S, 16.9.

Oxidation of (15) with potassium per mangante, following the procedure described for the 4S-sulphoxide (12), gave (2S, 6S)-2-acetoxy-6-methyl-1,4-oxathiane S,S-dioxide (69%), m.p. 147°, which was indistinguishable from the authentic sulphone described above.

(2S,4S,6S)-2-Acetoxy-6-methyl-1,4-oxathiane S-oxide (16)

A solution of the 2R,4S,6S-sulphoxide (12) (1 g) and toluene-p-sulphonic acid (7 mg) in acetic anhydride-acetic acid (1:1, 25 ml) was kept at room temperature for 3 hours and then poured into water (100 ml). The acid was neutralised with solid sodium hydrogen carbonate, the filtered solution was extracted with chloroform (3 x 100 ml), and the combined extracts were dried ($MgSO_4$) and concentrated to give a syrup (900 mg) that showed three components [R_f 0.36, 0.21, and 0.14 (minor)] in t.l.c. (chloroform). Fractionation of the syrup on a column of silica gel (Merck 7734, 100 g; chloroform) gave (a) a mixture (600 mg) containing approximately equal amounts of sulphoxides (12) (R_f 0.36) and (15) (R_f 0.21), and (b) sulphoxide (16) (R_f 0.14) as a chromatographically homogeneous syrup (100 mg), $[\alpha]_D^{27}$ - 12° (c 1 ethanol). N.m.r. data ($CDCl_3$): 6.33 (t, 1H, $J_{2e,3a}$ + $J_{2e,3e}$ ~ 5.2 Hz,H-2) and 4.98 (m, 1H, H-6); for further data, see ref. [9].

Anal. Calc. for $C_7H_{12}O_4S$: S, 16.65
Found: S, 16.5

The product was characterised by oxidation with potassium permanganate to give (2S,6S)-2-acetoxy-6-methyl-1,4-oxathiane S,S-dioxide (65%), m.p. 147°, which was identical with the authentic sulphone described above.

(4S,6S)-2-Hydroxy-6-methyl-1,4-oxathiane S-oxide (17)

0.1M sodium hydroxide (20.8 ml) was added dropwise to a stirred solution of the 2R,4S,6S-sulphoxide (12) (0.42 g) in acetone (4 ml). After 2.5 hours, the neutral (phenolphthalein) solution was continuously extracted with chloroform for 24 hours, the dried ($MgSO_4$) extract was evaporated, and the residue was crystallised from ethanol-light petroleum to give (17) (0.2 g, 62.5%), m.p. 163°, $[\alpha]_D^{23}$ + 63° (c 1.2, ethanol).

Anal. Calc. for $C_5H_{10}O_3S$: C, 40.0; H, 6.7; S, 21.3. Found C, 40.45; H, 6.7; S, 21.4.

(4R,6S)-2-Hydroxy-6-methyl-1,4-oxathiane S-oxide

Following the procedure used for (17), hydrolysis of the 2R,4R,6S-sulphoxide (13) gave the title sulphoxide, m.p. 175° (from ethanol-light petroleum).

Anal. Calc. for $C_5H_{10}O_3S$: C, 40.0; H, 6.7; S, 21.3. Found: C, 39.8; H, 6.6; S, 21.5.

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