Thio-sugars. Part 1. 4-Thiotetrose Derivatives *via* Pummerer Rearrangement

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A number of 4-thiotetrose derivatives have been prepared by Pummerer rearrangement of esters of thiolan-3,4-diol 1-oxides. This synthesis illustrates the key step in a general scheme for the elaboration of glycosides and nucleosides containing sulphur in the sugar ring. In using non-sugar starting materials, it differs from other methods of obtaining these compounds. Several esters have been studied, and the protecting and directing properties of the phenylboronate function were found especially useful. The stereochemistry of the Pummerer rearrangement products is discussed, and the bicyclic phenylboronate and carbonate systems are compared. Many of the reactions are of great preparative value. The *S*-oxidation and rearrangement steps can be repeated, giving symmetrical bicyclic derivatives of tartaraldehyde. (Diacetoxyiodo)benzene or t-butyl perbenzoate converts esters of thiolan-3,4-diol directly into α-acyloxy-compounds, but in poor yield.

We have devised a four-stage scheme for the synthesis of glycosides and nucleosides containing sulphur in the sugar ring, from non-sugar starting materials. It is of great versatility and a wide variety of novel sugars can be prepared, including many where the oxygen counterpart is not easily accessible. They may contain deoxy or *C*-methyl groups, as well as nitro, carboxy, acyl, aryl, or other substituents and, since unusual sugars are often associated with antibiotics, provide a wealth of material for testing for cancer chemotherapeutic and other biological properties.

First, a cyclic hydroxy-sulphide is prepared either (*a*) by reaction of inorganic sulphide with a linear compound having terminal leaving groups and one or more (possibly protected) hydroxy-substituents, or (*b*) by aldol condensation involving a linear oxo-sulphide and an active methylene group; this may be intermolecular or, if the groups are suitably distant, intramolecular. Secondly, the hydroxy-sulphide is oxidised to the sulphoxide level. Thirdly, the sulphoxide is converted by Pummerer rearrangement into an α-acetoxy-sulphide. Finally, this is subjected to acid-catalysed nucleophilic attack at the anomeric centre.

All the steps are simple in practice and the yields are nearly always acceptable and often high. The sugar derivatives formed are racemic. The stereoisomers

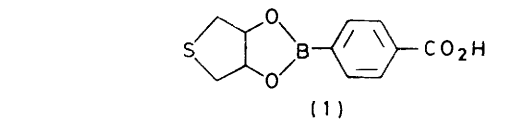
theoretically possible from some transformations have occasionally been separated. The ready availability and useful physical properties of these sulphur compounds facilitate the study of the stereochemistry of the Pummerer rearrangement and of displacements at the anomeric carbon atom.

These general principles will be illustrated in this series of papers. The present communication deals with the first three steps as applied to the synthesis of 1-*O*-acetyl-4-thiotetrose derivatives.[1] Further, we have repeatedly found throughout this work the great value of arylboronates [2] (in separating isomeric mixtures, as protected forms of diols, in the direction of incoming groups, and, most recently, as derivatives with potential for optical resolution) and some indication of their utility is given in this paper.

The hydroxy-sulphides which lead to the 4-thiotetroses are the thiolan-3,4-diols (2a) and (3a), now readily available [3] from the 1,4-dichlorobutane-2,3-diols and sodium sulphide. In addition to the esters described earlier,[3] the cyclic carbonate [4] (2f) has now been made by use of diphenyl carbonate or, better, methyl chloroformate. Several arylboronates (Table 1) separated conveniently from aqueous solutions, in contrast to the water-sensitive derivatives of many monosaccharides.[2] The *p*-carboxy-ester (1) yielded crystalline salts with (—)-α-phenylethylamine and with (—)-ephedrine, and it may eventually be possible to resolve some racemic compounds by using such acidic boronates.

Oxidation of the *trans*-diol with peroxide in acetic acid gave the sulphoxide in high yield. This could be converted into the diacetate (4b) with acetic anhydride, but benzoyl chloride and methanesulphonyl chloride caused decomposition, and the oxidation and esterification steps had to be reversed to obtain the diesters (4c and d). Although some *trans*-1,2-diols react with phenylboronic acid (2 mol. equiv.) to yield cyclic pyroboronates having seven-membered rings,[5] no crystalline derivatives could be obtained from the diols (3a) and (4a).

Oxidation of the *cis*-diol (2a) afforded both sulphoxides which are here theoretically obtainable. Since oxidation by peroxide–acetic acid in these systems is subject to steric approach control,[6,7] the predominant isomer (designated α-; moves faster in t.l.c.) may fairly confidently [8] be assigned the configuration (5a) with oxygen *trans* to the hydroxy-groups. The sulphoxides may be easily separated, since the phenylboronate (6e) of the β-isomer crystallises from a solution of the reactants in aqueous methanol, whereas that (5e) of the α-isomer must be made in anhydrous conditions. Again, each sulphoxide diol may be acetylated with acetic anhydride, but the sulphide (2d) was oxidised with peroxide–acetic acid or sodium periodate in order to obtain a sulphoxide bismethanesulphonate. This product consisted in either case of principally one isomer, probably the α-compound (5d). Oxidation of the dibenzoate (2c) and of the carbonate (2f) also yielded mixtures of isomers which were used directly for the Pummerer reaction. The β-sulphoxide carbonate (6f) was later isolated, and it and the isomer (5f) could also be obtained from the appropriate diol and methyl chloroformate.

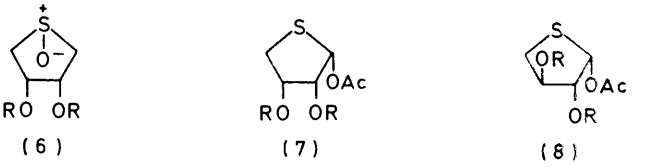


(1)

(2) (3)

a; R = H
b; R = Ac
c; R = COPh
d; R = SO_2Me
e; RR = BPh
f; RR = CO

(4) (5)



(6) (7) (8)

(9) X = BPh
(10) X = CO

(11) R^1 = H, R^2 = OAc
(12) R^1 = OAc, R^2 = H

The key step in this sugar synthesis is the Pummerer rearrangement. Horner and Kaiser [9] in 1959 revived interest in this reaction, particularly the conversion of simple sulphoxides into α-acetoxy-sulphides by hot acetic anhydride, and since then much effort has been devoted

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[4] L. Hough, J. E. Priddle, and R. S. Theobald, *Adv. Carbohydrate Chem.*, 1960, **15**, 91; *J. Chem. Soc.*, 1962, 1934; G. R. Barker, *Methods Carbohydrate Chem.*, 1963, **2**, 242.
[5] I. R. McKinley, H. Weigel, C. B. Barlow, and R. D. Guthrie, *Carbohydrate Res.*, 1974, **32**, 187 and references cited therein.
[6] (*a*) S. Glue, I. T. Kay, and M. R. Kipps, *Chem. Comm.*, 1970, 1158; (*b*) J. J. Rigau, C. C. Bacon, and C. R. Johnson, *J. Org. Chem.*, 1970, **35**, 3655.
[7] E. Jonsson and S. Holmquist, *Arkiv Kemi*, 1968, **29**, 301.
[8] R. Lett and A. Marquet, *Tetrahedron*, 1974, **30**, 3365, 3379.
[9] L. Horner and P. Kaiser, *Annalen*, 1959, **626**, 19.

to elucidation of the mechanism.[10] It is also of considerable preparative value as a source of masked aldehydes. We originally applied it to the synthesis of sugar derivatives some years ago, but the isolated yields of 4-thiotetrose acetates,[1] and of other compounds related to carbohydrates,[11] were low. We have now examined the rearrangement under different conditions with the range of thiolan-3,4-diol 1-oxide esters indicated above, and much better yields have resulted (Table 2).

Either of the phenylboronates (5e) and (6e) gives a single acetate isomer, shown to have a *trans*-acetoxy-group, *i.e.* (9), by the singlet (τ 3.85) due to the anomeric proton.[12] This simplifies the preparation of this acetate, since the sulphoxide diols need not be separated but can be converted directly into the boronate mixture, which is then ready for further reaction. The overall yield of the acetate (9) from the diol (2a) is 65—75%. The Pummerer rearrangement was carried out in boiling benzene, and when boiling acetic anhydride containing sodium acetate [13] was used, acetolysis took place and the phenylboronate (5e) yielded the triacetate (7b) (27%).

On the other hand, these more vigorous reaction conditions greatly improved the yield of triacetate from the diacetate (5b) over that obtained originally.[1] Again a single isomer resulted, which in this case probably had all three groups on the same side of the ring (7b). Assignment of configuration to the monocyclic esters [12] is difficult on account of pseudorotation. The dibenzoate mixture [(5c) and (6c)] underwent no significant acetolysis at 140 °C, and an acetate dibenzoate, again probably all-*cis*, (7c), was obtained.

The sulphoxide bismethanesulphonates were much more reactive than the other esters towards acetic anhydride. The mixed oxides (5d) and (6d) from the *cis*-diester gave only decomposition products after 5 min in boiling benzene, but at 40 °C or even room temperature an acetate [probably all-*cis*, (7d)] was obtained (*ca.* 45%).

More difficulty was experienced in isolating Pummerer products from the *trans*-diesters (4b—d) than from the corresponding *cis*-compounds (5) and (6). The rearrangement is evidently much less stereoselective, and in fact the product of sharp m.p. from the dibenzoate (4c) proved (n.m.r.) to be a 1 : 1 mixture of both possible acetate dibenzoates. It could not be separated on a column. The diacetate (4b) gave a homogeneous triacetate but in 21% yield; *cf.* 61% of (7b). The anomeric acetoxy-group is probably *cis* to the neighbouring group (8b), which also applies to the triester (8d) isolated from reaction of the bismethanesulphonate (4d).

The preparation of compound (8d) demonstrated a second difference between sulphonates and carboxylates. Although the rearrangement of *trans*-carboxylates is less stereoselective than of their *cis*-counterparts, the reactivity is of the same order. However the *trans*-ester (4d) was recovered (81%) after treatment with acetic anhydride at 40 °C. At 80 °C dark-coloured products were quickly formed, as with the *cis*-compounds, but now a Pummerer product could be isolated—in about the same yield (15%) in 15 min as the diacetate (4b) gave comparably in 5 h.

The sulphoxide carbonates (mixture of isomers) were largely unchanged even after treatment with acetic anhydride in boiling benzene. In boiling acetic anhydride with sodium acetate, a Pummerer product was obtained in low yield (8—10%). This has a *cis*-acetoxy-group (7f) since the anomeric proton signal appears as a doublet (τ 3.56, J 4.5 Hz). When the reaction is carried out at 100 °C the yield from the rearrangement is much higher (50—60%), but despite many attempts we were unable to define reproducible conditions under which this *cis*-compound was the major isomer; various amounts of the *trans*-acetate (10) (τ 3.79, singlet) were present on several occasions.

The individual sulphoxides (5f) and (6f) also afforded unpredictable proportions of the acetates (7) and (10). This may be due to some inversion of the sulphur configuration prior to rearrangement. (It is known that as well as bringing about the rearrangement acetic anhydride may also in certain experimental conditions exchange oxygen with sulphoxides, or cause racemisation.[14,15] The presence of acetic acid catalyses the racemisation reaction, which is also very sensitive to 'cocatalytic impurities'.)[16] Further, inversion of the anomeric carbon configuration after rearrangement is apparently excluded, since heating either *cis*- (7f) or *trans*-acetate (10) in acetic anhydride with acetic acid caused no anomerisation (toluene-*p*-sulphonic acid however generated some of the other isomer in each case, t.l.c.).

In summary, the principal mode of rearrangement of the sulphoxides of *cis*-diesters, with the major exception of the phenylboronates, is to yield (40—60%) all-*cis*-triesters (7) whether the oxide function is *cis* (6) or *trans* (5). Obviously the other isomer is also formed to some extent, and its proportion may be unpredictably large in the case of the carbonate (10). Moreover, since the generalisation is based on isolated yields, its validity depends in part on the relative solubility of each isomer. For the *trans*-diesters (4) on the other hand, both isomers are formed to perhaps comparable extents.

Under conditions where the boronate ring is retained, stereoselectivity is even greater for the phenylboronates than for other *cis*-diesters, but the product is the *trans*-

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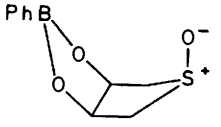
compound (9). These [3.3.0] bicyclic systems are more strained than the corresponding carbonates. Although the presence of a trigonal atom in each ester ring would be expected to confer a degree of similarity, yet (*a*) five-membered carbonate rings are more stable than six-,[17,18] whereas six-membered phenylboronate rings are generally more stable than five-,[19] and (*b*) *trans*-1,2-diol functions incorporated into a six-membered ring readily form carbonates ([4.3.0] type) [17,20] whereas the only products obtained from boronic acids are seven-membered pyroboronate rings ([5.4.0]).[5] Even a *trans*-fused [3.3.0] system containing a cyclic urea group has been prepared,[21] although we could find no examples of comparable esters.

It is not clear whether the greater steric requirements of the phenylboronates *vis-à-vis* carbonates are responsible for the observed difference in the stereochemical



(6e)

course of the Pummerer reaction. Both ester types probably exist in a highly preferred conformation, as is true of even the relatively flexible [22] isopropylidene acetals in which the thiolan ring is an ' envelope ' form with the sulphur out of the plane and *cis* to the other ring.[8] This could mean significant transannular interaction between boron and the exocyclic oxygen in the β-sulphoxide phenylboronate (6e). An attempt to provide evidence for such interaction by oxidising the sulphide phenylboronate was not very satisfactory owing to the sensitivity of the B–C bond to oxidising agents.[23] Some phenol was formed even when *m*-chloroperbenzoic acid was used, in addition to other, unidentified products, and the only sulphoxide phenylboronate isolated was the β-isomer (6e) (16%). The α-isomer (5e) present was very difficult to purify, making it impossible to state conclusively that the α : β oxidation ratio was lower for the boronate than for the free diol (3 : 1).

Stereoselective Pummerer rearrangements, at room temperature, yielding 1,3-oxathiolan-5-ones [6a] and a 3,1-benzoxathian-4-one [15] (two and one chiral centres, respectively) have been observed previously.

Further oxidation of the *cis*-acetate (7f) gave mainly one sulphoxide, which on Pummerer rearrangement yielded an all-*cis*-diacetate (11), as judged from the symmetry of the n.m.r. spectrum. A similar procedure with the *S*-oxide of the *trans*-acetate (10) again gave a single isomer. This is also symmetrical, with the *cis*-diacetate grouping now *trans* to the carbonate ring (12). We had earlier elaborated a similar α,α′-diacetoxy-sulphide function in a different way.[24] The diacetates (11) and (12) are masked forms of tartaraldehyde, resembling a cyclic diacetate prepared earlier.[25] Alkaline hydrolysis liberated the dialdehyde but attempts to open only the thiolan ring with methyl fluorosulphate [26] or mercury(II) chloride and mercury(II) oxide [27] were unsuccessful.

Oxidation of the phenylboronate (9) followed by further Pummerer rearrangement also gave a diacetoxy-compound, but the yield was poor and its configuration was not determined.

The acetate phenylboronate (9) can also be formed directly from *cis*-thiolan-3,4-diol phenylboronate by heating with (diacetoxyiodo)benzene, in relatively low yield. This reagent, unlike lead tetra-acetate, [28] has not hitherto yielded α-acetoxy-sulphides.[29] t-Butyl perbenzoate [30] gave the 1-*O*-benzoyl derivative, although the yield of isolated product was again poor. These results were not due to the sensitivity of the boronate function in the oxidising conditions: the carbonate behaved similarly with both reagents. In the case of (diacetoxyiodo)benzene, the isomer obtained was the *trans*-(10).

EXPERIMENTAL

M.p.s are corrected. I.r. spectra were recorded for KBr discs and n.m.r. spectra at 60 MHz. The hydrogen peroxide used was a 30% w/v solution. Light petroleum had b.p. 40—60 °C except where otherwise stated. Evaporation of aqueous solutions was completed by the addition and removal of several portions of methanol by distillation. Column chromatography was carried out on alumina (Brockmann grade II—III) or silica gel 60 (30—70 mesh ASTM) and t.l.c. on silica gel H (Merck products).

trans-*Thiolan-3,4-diol* 1-*Oxide* (4a).—A solution of *trans*-thiolan-3,4-diol (3a) (2.4 g, 0.02 mol) in ethanol (4 ml) and acetic acid (4 ml) was stirred, cooled to −5 °C, and treated dropwise with hydrogen peroxide (2.26 ml, 0.02 mol) at −5 to −1 °C. The mixture was refrigerated (negative result in peroxide test after 24 h) and evaporated. Ethyl acetate

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(10 ml) was added and the *sulphoxide* (4a) (2.68 g, 98%), m.p. 160.5—161.5° (from ethanol), collected (Found: C, 35.0; H, 6.0; S, 23.4. $C_4H_8O_3S$ requires C, 35.3; H, 5.9; S, 23.5%); $\lambda_{max.}$ (EtOH) 206 (log ε 3.17) and 219sh nm (2.96); $\nu_{max.}$ 3 300s, 1 052s, and 981s cm^{-1}. From ±-1,4-dichlorobutane-2,3-diol (0.32 mol), the sulphoxide was obtained in 82% yield without purification of the intermediate sulphide.

cis-*Thiolan*-3,4-*diol* 1-*Oxides* (5a) *and* (6a).—When *cis*-thiolan-3,4-diol (24 g) (2a) was oxidised by the method used for the *trans*-isomer, a mixture of sulphoxides (24.3 g, 89%) resulted. Fractional crystallisation from acetonitrile (550 ml) yielded almost entirely (t.l.c. in 1 : 1 benzene–methanol) the faster moving α-*oxide* (5a), m.p. 102.5—104° (Found: C, 35.3; H, 6.2; S, 23.5%); $\lambda_{max.}$ (EtOH) 209 nm (log ε 3.06) [the sulphide (2a) has $\lambda_{max.}$ 207 nm (log ε 3.15), and the corresponding sulphone $\lambda_{max.}$ 223 nm (log ε 2.38)]; $\nu_{max.}$ 3380s, 1092s, and 995s cm^{-1}. Chromatography of the residue on alumina with 9 : 1 chloroform–methanol as eluant gave the α-oxide (5a) (1.92 g; total yield 54%), and 8 : 2 methanol–water then eluted a further fraction (3.33 g) virtually free of α-oxide. Trituration with methanol (2 ml) yielded pure β-*oxide* (6a) (1.85 g, 6.8%), m.p. 119—124.5°, raised to 122.5—127.5° (from methanol) (Found: C, 35.8; H, 6.15; S, 23.1%).

In another experiment (30 mmol scale) the α-oxide (53%) was obtained as above by crystallisation. The β-oxide was then recovered as the *phenylboronate* (6e) (Table 1) (11%), m.p. 233—236°, from an aqueous solution of the residue. The α-oxide derivative does not separate under these conditions. Alternatively, the α-oxide (48%) and the β-oxide as the α-*naphthylboronate* (Table 1) (19%) have been obtained.

In a reversal of the above sequence of reactions the phenylboronate (309 mg, 1.5 mmol) of the diol (2a), in methylene chloride (7.5 ml), was oxidised at 3 °C by *m*-chloroperbenzoic acid (304 mg, 1.76 mmol) in methylene chloride (7.5 ml). The mixture was refrigerated (24 h) and the solvent replaced by water (20 ml). Removal of the *m*-chlorobenzoic acid by filtration and concentration (2 ml) yielded an insoluble portion (100 mg), m.p. 187—190°, which on recrystallisation afforded the phenylboronate (6e) (14%), m.p. 231—233°. Crystalline material (214 mg), m.p. 120—132°, with an i.r. spectrum similar to that of the α-isomer (5e), was recovered from the mother liquors but recrystallisation did not raise the m.p.

Derivatives of cis-*Thiolan*-3,4-*diol* (*Table* 1).—*Carbonate*. The *carbonate* (2f) separated when 2N-sodium hydroxide (22.8 ml) was added dropwise (5 min; slow addition decreases yield) to a stirred mixture (0 °C and pH *ca.* 8) of the diol (3.65 g, 30.4 mmol), water (38 ml), and methyl chloroformate (5.33 ml, 69 mmol). When the mother liquors were made alkaline to decompose unchanged chloroformate, then neutralised and evaporated, starting material (35%) could be recovered by extraction with hot chloroform.

The derivative (179 mg, 25%) was also formed from the diol (0.6 g, 5 mmol), diphenyl carbonate (1.28 g, 6 mmol), and sodium hydrogen carbonate (10 mg), in dimethylformamide (1.5 ml) after 1 h at 125—130 °C. The cooled mixture was poured into ice–water (50 ml) and the product collected and recrystallised; $\nu_{max.}$ 1 790 cm^{-1}.

Arylboronates. Addition of the diol (1 mmol) to phenylboronic acid (122 mg) in water (4 ml), or to *p*-dihydroxyborylbenzoic acid (166 mg crude; see below) in hot water (10 ml), or of the diol (1 mmol) in water (2 ml) to other arylboronic acids (1 mmol) in methanol (2 ml), caused immediate separation of the *arylboronate*. The phenylboronate of *cis*-thiolan-3,4-diol 1,1-dioxide was similarly prepared. I.r. peaks at 1600 and 1445 cm^{-1}, with stronger ones at 1410 and 1375 cm^{-1}, were characteristic of phenylboronates described in this paper.

Derivatives of trans- *and* cis-*Thiolan*-3,4-*diol* 1-*Oxides* (*Table* 1).—*Diacetates*. The diol (2.72 g, 20 mmol) was stirred with acetic anhydride (4 ml) and pyridine (4 ml) until

TABLE 1

Esters of *cis*- and *trans*-thiolan-3,4-diol and their *S*-oxides

Ester	Cryst. solvent [a]	M.p. (°C)	τ CH_2	τ CH	Yield (%)	Formula	Found (%) C	Found (%) H	Found (%) S	Required (%) C	Required (%) H	Required (%) S
(2f)	$CHCl_3$–Y	82—83			62 [b]	$C_5H_6O_3S$	40.8	4.3	22.0	41.1	4.15	21.95
(2e)	X	84.5—85.5	7.01 [c]	4.83 [c]	88	$C_{10}H_{11}BO_2S$	58.4	5.7	15.5	58.3	5.3	15.5
(2e) [d]	$CHCl_3$	233—235 [e]	6.50 [f]	4.59 [f]	89	$C_{10}H_{11}BO_4S$	50.8	4.8	13.5	50.4	4.6	13.4
(2e) [g]	Z	129—130			92	$C_{10}H_{10}BNO_4S$ [h]	48.2	4.2	12.4	47.8	4.0	12.75
(2e) [i]	Y	102—103			93	$C_{14}H_{13}BO_2S$	65.7	5.2	12.6	65.65	5.1	12.5
(2e) [j]	Y	134—135			89	$C_{11}H_{13}BO_2S$	61.0	5.85	14.7	60.05	5.95	14.55
(1)	AcOH	277—278.5			44	$C_{11}H_{11}BO_4S$	52.4	4.5	12.7	52.8	4.4	12.8
(4b)	C_6H_6–X	82—83.5			82		43.6	5.5	14.4	43.6	5.5	14.5
(5b)	Et_2O–X	64—66			64	$C_8H_{12}O_5S$	43.6	5.5	14.5			
(6b)	C_6H_6–X	104.5—107			54		43.6	5.6				
(4c)	MeOH	138—139			99	$C_{18}H_{16}O_5S$	62.9	5.0	9.3	62.75	4.7	9.3
(4d)	DMF–MeOH	152—152.5 [k]			90		24.7	4.1	32.9	24.65	4.1	32.9
(5d)	MeOH	120.5—121.5			48	$C_6H_{12}O_7S_3$	24.5	4.1	33.0			
(5e)	C_6H_6–X	143—145	6.3—6.8 [c]	4.4 [c]	91		54.2	5.2	14.5	54.05	4.95	14.4
(6e)	$CHCl_3$–X	233—235	6.3—6.6 [f] 6.9—7.3 [f]	4.9 [f]	74	$C_{10}H_{11}BO_3S$	53.5	5.1	14.3			
(5e) [g]	C_6H_6	185—187			89	$C_{10}H_{10}BNO_5S$ [l]	45.5	4.0	11.2	44.95	3.7	12.0
(6e) [i]	MeOH	214.5—216.5			89	$C_{14}H_{13}BO_3S$	62.3	5.0	11.3	61.8	4.8	11.8
(5f)	MeOH	159—161 [m,n]			35		37.2	3.8	19.7	37.0	3.7	19.75
(6f)	MeOH	160—161 [m,o]			47	$C_5H_6O_4S$	37.0	3.7	19.3			

[a] X, Y, and Z refer to light petroleum of b.p. 40—60, 60—80 and 80—100 °C respectively; DMF refers to $Me_2N{\cdot}CHO$. [b] Starting material (35%) recovered. [c] In $CDCl_3$; multiplets. [d] Sulphone. [e] Depressed to 207° with sulphoxide (6e). [f] In $(CD_3)_2SO$; multiplets. [g] With *m*-nitro-substituent. [h] Found: N, 5.6. Required: N, 5.6%. [i] With α-naphthyl for phenyl. [j] With *p*-methyl substituent. [k] Lit.,[31] m.p. 159—160°. [l] Found: N, 5.1. Required: N, 5.2%. [m] Variable; with decomp. [n] $\nu_{max.}$ 1 230 cm^{-1} [not for (6f)]. [o] $\nu_{max.}$ 882, 820, and 675 cm^{-1} [not for (5f)].

it dissolved. Next day the solution was worked up as follows:

(i) *From the* trans-*diol* (4a). After pouring on ice, the product was extracted with chloroform, washed ($NaHCO_3$ solution), and dried. Replacement of the solvent by light petroleum (25 ml) yielded the crystalline *ester* (4b).

(ii) *From the* cis-*diol* (5a). The solution was shaken vigorously with light petroleum (3 × 50 ml) and the insoluble portion taken up in ether. Treatment with charcoal, concentration (120 ml), and addition of light petroleum (70 ml) yielded the *diacetate* (5b).

(iii) *From the* cis-*diol* (6a). After similar shaking with light petroleum, the *product* (6b) was extracted into boiling benzene, gradually crystallising after evaporation.

Bismethanesulphonates. Oxidation by peroxide–acetic acid of the *trans*-sulphide [31] (3d) at 80 °C gave the ester (4d); treatment of the *cis*-sulphide (2d) in this way gave (84%) a mixture, m.p. 107—112°, of isomers not separated by fractional crystallisation. When sodium periodate (1 mmol) in water (10 ml) was used as oxidant, the solution was kept for 7 days at 3 °C with the *cis*-sulphide (1 mmol) in acetone (17 ml). Filtration, evaporation below 30 °C, extraction with chloroform (4 × 10 ml), and two recrystallisations gave essentially pure *oxide* (142 mg, 48%), m.p. 118.5—120°. This isomer, probably (5d), is the major component in the peroxide oxidation product.

Dibenzoates. These were obtained from the sulphides and peroxide–acetic acid at 80 °C.[31]

Arylboronates. Addition of the β-oxide (6a) (1.5 mmol) to phenylboronic acid (183 mg, 1.5 mmol) in water (3.5 ml) precipitated the *derivative* (6e). Similarly, by mixing an aqueous solution of the same diol (68 mg) with a methanolic solution of α-naphthylboronic acid (86 mg) the α-*naphthylboronate* was obtained. The phenylboronate (5e) and m-*nitrophenylboronate* of the α-oxide (5a) do not separate from aqueous solutions but their preparation was smoothly effected by refluxing equimolar amounts of the reagents in benzene in a Dean–Stark apparatus.

Carbonates. The method given for esterifying the sulphide (2a) yielded the *carbonates* (5f) and (6f). The derivatives did not separate but were isolated by immediately adjusting to 5 the pH of the mixture, evaporating, and extracting with boiling acetone.

Oxidation of the sulphide (2f) with peroxide–acetic acid at 80 °C,[31] followed by fractional crystallisation of the oxide mixture from acetonitrile, then methanol, gave the β-isomer (6f) (8%). The α-oxide moves much faster than the β- on t.l.c. (4 : 1 chloroform–methanol).

Recovery of the Diol (5a) *from its Phenylboronate* (5e).—The ester (444 mg, 2 mmol) in dry ($MgSO_4$) acetone (15 ml) was treated with propane-1,3-diol (0.15 ml, 2 mmol). Crystals of the diol (5a) (155 mg, 57%), m.p. 100—103.5°, gradually separated. More (111 mg, 41%), m.p. 93—103°, was obtained by evaporation of the acetone solution and trituration with light petroleum.

p-*Dihydroxyborylbenzoic Acid.*—Oxidation of *p*-tolylboronic acid (1.36 g, 10 mmol) with alkaline potassium permanganate [32] for reaction times varying from 70 min to 6 h gave material (1.1—1.2 g) of m.p. 295—318° (decomp.). Recrystallisation from water raised the m.p. to 309—311° (decomp.) (Found: C, 54.2; H, 5.35. Calc. for $C_7H_7BO_4$: C, 50.6; H, 4.2%) (lit.,[32] m.p. 225°; lit.,[33] 240°). A little unchanged *p*-tolylboronic acid (lit.,[32] m.p. 253—254°) is present, since treatment of the crude product with the diol (2a) gave, in addition to the *p*-carboxy-ester (1) (44%), some of the *p*-methyl ester (14%). Since in every experiment the oxidant was entirely consumed, some oxidation at boron has also taken place.

p-*Carboxyphenylboronate of* 2,2-*Dimethylpropane*-1,3-*diol.*—The *derivative* (60 mg, 26%), m.p. 209—216.5° (with sublimation), was obtained when the product which separated on addition of the diol (104 mg, 1 mmol) to a hot, aqueous solution of crude *p*-dihydroxyborylbenzoic acid (166 mg, 10 ml) was recrystallised from acetonitrile. A further recrystallisation raised the m.p. to 229—231.5° (Found: C, 61.8; H, 6.9. $C_{12}H_{15}BO_4$ requires C, 61.5; H, 6.4%).

Optically Active Salts of the Ester (1).—The ester (40 mg, 0.16 mmol) and (−)-ephedrine (26.4 mg, 0.16 mmol) were heated at 100 °C in nitromethane (2.5 ml) until complete dissolution (*ca.* 5 min). Cooling caused deposition of crystals of the *salt* (57.5 mg, 87%), m.p. 169.5—170.5° (from nitromethane); $[\alpha]_D^{23}$ −19.6° (*c* 1.2 in EtOH) (Found: C, 60.1; H, 6.6; N, 3.5; S, 7.4. $C_{21}H_{26}BNO_5S$ requires C, 60.7; H, 6.3; N, 3.4; S, 7.7%). The (−)-α-*phenylethylamine salt* (90%), m.p. 275—279° (decomp. with sublimation) was also obtained in nitromethane (60 ml per mmol) (Found: C, 60.9; H, 6.0; N, 3.55; S, 8.6 $C_{19}H_{22}BNO_4S$ requires C, 61.4; H, 5.9; N, 3.8; S, 8.6%). It was too insoluble in the usual organic solvents for measurement of its specific rotation. An aqueous solution was obtained with heating but this had almost zero rotation, indicating some decomposition

Action of Hydrogen Peroxide on the Phenylboronate (2e).—The ester (206 mg, 1 mmol) in acetic acid (2 ml) was treated with hydrogen peroxide (0.57 ml, 5 mmol). When the exothermic reaction had ceased the mixture was refluxed (40 min; peroxide now absent) and evaporated, and the red, solid residue recrystallised from ethanol to yield *cis*-thiolan-3,4-diol 1,1-dioxide (107 mg, 70%), m.p. 123—126°.

Pummerer Rearrangement (*Table* 2).—The sulphoxide was treated with freshly distilled acetic anhydride under appropriate conditions (A—E). In A, refluxing and stirring in anhydride (35 equiv) with sodium acetate (3 equiv) proceeded for 3 h, and if the sulphoxide contained free hydroxy-groups, an additional period (30 min), during which the solvent was brought to the b.p., was allowed for *O*-acetylation; in B, the solution in anhydride (6—7 equiv.) was heated at 100 °C for 18 h; in C, the sulphoxide (5 mmol) and anhydride (5.5 mmol) were refluxed in dry benzene (1—2 ml); in D, the powdered sulphoxide and anhydride (4 equiv.) were warmed at 40 °C for 5 h; in E, they were kept for 3 days at room temperature.

After the reaction the mixture was evaporated (see however footnote *g*, Table 2) and the crude product recrystallised after extraction from any sodium acetate with benzene. Oxidation of the sulphide (2a) followed by boronation (in benzene) and rearrangement to (9) (71% overall yield) can be performed without purification of intermediates; the dibenzoate (7c) was similarly obtained in 44% overall yield.

1-O-*Acetyl*-4-*thio*-DL-*erythrofuranose* 2,3-*Phenylboronate* S-*Oxide.*—The ester (9) (528 mg, 2 mmol) in methylene chloride (10 ml) was treated dropwise at 0—2 °C with a solution of *m*-chloroperbenzoic acid (85%; 406 mg, 2 mmol) in methylene chloride (10 ml). The solution was kept for 1.5 h at 3 °C and for 24 h at room temperature, shaken with aqueous sodium hydrogen carbonate (2 × 10 ml), dried

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[33] B. Bettman, G. E. K. Branch, and D. L. Yabroff, *J. Amer. Chem. Soc.*, 1934, **56**, 1865.

($MgSO_4$), and evaporated. The residue (163 mg), smelling of phenol, was recrystallised from 1 : 9 chloroform–light petroleum to give the *oxide* (66 mg, 12%), m.p. 177—185°. The sample for analysis had m.p. 186—187.5° (Found: C, 51.7; H, 4.9; S, 11.4. $C_{12}H_{13}BO_5S$ requires C, 51.4; H, 4.6; S, 11.4%).

In a similar experiment (4 mmol scale) the product was separated from *m*-chlorobenzoic acid by extraction of the evaporated reaction mixture with water (4 × 20 ml) and recrystallised from chloroform–light petroleum; the material (756 mg) was then subjected to Pummerer rearrangement conditions C (17 h). The product extracted by benzene was triturated with light petroleum and recrystallised from methanol. Chromatography of the mother liquors on silica gel (ether) slightly increased the yield of a *diacetoxythiolan-2,3-diol phenylboronate* (57 mg in all), m.p. 186.5—189° (Found: C, 52.5; H, 4.5; S, 10.8. $C_{14}H_{15}BO_6S$ requires C, 52.2; H, 4.7; S, 10.0%).

S-*Oxides of* cis- *and* trans-1-O-*Acetyl*-4-*thio*-DL-*erythrofuranose* 2,3-*Carbonate*.—The *cis*-acetate (7f) (612 mg, 3 mmol) was oxidised at 80 °C [31] with hydrogen peroxide–acetic acid. Reaction was complete after 1 h in a bath at 90 °C. Evaporation followed by trituration with methanol (2 ml) gave the *oxide* (469 mg, 71%), m.p. 138—143°. The analytical sample had m.p. 144—145.5° (from methanol) (Found: C, 37.9; H, 3.8; S, 14.5. $C_7H_8O_6S$ requires C, 38.2; H, 3.6; S, 14.5%). An isomeric *oxide* (70%; m.p. 143—148°) was similarly obtained from the *trans*-acetate (10). Recrystallisation from methanol raised the m.p. to 149.5—151.5° (Found: C, 38.5; H, 3.8; S, 14.4%).

1,2,3-*Tri*-O-*acetyl*-4-*thio*-DL-*threofuranose* SS-*Dioxide*.—The sulphide (8b) (262 mg, 1 mmol) in acetic acid (3.3 ml) was oxidised during 2 days with hydrogen peroxide (1.33 ml). Water (16 ml) was added and the product extracted with chloroform and recrystallised from 1 : 1 benzene–light petroleum to give the *sulphone* (169 mg, 57%), m.p. 124—127° (Found: C, 40.6; H, 4.7; S, 10.8. $C_{10}H_{14}O_8S$ requires C, 40.8; H, 4.8; S, 10.9%).

1,2,3-*Tri*-O-*acetyl*-4-*thio*-DL-*erythrofuranose* SS-*Dioxide*.—The *sulphone* (103 mg, 70%), m.p. 168—170° (from methanol), was obtained by the above procedure from the sulphide (7b) (131 mg, 0.5 mmol) (Found: C, 41.0; H, 4.8; S, 11.0%).

Reaction of t-Butyl Perbenzoate with Esters of the Diol (2a).—(a) *Phenylboronate* (2e). The ester (412 mg, 2 mmol), t-butyl perbenzoate (0.35 ml, 2 mmol), copper(I) bromide (574 mg), and dry benzene (10 ml) were refluxed (6 h; bath at 90 °C) with stirring. The cooled mixture was filtered, shaken with aqueous sodium hydrogen carbonate, treated with charcoal, dried, and evaporated to a syrup almost totally soluble in hot light petroleum (b.p. 60—80 °C). It was chromatographed (chloroform) on a column of silica gel (21 g), and fractions 1—4, eluted by chloroform (120 ml), were recrystallised twice from light petroleum (b.p. 60—80°) to give 1-O-*benzoyl*-4-*thio*-DL-*erythrofuranose* 2,3-*phenylboronate* (36 mg), m.p. 131—132° (Found: C, 62.9; H, 4.7; S, 9.7. $C_{17}H_{15}BO_4S$ requires C, 62.6; H, 4.6; S, 9.8%).

(b) *Carbonate* (2f). Chromatography of a chloroform solution (7 mmol) obtained as above yielded (fractions 18—22, eluted by chloroform) a product (43 mg), m.p. 85—97° (from benzene–light petroleum). Crystallisation from methanol afforded 1-O-*benzoyl*-4-*thio*-DL-*erythrofuranose* 2,3-*carbonate*, m.p. 107—109° (Found: C, 54.5; H, 3.8; S, 12.0. $C_{12}H_{10}O_5S$ requires C, 54.1; H, 3.8; S, 12.0%); $\nu_{max.}$ 1825 and 1724 cm^{-1}.

Reaction of (*Diacetoxyiodo*)*benzene with Esters of the Diol* (2a).—(a) *Phenylboronate* (2e). The ester (1.03 g, 5 mmol) and (diacetoxyiodo)benzene (1.77 g, 5.5 mmol) were refluxed (4 h) in dry benzene (4 ml). The mixture was evaporated, and the residual syrup repeatedly extracted with hot light

TABLE 2

Pummerer rearrangements

Starting material	Conditions	Product	τ [a] (H-1)	$J_{1,2}$/Hz	Yield (%)	Cryst. solvent [b]	M.p. (°C)	Formula	Found (%) C	Found (%) H	Found (%) S	Required (%) C	Required (%) H	Required (%) S
(5b)	C [c]	(7b) [d]	4.12 (d)	2	16	MeOH–H_2O	103—104	$C_{10}H_{14}O_6S$	45.4	5.4	12.1	45.8	5.3	12.2
(5a)	A	(7b)			61									
(4b)	C [e]	(8b) [f]	3.83 (d)	4	20	C_6H_6–X	84.5—85.5		46.0	5.3	12.2			
(4a)	A	(8b)			21									
(5d) + (6d)	D	(7d) [g]	4.09 (d) [h]	3	44	MeOH	106—106.5	$C_8H_{14}O_8S_3$	28.6	4.3	29.0	28.7	4.2	28.7
(5d) + (6d)	E	(7d) [i]			43									
(4d)	C [j]	(8d) [k]	3.99 (q) [h]	2	15	MeOH	103—104		29.2	4.4	28.6			
(5c) + (6c)	A	(7c)	3.87 (d)	2	48	MeOH	113.5—115.5	$C_{20}H_{18}O_6S$	61.9	4.6	8.3	62.2	4.7	8.3
(4c)	A	(8c) [l]	3.55 (d) 3.70 (d)	4 2	81	MeOH or Y	101—103		62.1	4.8	8.2			
(5e)	C [m]	(9) [n]	3.85 (s)		60—70	MeOH or Z	115—116.5	$C_{12}H_{13}BO_4S$	55.0	5.15	12.1	54.6	4.9	12.1
(5e)	A	(7b) [d]			27									
(6e)	C [m]	(9)			55									
(5f)	B	(7f)	3.56 (d)	4.5	72	MeOH	137—138.5	$C_7H_8O_5S$	41.4	4.1	15.7	41.2	3.9	15.7
(5f)	B	(10)	3.79 (s)		42	MeOH	79.5—81		40.8	4.0	15.2			
(6f)	B	(7f)			53									
(5f) + (6f) [o]	B	(7f) + (10)			39+ 17									
(5f) + (6f)	A	(7f)			9.5									
Oxide of (7f)	B	(11)	3.6 (dd)		62	MeOH	149.5—151.5	$C_9H_{10}O_7S$	41.0	3.8	12.1	41.2	3.8	12.2
Oxide of (10)	B	(12)	3.7 (s)		56	MeOH	222.5—225		41.2	4.0	12.1			

[a] In $CDCl_3$ except as indicated. [b] X, Y, and Z as in Table 1. [c] 4 h. [d] Crude product triturated with water. [e] 7 h. [f] Extracted with boiling Y. [g] Filtered off after cooled mixture diluted with benzene (2—3 volumes); evaporation deleterious. [h] In $(CD_3)_2SO$. [i] Mixture filtered from a trace of crystals (m.p. 200 °C) and evaporated as usual. [j] 15 min. [k] Required several recrystallisations. [l] 1 : 1 Mixture of isomers. [m] 20 h. [n] Extracted with boiling Z (100 ml; 30 mmol scale). [o] From sulphide by peroxide–acetic acid (80 °C), or *m*-chloroperbenzoic acid in methylene chloride (10 min at 0 °C; then 18 h at 15 °C).

petroleum (b.p. 80—100 °C) to yield the ester (9) (122 mg, 9%), m.p. 102—110°.

(b) *Carbonate* (2f). The carbonate (730 mg, 5 mmol) was treated (16 h) as above. The evaporated mixture was extracted with boiling light petroleum (4 × 10 ml) and the insoluble residue recrystallised (charcoal) from methanol (1.5 ml) to give the acetate (10) (281 mg, 27.5%), m.p. 68—78° (pure by t.l.c. in 9 : 1 benzene–methanol).

meso-*Tartaraldehyde Bis*-(2,4-*dinitrophenylhydrazone*).—A solution of the diacetate (12) (86 mg) in chloroform (5 ml) was shaken (5 min) with N-sodium hydroxide (1.6 ml). The aqueous layer was quickly added to methanolic 2,4-dinitrophenylhydrazine sulphate. Hydrogen sulphide was evolved and an orange solid (51.5 mg, 33%) separated. Starting material (55%) was recovered from the chloroform layer. The product deteriorated when heated in various solvents, but recrystallisation at room temperature from dimethylformamide–water gave a 1 : 1 dimethylformamide solvate. After freeing from solvent at 110 °C *in vacuo* the *derivative* had m.p. 213.5° (decomp.) (Found: C, 40.4; H, 2.7; N, 23.2. $C_{16}H_{14}N_8O_{10}$ requires C, 40.2; H, 2.9; N, 23.4%). It was also obtained by this procedure from the isomeric diacetate (11).

2,6-Diacetoxy-1,4-dithian 4,4-dioxide [24] when refluxed (3 h) with methanolic 2,4-dinitrophenylhydrazine sulphate yielded 3-thiaglutaraldehyde 3,3-dioxide bis-(2,4-dinitrophenylhydrazone) (57%), m.p. 224—230°.[24] Under the same conditions, the diacetate (12) afforded a negligible amount of product.

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