Thio-sugars. Part 2.[1] Glycosides from Acid-catalysed Reactions of 1-*O*-Acetyl-2,3-di-*O*-acyl-4-thiotetrofuranoses

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Alcohols and thiols in presence of toluene-*p*-sulphonic acid readily displace the 1-*O*-acetyl group from the title compounds, now available by Pummerer rearrangement of the appropriate sulphoxides, thus providing a very convenient synthesis of these thio-sugar glycosides. Glycosyl bromides can also be prepared. The advantages of the phenylboronate function described in Part 1 are further illustrated. *O*-Glycosides are formed with a high degree of stereoselectivity. *S*-glycosides are not. Toluene-ω-thiols with electron-repelling substituents react normally, but the corresponding alcohols are acetylated rather than glycosylated. A disaccharide (glycosyl glycoside) has been prepared. Other esters give lower yields of glycosides than the phenylboronates. The reactions with hydrazides of the substituted 3-heteraglutaraldehydes from periodate oxidation of some of these glycosides and related nucleosides were compared with earlier examples.

MOST reported displacements at the anomeric carbon atom of sugars having a ring sulphur atom are either Fischer glycosidations or lead from halides to glycosides (Koenigs–Knorr reactions, with acid acceptor present) or nucleosides.[2] Such halides are less reactive [3] than those from ordinary sugars, and an alternative synthetic

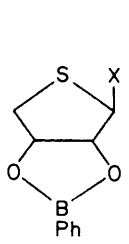
[1] Part I, J. E. McCormick and R. S. McElhinney, *J.C.S. Perkin I*, 1976, 2533.

[2] H. Paulsen and K. Todt, *Adv. Carbohydrate Chem.*, 1968., **23**, 206; M. Bobek, A. Bloch, R. Parthasarathy, and R. L. Whistler, *J. Medicin. Chem.*, 1975, **18**, 784. See however N. Ototani and R. L. Whistler, *ibid.*, 1974, **17**, 535; R. G. S. Ritchie and W. A. Szarek, *J.C.S. Chem. Comm.*, 1973, 686.

[3] R. L. Whistler and T. van Es, *J. Org. Chem.*, 1963, **28**, 2303.

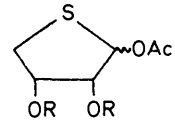
procedure would be useful. We now describe some simple but efficient transformations of 1-*O*-acetyl-4-thiotetrofuranose derivatives, representing the fourth step in the four-stage scheme outlined in Part 1.[1]

An attempt to illustrate the masked aldehyde nature of the Pummerer rearrangement product (1a) involved its treatment with 2,4-dinitrophenylhydrazine in hot methanolic sulphuric acid, in the expectation that both the furanose and boronate ester rings would be ruptured. Neither was, and only the crystalline methyl erythroside (1c) was isolated.

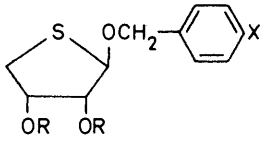


(1)

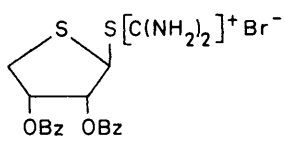
a; X = OAc
b; X = Br
c; X = OMe
d; X = OPr^i
e; X = O(cyclohexyl)
f; X = OCH_2CH_2N(phthaloyl)
g; X = OCH_2Ph
h; X = $OCH_2{\cdot}C_6H_4Cl-4$
i; X = $OCH_2{\cdot}C_6H_4NO_2-4$
j; X = $OCH_2{\cdot}C_6H_4(CH_2OR)-4$ } where RX = (1)
k; X = OR
m; X = $OC_6H_4NO_2-4$
n; X = SPr^i
p; X = SCH_2Ph
q; X = $SCH_2{\cdot}C_6H_3(OCH_2O)-3,4$
r; X = $S[C(NH_2)_2]^+Br^-$



(2) a; R = Ac
b; R = Bz
c; R = SO_2Me

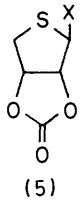


(3)



(4)

	R	X
a;	H	H
b;	H	NO_2
c;	Ac	NO_2
d;	Bz	NO_2
e;	$MeSO_2$	NO_2



(5)

a; X = OAc
b; X = $OCH_2{\cdot}C_6H_4NO_2-4$
c; X = $OCH_2{\cdot}C_6H_4Cl-4$
d; X = Br
e; X = SPr^i

This glycoside and its isopropyl analogue (1d) were formed (*ca.* 85%) when the acetate (1a) was refluxed briefly in the alcohol with a little toluene-*p*-sulphonic acid. As with the formation of the acetate (1a), the stereoselectivity is noteworthy and the configuration *trans* to the boronate ring retained, the anomeric proton producing a singlet (τ 4.77) in the n.m.r. spectrum. Even alcohols (1 equiv.) in chloroform gave erythrosides (1e—j) in good yield. *p*-Nitrophenol yielded the aryl glycoside (1m), but crystalline derivatives could be obtained from neither phenol nor t-butyl alcohol. Deboronation using propane-1,3-diol readily gave the free glycosides, *e.g.* (3a and b).

Displacement by thiols is much less stereoselective than by alcohols and both anomers are formed, in about equal proportions. They were isolated in the case of propane-2-thiol, the *cis* (n.m.r. doublet for H-1 at τ 5.67, $J_{1,2}$ 5 Hz) first by fractional crystallisation, and the more soluble *trans* (1n) (singlet at τ 5.39) by chromatography on silica. A substantial amount of *cis*-product in addition to the usual *trans* might arise through a stronger transannular influence of boron on the incoming sulphur group than on oxygen. There is apparently no marked difference between the rate of anomerisation in the presence of acid of acetylated alkyl 1-thio-α-D-glucopyranosides and that of their oxygen counterparts.[4]

Although 3,4-methylenedioxytoluene-ω-thiol behaves like other thiols towards the acetate (1a), yielding an anomeric mixture from which the *trans*-isomer (1q) was isolated, no *O*-erythroside can be obtained from the corresponding alcohol (piperonyl alcohol). It seems that this alcohol forms a carbocation much faster than does the erythrose C-1 ester. The only piperonyl compound isolated was the acetate, and the sugar residue was recovered as a disaccharide derivative (1k) of the glycosyl glycoside or trehalose type, which can be prepared in similar moderate yield in the absence of the alcohol. [Poor solubility retards the deboronation of this ester, but the tetraol (7) was eventually obtained satisfactorily.]

Since the acetate (1a) reacts readily with the secondary alcohols propan-2-ol and cyclohexanol, it was hoped that reaction with (—)-menthol would afford a means of resolving the DL-erythrose residue. However, no crystalline glycoside was isolated. The 2,4-phenylboronate of benzyl β-D-xylopyranoside contains a reactive, hydrogen-bonded hydroxy-group, and has been used successfully in disaccharide synthesis.[5] In the present work, the product of the reaction of this compound with the ester (1a) was chromatographed and the fractions were monitored polarimetrically. However, only a little of the relatively insoluble (optically inactive) disaccharide phenylboronate (1k) was obtained.

The ready preparation of single glycoside anomers in high yield from acetates is unusual. Prolonged alcoholysis in alcohol–chloroform of β-D-glucopyranose penta-acetate catalysed by toluene-*p*-sulphonic acid yields the deacylated α- and β- (3 : 1) glucosides.[6] Earlier, Lemieux[7] showed that alcohols and thiols displace a 1-acetoxy-group in certain hexopyranoses with tin(IV) chloride as catalyst. The stereoselective replacement of benzoyloxy- by phenylthio-groups in *s*-trithians has recently been described.[8]

The stability to acid of the boronate ring in the acetate (1a) was further exemplified by its conversion into the

[4] B. Erbing and B. Lindberg, *Acta Chem. Scand.* (*B*), 1976, **30**, 611.
[5] R. J. Ferrier and D. Prasad, *J. Chem Soc.*, 1965, 7429.
[6] R. E. Wing and J. N. BeMiller, *Carbohydrate Res.*, 1969, **10**, 441.
[7] R. U. Lemieux, *Canad. J. Chem.*, 1951, **29**, 1079; R. U. Lemieux and W. P. Shyluk, *ibid.*, 1953, **31**, 528; R. U. Lemieux, *Adv. Carbohydrate Chem.*, 1954, **9**, 9, 29, 53.
[8] T. Sugawara, H. Iwamura, and M. Ōki, *Tetrahedron Letters*, 1975, 879.

stable, crystalline *trans*-bromide (1b). In this connection, trifluoroacetic anhydride [9] is a very convenient Pummerer reagent for the sulphoxide precursor [1] of the acetate (1a), since the intermediate trifluoroacetate is formed rapidly and yields the bromide (1b) without isolation. That the anhydride is necessary is shown by the effect of hydrogen bromide in acetic acid directly on the sulphoxide: deoxygenation quickly occurs, giving the corresponding sulphide, and the α-carbon atom is unaffected. In certain aromatic systems, hydrogen bromide interacts with the sulphoxide function to yield a bromoaryl sulphide.[10]

The reactions of sugar bromides under acidic conditions were studied in some detail by Fletcher and his co-workers about 25 years ago,[11] but little attention has been paid since. Although polyacetates were partially deacylated, the benzoates were very useful and afforded glycosides in high yield in situations where conventional Koenigs–Knorr reactions using silver carbonate were unsatisfactory. The thio-sugar bromide (1b) proved less reactive towards alcohols than the acetate (1a) (Table 2), especially in the absence of catalyst.

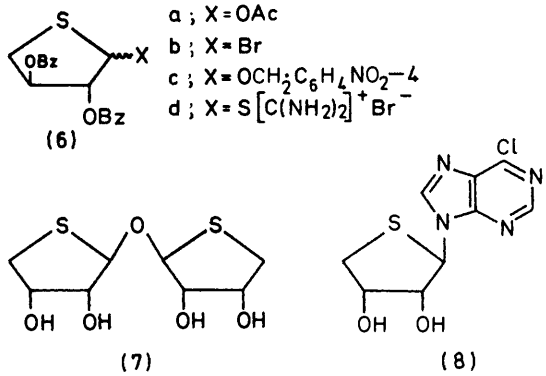
The bromide readily yields (84%) an isothiouronium salt which is apparently homogeneous, although the n.m.r. spectrum is difficult to interpret. The absence of any recognisable doublet for H-1 indicates the *trans*-configuration (1r), the singlet at τ 6.64 possibly being the relevant signal. The stereochemistry of the reaction is thus different from that of the reaction between thiols and the acetate (1a). Attempts to convert [12] the salt into thioglycosides such as (1p) have not so far been successful.

The phenylboronate group in (1a) was compared with other [1] protecting groups. The triacetate (2a), dibenzoate (2b), and bismethanesulphonate (2c) can be converted into the *p*-nitrobenzyl derivatives (3c—e) in *ca.* 30% yield (Table 2) and no other products were isolated; longer reaction times or replacing toluene-*p*-sulphonic acid by tin(IV) chloride did not improve the yields. These products must have the anomeric group *trans* to the ester groups since all were also obtained by esterification of *p*-nitrobenzyl *trans*-4-thioerythrofuranoside (3b). The n.m.r. signal due to the benzylic methylene group in the bismethanesulphonate (3e) is a singlet (τ 5.20), in contrast to the quartet observed in the dibenzoate (3d) (τ 5.23) and in the bicyclic systems (1g) and (5b). [The close analogues (1p) and (1q) with bulky exocyclic sulphur atoms have singlets at τ 6.07 and 6.19, respectively.]

The assignment of anomeric configuration based on the value of $J_{1,2}$ is, from the evidence at hand, satisfactory with the relatively rigid bicyclic systems. In cases where pairs of isomers were available, *trans*-compounds simply showed a singlet and *cis*-compounds a doublet ($J_{1,2}$ 3.5—5 Hz). A similar situation has been established for 2,3-*O*-isopropylidene derivatives.[13] However values of 0—8 Hz are possible [14] for *trans*-compounds in monocyclic systems, and the erythrosides (3d and e) show doublets in the 1.5—3 Hz range. The values for the corresponding 1-acetates (2a—c) are in the same range, and their assignment [1] as all-*cis*-compounds must be in doubt.

The carbonate acetate (5a) and its anomer gave the *p*-nitrobenzyl glycoside (5b) in higher yield (45—55%) than was attained in comparable transformations of the esters (2a—c). The *trans*-configuration of (5b) was confirmed by its synthesis from diphenyl carbonate and the diol (3b). *p*-Chlorobenzyl alcohol and propane-2-thiol also reacted readily, and, as in reaction with the phenylboronate (1a), two isomeric isopropyl thioglycosides, (5e) and its anomer, were isolated (identified by their $J_{1,2}$ values). A *trans*-bromide carbonate (5d) was isolated, but no crystalline bromides were obtained from the monocyclic esters (2a—c). However the product from the dibenzoate (2b) gave an isothiouronium salt with n.m.r. spectrum similar to that of the phenylboronate (1r), and probably of *trans*-configuration (4).

In the 4-thiothreose series, the anomeric mixture [1] of dibenzoate 1-acetates (6a) from the Pummerer rearrangement gave a crystalline bromide (6b). This is a mixture of anomers, but the derived (77%) isothiouronium salt (6d) again seems to be homogeneous. As in the erythrose derivative (4), H-2 and H-3 give coincident n.m.r.



singlets (τ 4.08), suggesting that H-1 is *trans* to H-2. The mixed bromide (6b) yields both *p*-nitrobenzyl threoside anomers, one of which was isolated. This

[9] N. Finch and C. W. Gemenden, *J. Org. Chem.*, 1975, **40**, 569; S. L. Huang, K. Omura, and D. Swern, *ibid.*, 1976, **41**, 3329; R. Tanikaga, Y. Yabuki, N. Ono, and A. Kaji, *Tetrahedron Letters*, 1976, 2257.

[10] H. Gilman and D. R. Swayampati, *J. Amer. Chem. Soc.* 1955, **77**, 5944. *Cf.* G. V. Kaiser, R. D. G. Cooper, R. E. Koehler, C. F. Murphy, J. A. Webber, I. G. Wright, and E. M. van Heyningen, *J. Org. Chem.*, 1970, **35**, 2430.

[11] R. K. Ness, H. G. Fletcher, jun., and C. S. Hudson, *J. Amer. Chem. Soc.*, 1951, **73**, 959 and papers cited therein. *Cf.* W. W. Zorbach and T. A. Payne, *ibid.*, 1960, **82**, 4979.

[12] F. M. Delmotte and M. L. P. Monsigny, *Carbohydrate Res.*, 1974, **36**, 219; K. L. Matta, R. N. Girotra, and J. J. Barlow, *ibid.*, 1975, **43**, 101.

[13] N. J. Leonard and R. A. Laursen, *J. Amer. Chem. Soc.*, 1963, **85**, 2026; H. Maehr, T. H. Williams, M. Leach, and A. Stempel, *Helv. Chim. Acta*, 1974, **57**, 212; S. de Bernardo and M. Weigele, *J. Org. Chem.*, 1976, **41**, 287.

[14] R. L. Tolman, R. K. Robins, and L. B. Townsend, *J. Heterocyclic Chem.*, 1967, **4**, 230; R. J. Rousseau, R. K. Robins, and L. B. Townsend, *ibid.*, p. 311; J. A. Montgomery and H. J. Thomas, *J. Org. Chem.*, 1971, **36**, 1962. *Cf.* J. D. Stevens and H. G. Fletcher, jun., *ibid.*, 1968, **33**, 1799.

shows a doublet for H-1 at τ 4.65 with $J_{1,2}$ 2 Hz and probably has H-1 *trans* to H-2 since H-1 for the other

TABLE 1

Reactions of 3-heteraglutaraldehydes (9) with hydrazides

X	R	Product	Ref.
O	H	(10) or (11)	16*b*
O	OCH_2Ph	(11)	16*a*
O	Uracil-1-yl	(11)	17
ArN	H	(10)	16*b*
S	H	(10)	†
S	OCH_2Ph	(10)	
S	6-Chloropurin-9-yl	(11)	

† V. C. Barry, M. L. Conalty, J. E. McCormick, R. S. McElhinney, M. R. McInerney, and J. F. O'Sullivan, *J. Medicin. Chem.*, 1970, **13**, 421.

acetate); using tin(IV) chloride, *p*-nitrobenzyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (41%) was isolated. When the reaction does work in the sulphur series it is particularly convenient, since the required 1-*O*-acetates are formed directly by Pummerer rearrangement.

The reactions of the periodate oxidation products of the glycoside (3a) and the nucleoside (8) [15] are of some interest. We have found [16] (Table 1) that when 3-heteraglutaraldehydes (9) react with a hydrazide, one product only [(10) or (11)] can be isolated, irrespective of the molecular proportions of reactants, except in the case of 3-oxaglutaraldehyde. Oxidation of the now available benzyl 4-thioerythrofuranoside (3a) yielded

TABLE 2

2,3-Di-*O*-acyl-4-thio-DL-tetrofuranosides and -1,4-dithio-DL-tetrofuranosides

Compd.	Yield [a,b] (%)	Cryst. solvent	M.p. (°C)	τ[c](H-1)	Formula	Found(%) C	H	N	S	Required (%) C	H	N	S
(1c)	86[d,e](59)	Aq.MeOH	70—71.5		$C_{11}H_{13}BO_3S$	55.9	5.7		13.9	55.9	5.5		13.6
(1d)	85[d]	Aq.MeOH	82—83.5	4.77(s)[f]	$C_{13}H_{17}BO_3S$	59.1	6.7		12.4	59.1	6.4		12.1
(1e)	71	MeOH	99.5—100.5		$C_{16}H_{21}BO_3S$	63.2	7.1		10.4	63.2	6.9		10.5
(1f)	66	EtOH	137—138		$C_{20}H_{18}BNO_5S$	60.6	4.65	3.65	8.1	60.8	4.6	3.55	8.1
(1g)	90	Aq.MeOH	76.5—77	4.78(s)[f]	$C_{17}H_{17}BO_3S$	65.8	5.55		10.5	65.4	5.45		10.3
(1h)	71	EtOH	126—127		$C_{17}H_{16}BClO_3S$[g]	58.8	4.65		9.0	58.9	4.65		9.25
(1i)	74(56[h])	C_6H_6–LP †	152.5—153.5		$C_{17}H_{16}BNO_5S$	56.6	4.4	3.9	9.1	57.1	4.5	3.9	9.0
(1j)	54	EtOAc	196—198		$C_{28}H_{28}B_2O_6S_2$	61.2	5.3		11.6	61.55	5.15		11.75
(1m)	39	C_6H_6	185.5—186.5		$C_{16}H_{14}BNO_5S$	56.5	3.9	4.0	9.0	56.0	4.1	4.1	9.3
(1n)	31[i,j]	Aq.Me_2CO	64.5—66	5.39(s)	$C_{13}H_{17}BO_2S_2$	55.2	6.1		22.9	55.7	6.1		22.9
(1p)	34	Aq.Me_2CO	81—83[k]	5.62(s)	$C_{17}H_{17}BO_2S_2$	62.0	5.1		19.4	62.2	5.2		19.5
(1q)	22	Aq.Me_2CO	109.5—110.5[k]	5.62(s)	$C_{18}H_{17}BO_4S_2$	58.2	4.8		17.0	58.1	4.6		17.25
(3c)	33[l]	Aq.MeOH	89—90.5		$C_{15}H_{17}NO_7S$	50.8	4.95	3.9	8.9	50.7	4.8	3.9	9.0
(3d)	31[m](16)[n]	MeOH	121—122	4.67(d)[o]	$C_{25}H_{21}NO_7S$	62.5	4.4	2.8	6.75	62.6	4.4	2.9	6.7
(3e)	36[p]	MeOH	132.5—134	4.56(d)[f,q]	$C_{13}H_{17}NO_9S_3$	36.3	4.2	3.0	22.7	36.5	4.0	3.3	22.5
(5b)	55[r](6)	MeOH	130—131	4.68(s)	$C_{12}H_{11}NO_6S$	48.0	3.7	4.6	10.8	48.5	3.75	4.7	10.8
(5c)	43	MeOH	109.5—111.5		$C_{12}H_{11}ClO_4S$	50.4	4.0		11.3	50.3	3.8		11.2
(5e)	10[i,s]	$CHCl_3$–LP [x]	68.5—70.5	5.32(s)	$C_8H_{12}O_3S_2$	44.0	5.6		29.4	43.6	5.5		29.1
(6c)	16[t](48)[u]	MeOH, then MeCN	122—123.5[v]	4.65[t](d)[w]	$C_{25}H_{21}NO_7S$	62.4	4.5	3.0	6.7	62.6	4.4	2.9	6.7

[a] Under conditions (*A*) except where indicated. [b] In parentheses, from the bromide. [c] In $CDCl_3$ except as indicated. [d] Conditions (*B*). [e] 82% from (1; X = $O_2C{\cdot}CF_3$). [f] In $(CD_3)_2SO$. [g] Found: Cl, 10.2. Required: Cl, 10.25%. [h] 38% in the absence of a catalyst. [i] Using RSH (3 equiv.). [j] The *cis*-anomer (25%) had m.p. 119.5—121.5° [from light petroleum (b.p. 60—80 °C)] (Found: C, 55.9; H, 6.2; S, 22.9%); τ($CDCl_3$) 5.67 (d, $J_{1,2}$ 5 Hz, H-1). [k] After 3 recrystallisations. [l] 21% under conditions (*C*); 98% from diol (3b) using acetic anhydride–pyridine. [m] 29% under conditions (*C*); 45% from diol (3b) with benzoyl chloride–pyridine. [n] From crude material [o] $J_{1,2}$ 1.5 Hz. [p] 56% from diol (3b) using methanesulphonyl chloride–pyridine. [q] $J_{1,2}$ 3 Hz. [r] From the *cis*-acetate; 44% from the *trans*-acetate (5a); 69% from the diol (3b) using diphenyl carbonate (see Experimental section). [s] The *cis*-anomer (31%) had m.p. 75.5—80 °C (from the same solvents) (Found: C, 43.4; H, 5.55; S, 29.2%); τ($CDCl_3$) 5.63 (d, $J_{1,2}$ 3.5 Hz, H-1). [t] Pure isomer. [u] Mixture of isomers, m.p. 82—115 °C (after 2 recrystallisations from methanol) (Found: C, 62.9; H, 4.4; N, 3.2; S, 6.8%); τ ($CDCl_3$) 4.57 (d, $J_{1,2}$ 7 Hz, H-1) in addition to signals for pure isomer. [v] After 5 recrystallisations. [w] $J_{1,2}$ 2 Hz. [x] Light petroleum

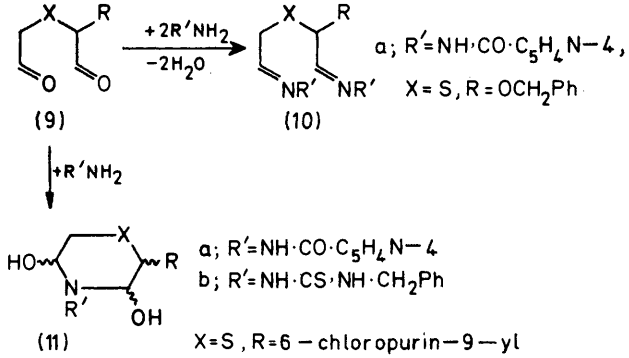
anomer (τ 4.57) has $J_{1,2}$ 7 Hz. The acetate (6a) gives these derivatives in lower yield (the only instance in the present work where bromide was superior to acetate), but an attempt to use the corresponding (unisolated) trifluoroacetate led only to oils.

Preliminary work with some 1-acetates of pyranose thio-sugars indicates that, as for pyranose derivatives with ring oxygen,[7] acid-catalysed glycosidation is not a general reaction. Further, the nature of the catalyst is sometimes critical. With *p*-nitrobenzyl alcohol under our usual conditions using toluene-*p*-sulphonic acid, β-D-glucopyranose penta-acetate merely undergoes partial transesterification (29% recovery; 34% *p*-nitrobenzyl

[15] J. E. McCormick and R. S. McElhinney, *J.C.S. Perkin I*, in the press.

[16] (*a*) J. E. McCormick, *J. Chem. Soc.* (*C*), 1966, 2121; (*b*) V. C. Barry, J. E. McCormick, and R. S. McElhinney, *Carbohydrate Res.*, 1968, **7**, 299.

2-benzyloxy-3-thiaglutaraldehyde which gave bis-hydrazones (10) as the only isolable products. Similar



treatment of the nucleoside (8) however yielded only cyclic compounds (11). This appears to be the normal

reaction with nucleosides,[17,18] overcoming the tendency of the bulky sulphur atom to prevent cyclisation in cases where oxygen permits it. A number of periodate-oxidised nucleosides and derivatives have shown useful anti-tumour activity.[19]

The more complex system (7) consumes periodate (2 mol. equiv.) in the normal way to yield a tetra-aldehyde (T), but this behaves anomalously with hydrazide reagents. When treated with isonicotinic acid hydrazide or 4-methylthiosemicarbazide (4 mol. equiv. of each), it yields products having the composition respectively ($T + 4RNHNH_2 - 2H_2O$) and ($T + 3RNHNH_2 - H_2O$). The latter shows u.v. peaks at 245 and 276 nm, indicating the presence of hydrazide and hydrazone bonds.[16] Several structures involving cyclisation between aldehyde groups numbers 1 and 2, 3 and 4, 2 and 3, or even 1 and 4 are possible.

Direct oxidation of the glycoside (1g) gave a sulphoxide phenylboronate in poor yield. Oxidation of the diol (3a) followed by boronation was preferable. When this compound was treated with acetic anhydride, only the sulphide (1g) was obtained, and not a Pummerer product. A similar sequence of reactions with the acetate (1a) had given a diacetate,[1] with no recovery of (1a). However, the low yields do not permit valid comparisons. Pyrolysis of sulphoxides is complex and can lead to the corresponding sulphides. The transformation of the *S*-oxide of (1g) in acetic anhydride is evidently not a simple thermal effect,[10,20] since it can be recovered in good yield from boiling toluene.

EXPERIMENTAL

The hydrogen bromide–acetic acid used was a 45% w/v solution. Other general conditions were as outlined in Part 1,[1] except that all chromatography was carried out on silica gel.

1-O-*Acetyl*-2,3-*di*-O-*benzoyl*-4-*thio*-DL-*threofuranose* (6a) (with J. O. JONES).—Crystallisation of the Pummerer rearrangement product [1] from benzene gave an isomer (18%), probably 1,2-*trans*, m.p. 138—139.5° (from methanol) (Found: C, 61.8; H, 4.6; S, 8.4%); $\tau(CDCl_3)$ 3.7 (d, $J_{1,2}$ 2 Hz, H-1). Addition of light petroleum (b.p. 60—80 °C) to the mother liquors then afforded (68%) the mixture of anomers as described,[1] which was used for further reaction.

2,3-*Di*-O-*acyl*-4-*thio*-DL-*tetrofuranosides and* -1,4-*dithio*-DL-*tetrofuranosides* (*Table* 2).—(*A*) Equimolar amounts of alcohol (or thiol) and 1-*O*-acetyl-2,3-di-*O*-acyl-4-thio-DL-tetrofuranose (or the corresponding bromide) were refluxed (2 h) in chloroform (alcohol-free; 5 ml $mmol^{-1}$) containing toluene-*p*-sulphonic acid monohydrate ($TsOH,H_2O$) (35 mg $mmol^{-1}$). The resulting mixture was shaken with aqueous sodium hydrogen carbonate, dried ($MgSO_4$; charcoal), and evaporated.

(*B*) The acetate or bromide was refluxed (2 h) in an excess of a volatile alcohol containing $TsOH,H_2O$ (7 mg ml^{-1}). After addition of water and evaporation of alcohol the product crystallised.

(*C*) Anhydrous tin(IV) chloride (0.5 ml $mmol^{-1}$) replaced $TsOH,H_2O$ in conditions (*A*) and reaction was carried out at 40 °C (1 h). In working up, filtration (Celite) facilitated separation of layers.

The crude erythrofuranosides (other than those derived from thiols) usually required only one recrystallisation. After crystallisation of the *cis*-anomer from the condensation product of the acetate (1a) with propane-2-thiol, the *trans*-anomer (1n) was isolated on a column using chloroform–light petroleum. Similarly, the carbonate (5e) and its anomer were separated using chloroform.

The yield of *p*-nitrobenzyl glycoside (1i) was used to assess more accurately the extent of formation of the 1-*O*-acetyl precursors in certain preparations. Thus, while the acetate (1a) (9%) was isolated [1] from *cis*-thiolan-3,4-diol phenylboronate after reaction with (diacetoxyiodo)benzene we have obtained the glycoside (1i) (26% overall) from the crude product. Similarly, the yields of isolated 1-*O*-benzoate (1; X = OBz) and glycoside (1i) after reaction of the phenylboronate with t-butyl perbenzoate were 5.6[1] and 27%, respectively.

4-*Thio*-DL-*erythrofuranosyl* 4-*Thio*-DL-*erythrofuranoside* 2,3;2′,3′-*Bisphenylboronate* (1k).—The acetate (1a) (6.6 g, 25 mmol) was subjected, alone, to conditions (*A*) (see above). The crude product was extracted with hot light petroleum (b.p. 60—80 °C; 5 × 100 ml) and the insoluble, crystalline portion (1.48 g) dissolved in hot acetonitrile (160 ml). Concentration of the solution (40 ml) caused separation of the *bisphenylboronate* (1k) (1.34 g, 25%), m.p. 216—217° (Found: C, 56.0; H, 4.8; S, 15.0. $C_{20}H_{20}B_2O_5S_2$ requires C, 56.4; H, 4.7; S. 15.05%); $\tau(CDCl_3)$ 4.47 (s, H-1).

The derivative (17%) was also isolated when the acetate (1a) (10 mmol) was treated with piperonyl alcohol under conditions (*A*). In addition, the light petroleum-soluble portion of the crude product yielded piperonyl acetate (381 mg, 20%), b.p. 100—108° at 0.15 mmHg, n_D^{19} 1.526 0; i.r. spectrum identical with that of an authentic sample (b.p. 106—107° at 0.4 mmHg, n_D^{19} 1.526 8).

The bisphenylboronate (10%) and triphenylboroxole (3%) were isolated from an attempt to condense the acetate (1a) with benzyl β-D-xylopyranoside 2,4-phenylboronate under conditions (*A*).

p-*Nitrobenzyl Tetra*-O-*acetyl*-β-D-*glucopyranoside*.—Penta-*O*-acetyl-β-D-glucopyranose (390 mg, 1 mmol) was treated with *p*-nitrobenzyl alcohol (153 mg, 1 mmol) under conditions (*A*) (above), but with tin(IV) chloride (0.06 ml, 0.5 mmol) instead of $TsOH,H_2O$. The crude product, after two recrystallisations from methanol–water, afforded the *glucoside* (198 mg, 41%), m.p. 132—134° (Found: C, 52.5; H, 5.3; N, 2.8. $C_{21}H_{25}NO_{12}$ requires C, 52.2; H, 5.2; N, 2.9%). Under conditions (*C*) the yield was 22%. With $TsOH,H_2O$ as catalyst, *i.e.* conditions (*A*), and column chromatography (chloroform), penta-*O*-acetyl-β-D-glucopyranose (29%) was recovered together with *p*-nitrobenzyl acetate (34%), m.p. 76—77.5° (from methanol–water) (lit.,[21] 78°) (Found: C, 55.4; H, 4.6; N, 7.0. Calc. for $C_9H_9NO_4$: C, 55.4; H, 4.6; N, 7.2%).

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Bromides (1b), (5d), *and* (6b).—The acetate (1a) (264 mg, 1 mmol) in acetic acid (1 ml) was treated during 1 h with hydrogen bromide–acetic acid (2.2 ml). Evaporation of the mixture and recrystallisation (charcoal) from light petroleum (b.p. 60—80 °C) yielded the *bromide* (1b) (230 mg, 81%), m.p. 120—123° (Found: C, 42.0; H, 3.65; Br, 27.1; S, 11.4. $C_{10}H_{10}BBrO_2S$ requires C, 42.1; H, 3.5; Br, 28.1; S, 11.2%); τ($CDCl_3$) 4.51 (s, H-1).

Similarly prepared from the appropriate acetates (5a) (and its anomer) and (6a), respectively, were the *bromides* (5d) (83%), m.p. 73—75.5° (from benzene–light petroleum) (Found: C, 27.0; H, 2.4; Br, 34.8. $C_5H_5BrO_3S$ requires C, 26.7; H, 2.2; Br, 35.6%); τ($CDCl_3$) 4.29 (d, $J_{1,2} < 1$ Hz, H-1), and (6b) (81%; 2 : 1 mixture of isomers not resolved by recrystallisation or chromatography), m.p. 81—92° [from light petroleum (b.p. 60—80 °C)] (Found: C, 53.2; H, 3.9; Br, 18.5; S, 8.3. $C_{18}H_{15}BrO_4S$ requires C, 53.1; H, 3.7; Br, 19.7; S, 7.9%); τ($CDCl_3$) 4.35 (d, $J_{1,2} < 1$ Hz, H-1 of major anomer, probably *trans* to H-2) and in 4.3—4.55 region (d, H-1 of minor anomer).

The bromide (1b) (352 mg, 82%) was obtained directly from *cis*-thiolan-3,4-diol 1-oxide phenylboronate (α-isomer [1]). The sulphoxide (333 mg, 1.5 mmol), in methylene chloride (2.25 ml), was treated dropwise at 5—10 °C with trifluoroacetic anhydride (1.5 ml). The solution was kept for 2 h at room temperature then evaporated, and the oil treated with hydrogen bromide–acetic acid.

Deoxygenation of cis-*Thiolan*-3,4-*diol* 1-*Oxide Phenylboronate*.—The sulphoxide (α-isomer [1]) (333 mg) in acetic acid (1.5 ml) was treated dropwise with hydrogen bromide–acetic acid (3.3 ml), causing rapid separation of solid. After 2 h, evaporation and recrystallisation from light petroleum (b.p. 60—80 °C), gave *cis*-thiolan-3,4-diol phenylboronate (187 mg, 61%).

Isothiouronium Bromides (1r), (6d), *and* (4).—A mixture of the bromide (1b) (798 mg, 2.8 mmol) and powdered thiourea (213 mg, 2.8 mmol) in nitromethane (14 ml) on stirring (5 min) at 100 °C deposited the *isothiouronium bromide* (1r) (847 mg, 84%), m.p. 184—185° (decomp.) (Found: C, 35.9; H, 4.05; Br, 22.0; N, 8.0; S, 17.7. $C_{11}H_{14}BBrN_2O_2S_2$ requires C, 36.6; H, 3.9; Br, 22.2; N, 7.8; S, 17.7%); τ[$(CD_3)_2SO$] 6.64 (s, possibly H-1).

The *salt* (6d) (77%) from the bromide (6b) had m.p. 167.5° (decomp.) (from nitromethane) (Found: C, 46.5; H, 4.1; Br, 16.1; N, 6.3; S, 12.8. $C_{19}H_{19}BrN_2O_4S_2$,-$0.25CH_3NO_2$ requires C, 46.4; H, 4.0; Br, 16.1; N, 6.3; S, 12.8%); τ[$(CD_3)_2SO$] 6.39 (d, J 2.5 Hz, possibly H-1), 5.53 (s, CH_3NO_2), and 4.08 (s, H-2 and -3).

Although the dibenzoate (2b) could not be converted into a crystalline bromide, the crude product formed the *isothiouronium bromide* (4) (14%), m.p. 168—169.5° (from nitromethane) (Found: C, 46.7; H, 3.9; N, 5.9. $C_{19}H_{19}$-$BrN_2O_4S_2$ requires C, 47.2; H, 3.9; N, 5.8%); τ[$(CD_3)_2SO$] 6.54 (s, possibly H-1) and 4.08 (s, H-2 and -3).

Deboronation of Esters of 4-*Thio*-DL-*erythrofuranosides*.—Phenylboronic acid was removed by repeated distillation (bath temp. 100—145 °C; pressure 0.1—1.0 mmHg) of mixtures of the esters and propane-1,3-diol. Two or three portions (up to 5 ml per mmol of ester) were sufficient for the more soluble derivatives: propane-1,3-diol phenylboronate was visible as a separate phase in the distillate; the starting material dissolved readily. In other cases, solid disappeared gradually or was still present even after 10—12 distillations (by then consisting of product) and the distillate was a single phase throughout. The *erythrofuranosides* were isolated after trituration with water: *benzyl* (3a) (88%), m.p. 63—65.5° (from benzene–light petroleum) (Found: C, 58.5; H, 6.3; S, 14.0. $C_{11}H_{14}O_3S$ requires C, 58.4; H, 6.2; S, 14.2%); p-*nitrobenzyl* (3b) (90%), m.p. 103.5—105.5° (from methanol–water or benzene) (Found: C, 48.6; H, 5.0; N, 5.1; S, 11.7. $C_{11}H_{13}NO_5S$ requires C, 48.7; H, 4.8; N, 5.2; S, 11.8%). The *disaccharide* (7) (54%) had m.p. 160.5—162.5° (from acetonitrile; trituration unnecessary) (Found: C, 37.9; H, 5.5; S, 25.0. $C_8H_{14}O_5S_2$ requires C, 37.8; H, 5.5; S, 25.2%).

Periodate Oxidations.—(i) *Benzyl* 4-*Thio*-DL-*erythrofuranoside* (3a). The glycoside (678 mg, 3 mmol), in acetone (50 ml), was treated dropwise (−1 to 3 °C) during 10 min with sodium periodate (642 mg, 3 mmol) in water (30 ml). Acetone was removed and the product extracted with chloroform. The residue from evaporation of the extract was dissolved in methanol (6 ml) and a portion (≡ 1 mmol) added to isonicotinoylhydrazine (INH) (274 mg, 2 mmol) in water (4 ml). Addition of acetic acid (0.04 ml) to the opalescent mixture caused gradual separation of the *bishydrazone* (10a) (413 mg, 89%), m.p. 143—144° (decomp.) (from 3 : 4 dimethylformamide–water; temp. <70 °C) (Found: C, 59.6; H, 4.8; N, 18.2; S, 7.1. $C_{23}H_{22}N_6O_3S$ requires C, 59.7; H, 4.8; N, 18.2; S, 6.9%). INH (1 mol. equiv.; no acetic acid) gave a mixture of gum and crystals which could not be purified.

4-Methylthiosemicarbazide (2 mol. equiv. with acetic acid, or 1 mol. equiv. without) yielded only gummy products which had characteristic [16] u.v. peaks at *ca.* 245 and 275 nm. In the spectrum of the former product, the 275 nm peak was more intense, and *vice versa*.

(ii) 6-*Chloro*-9-(4-*thio*-DL-*erythrofuranosyl*)*purine* (8). The nucleoside (4.09 g, 15 mmol) was dissolved in acetone (90 ml). Water (225 ml) was added, and the acetone evaporated off. The aqueous solution (at 50 °C) was added quickly dropwise with stirring to aqueous sodium periodate (15 mmol; 120 ml) at 2—5 °C and after 10 min iodate was removed.[16b] A portion (≡ 7 mmol) of the resulting solution was treated with INH (7 mmol), in water (17.5 ml), yielding the *cyclic derivative* (11a) (2.37 g, 83%), m.p. indeterminate (gradual darkening from 100 °C; black at 135 °C) (from 1 : 3 dimethylformamide–water; temp. <70°) (Found: C, 43.6; H, 3.4; Cl, 8.5; N, 23.7; S, 7.7. $C_{15}H_{14}ClN_7O_3S$ requires C, 44.2; H, 3.4; Cl, 8.7; N, 24.05; S, 7.85%). The same compound (55%) was obtained from INH (2 mol. equiv.) in aqueous acetic acid.

Another portion (≡ 7 mmol) was treated with 4-benzylthiosemicarbazide (1.27 g, 7 mmol) in methanol (56 ml). The *cyclic derivative* (11b) gradually separated as a cream-coloured solid (2.32 g, 73%), m.p. 105—107°, which proved too unstable for recrystallisation, even at room temperature (Found: C, 45.7; H, 4.2; Cl, 7.9; N. 21.6; S, 14.3. C_{17}-$H_{18}ClN_7O_2S_2$ requires C, 45.2; H, 4.0; Cl, 7.9; N. 21.7; S, 14.2%); $\lambda_{max.}$ 245 nm.

(iii) 4-*Thio*-DL-*erythrofuranosyl* 4-*Thio*-DL-*erythrofuranoside* (7). The tetraol (76 mg, 0.3 mmol) in water (1.5 ml) was oxidised during 15 min at 2—4 °C with aqueous sodium periodate (0.6 mmol; 2.5 ml). Removal of iodate and treatment with aqueous INH (1.2 mmol; 2 ml), then acetic acid (2 drops), gradually yielded a gel-like *solid* (112 mg, 49%), m.p. 156—160° (decomp.). It was dissolved at room temperature in dimethylformamide and reprecipitated by water (Found: C, 50.4; H, 4.6; N, 21.6; S, 8.2. $C_{32}H_{34}$-$N_{12}O_7S_2$ requires C, 50.4; H, 4.5; N, 22.05; S, 8.4%).

Another portion (0.25 mmol) of tetraol, similarly oxidised,

was treated with aqueous 4-methylthiosemicarbazide (105 mg, 1 mmol; 1.2 ml). Addition of acetic acid (2 drops) caused separation of an unidentified solid (110 mg, 80%), m.p. 147—149° (decomp.), which was analysed directly (Found: C, 30.9; H, 5.1; N, 23.2; S, 29.4. Calc. for $C_{14}H_{29}N_9O_4S_5$: C, 30.7; H, 5.3; N, 23.0; S, 29.25%); $\lambda_{max.}$ 245 and 276 nm.

Benzyl 4-*Thio*-DL-*erythrofuranoside* S-*Oxide Phenylboronate*.—The glycoside (3a) (1.81 g, 8 mmol), in ethanol (8 ml) and acetic acid (1.6 ml), was treated dropwise at 0—1 °C with aqueous hydrogen peroxide (1.0 ml, 8.8 mmol). The mixture, kept at 3 °C overnight, did not give an immediately positive test for peroxide. Evaporation, dissolution in methanol (10 ml), and treatment with aqueous phenylboronic acid (976 mg, 8 mmol; 20 ml) gave the *sulphoxide phenylboronate* (1.25 g, 47%), m.p. 154.5—156° (from benzene–light petroleum) (Found: C, 62.4; H, 5.45; S, 9.8. $C_{17}H_{17}BO_4S$ requires C, 62.2; H, 5.2; S, 9.75%); τ[$(CD_3)_2$SO] 4.57 (s, H-1). Oxidation of the phenylboronate (1g) with *m*-chloroperbenzoic acid as described for the acetate (1a) [1] gave the same sulphoxide (15%).

Reaction of Benzyl 4-*Thio*-DL-*erythrofuranoside* S-*Oxide Phenylboronate with Acetic Anhydride*.—The sulphoxide (656 mg, 2 mmol) was refluxed (16.5 h) in dry benzene (1 ml) and acetic anhydride (0.21 ml). After evaporation, the residual gum was extracted with boiling light petroleum (b.p. 80—100 °C) and the extract was evaporated. The residue (517 mg) was dissolved in 1 : 3 benzene–light petroleum. The phenylboronate (1g) (95 mg, 15%), m.p. and mixed m.p. 77—78°, was eluted from a column by 1 : 1 benzene–light petroleum. Further elution, with 9 : 1 chloroform–methanol, gave material (222 mg) which possibly [t.l.c. (chloroform)] contained some of the sulphone (see below) derived from the glycoside (1g).

The sulphoxide (2 mmol) when refluxed for 18 h in toluene (2 ml), was recovered (84%), m.p. 153—155° (from benzene–light petroleum).

Benzyl 4-*Thio*-DL-*erythrofuranoside* SS-*Dioxide and Derivatives*.—The sulphide (3a) (678 mg, 3 mmol) in acetic acid (10 ml) was treated at 9—11 °C with aqueous hydrogen peroxide (4 ml). The mixture was left 2 days at room temperature, and poured into water. Sodium hydrogen carbonate (15 g) was added and the solution saturated with sodium chloride. Repeated extraction with chloroform afforded the *sulphone* (656 mg, 85%), m.p. 139—140.5° (from water) (Found: C, 50.8; H, 5.6; S, 12.2. $C_{11}H_{14}O_5S$ requires C, 51.2; H, 5.4; S, 12.4%). Treatment with acetic anhydride–pyridine gave the *diacetate* (98%), m.p. 104.5—106° (from methanol–water) (Found: C, 52.8; H, 5.3; S, 9.4. $C_{15}H_{18}O_7S$ requires C, 52.6; H, 5.3; S, 9.4%).

The *phenylboronate* (92%), m.p. 175—178.5° (from 1 : 3 benzene–light petroleum), was formed by mixing warm, aqueous solutions of the sulphone (101 mg; 0.8 ml) and phenylboronic acid (48 mg; 1.2 ml) (Found: C, 59.1; H, 5.0; S, 9.1. $C_{17}H_{17}BO_5S$ requires C, 59.3; H, 4.9; S, 9.3%).

p-*Nitrobenzyl* 4-*Thio*-DL-*erythrofuranoside* 2,3-*Carbonate* (5b).—A mixture of the diol (3b) (678 mg, 2.5 mmol), diphenyl carbonate (640 mg, 3 mmol), and sodium hydrogen carbonate (5 mg) in dimethylformamide (5 ml) was heated (1 h; 125—130 °C), and poured into ice–water (25 ml). The product, separating initially as an oil, was extracted with light petroleum (b.p. 60—80°; 4 × 5 ml) and the insoluble portion on recrystallisation from methanol yielded the carbonate (5b) (512 mg, 69%), m.p. 130—131°.

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