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5-THIO-D-RIBOPYRANOSE

PART II[1]. METHYL 1,5-DITHIO-D-RIBOPYRANOSIDES

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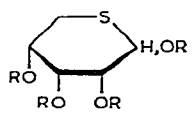
ABSTRACT

Treatment of 5-thio-D-ribopyranose (**1**) with methanethiol and hydrochloric acid leads to the methyl 1,5-dithio-α- and -β-D-ribopyranosides (**4a** and **4b**), and not to an acyclic dithioacetal. The dithioglycosides **4** are resistant to acidic hydrolysis or methanolysis, and possible explanations for this stability are proposed. The methylthio groups can be cleaved from the dithioglycosides **4** by acetolysis of their triacetates **11**, giving 1,2,3,4-tetra-*O*-acetyl-D-ribopyranose (**12**).

INTRODUCTION

Part I[1] of this series described the synthesis of 5-thio-D-ribopyranose (**1**) and methyl 5-thio-α- and -β-D-ribopyranosides (**2a** and **2b**). The isomeric methyl 1-thio-α- and -β-D-ribopyranosides (**3a** and **3b**) have also been synthesised recently in these laboratories[2]. It was of interest to obtain the methyl 1,5-dithio-α- and -β-D-ribopyranosides (**4a** and **4b**) in order to compare their properties with those of the thioribopyranosides **2** and **3** and methyl α- and β-D-ribopyranosides[1,3] (**5a** and **5b**).



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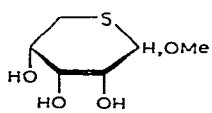

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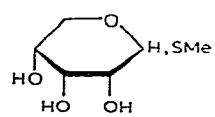

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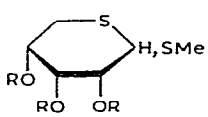

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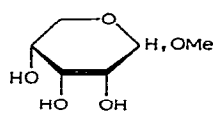

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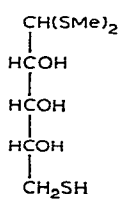

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DISCUSSION

An obvious route to the dithioglycosides **4** was to treat 5-thio-D-ribopyranose (**1**) with methanethiol in the presence of hydrochloric acid. Under these conditions, simple sugars give the open-chain dithioacetals but, in this case, it was thought that the cyclic dithioglycosides **4** would be the preferred products rather than the acyclic 5-thio-D-ribose dimethyl dithioacetal (**6**) or a disulphide arising therefrom. This proved to be the case, and two isomeric, crystalline compounds were obtained which were readily separated by chromatography on a basic ion-exchange resin[4]. Elemental analyses suggested that these two products were the desired dithioglycosides **4**. Reductive desulphurisation of each compound gave the expected 1,5-dideoxyribitol, identified as the known[5] 2,4-*O*-methylene derivative. Both isomers gave virtually superimposable mass spectra. Unlike simple glycosides, the dithioglycosides **4** gave prominent molecular ions (*m/e* 196). Other prominent ions were: *m/e* 178 ($M-H_2O$), 149 (M−SMe), 131 (base peak) [$M-(H_2O+SMe)$], and 103 [$M-(H_2O+SMe+CO)$]. The anomeric configurations of the dithioglycosides **4** were assigned from considerations of their optical rotations (**4a**, $[\alpha]_D$ +222°; **4b**, $[\alpha]_D$ −83°). The α-anomer **4a** was eluted first from the basic ion-exchange resin, in keeping with the general behaviour of D-ribosides on such resins[1,2]. Final proof of the structures **4** and the anomeric assignments came from n.m.r. evidence (see following paper, p. 97).

The dithioglycosides **4** are surprisingly stable under acidic conditions. In 0.2M hydrochloric acid at 80°, which brought about[1,2] the hydrolysis of the glycosides **2**, **3**, and **5** in times ranging from 1–30 h, the dithioglycosides **4** were unaffected. After a one-hour reflux in 1.2M hydrochloric acid, the dithioglycosides **4** were largely unchanged, although a slight odour of methanethiol or dimethyl disulphide was apparent during the reaction and paper chromatography showed traces of decomposition products. By contrast, D-ribose dimethyl dithioacetal was completely hydrolysed to D-ribose under these conditions. In these experiments, no evidence was obtained for anomerisation, such as had accompanied[2] the hydrolysis of the 1-thioglycosides **3**. However, when the dithioglycosides **4** were kept in concentrated hydrochloric acid at room temperature for ninety minutes, paper chromatography indicated that, although the main component of the mixture was still the starting material, some anomerisation had occurred and traces of 5-thio-D-ribose (**1**) had been formed.

Two possible mechanisms have been suggested[6] for the acid-catalysed hydrolysis of glycosides (Fig. 1; mechanisms *A* and *B*). Mechanism *A* has generally been preferred for oxygen glycosides, although the anomerisation and ring contraction which accompanied the hydrolysis of methyl 1-thio-D-ribopyranosides (**3**) must have occurred by mechanism *B* even if the hydrolysis did not[2]. The facile hydrolysis of methyl 5-thiopentopyranosides has been explained[7] in terms of mechanism *A* where a larger concentration of conjugate acid **7** (X = S; Y = O; R = Me), owing to the inductive electron-release from sulphur to oxygen, more than offsets the lesser stability of the carbonium ion **8** (X = S; R = Me). A possible explanation for the difficulty of hydrolysis of the dithioglycosides **4** is that these compounds are less basic

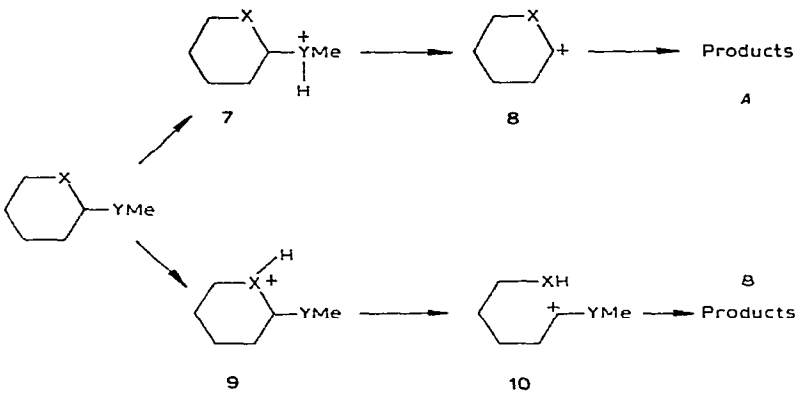

Fig. 1. Possible mechanisms for the acid-catalysed hydrolysis of glycosides.

than the previous glycosides studied and consequently the concentration of conjugate acid **7** or **9** (X = Y = S; R = Me) is low. This possibility, taken together with the lesser stability relative to oxygen analogues of the carbonium ion **8** or **10** (X = S; R = Me), would lead to a very slow rate of hydrolysis. The observation of some hydrolysis and anomerisation in concentrated hydrochloric acid is in keeping with this suggestion. The greater rate of hydrolysis of the acyclic dithioacetal may be due to anchimeric assistance by an hydroxyl group. Such assistance has been demonstrated in the hydrolysis of the dimethyl acetals of D-glucose and D-galactose[8], but is not possible in the dithioglycosides **4** because of their cyclic nature.

Similar results were observed when the dithioglycosides **4** were treated with boiling, methanolic hydrogen chloride. The compounds were largely unchanged, but under the same conditions the dithioacetal was converted into a mixture of methyl D-ribosides and methyl 1-thio-D-ribosides.

These results are in sharp contrast to those reported by Whistler and Rowell[9] for methyl 1,5-dithio-β-D-xylopyranoside made by the action of a methanolic solution of potassium methanethiolate on 2,3,4-tri-*O*-acetyl-5-thio-α-D-xylopyranosyl bromide. They claimed that the dithioxyloside underwent hydrolysis readily, and gave methyl 5-thio-β-D-xylopyranoside on treatment with methanol and an acidic ion-exchange resin at room temperature. Re-examination (by J. Harness) of the stability of methyl 1,5-dithio-β-D-xylopyranoside to dilute hydrochloric acid and methanolic hydrogen chloride showed that the dithioxyloside, like the dithioribosides **4**, was unaffected by these reagents and could be recovered unchanged. The earlier results[9] were based on a change of optical rotation, in the case of the hydrolysis, and the use of impure material, which probably contained methyl 5-thio-α- and -β-D-xylopyranosides, in the methanolysis.

Cleavage of the methylthio group of the dithioglycosides **4** could be achieved by acetolysis catalysed by sulphuric acid or mercuric acetate. Both the dithioglycosides **4** gave crystalline triacetates **11**. Sulphuric acid-catalysed acetolysis of acetylated aldose dithioacetals leads to the corresponding 1,1-diacetates[10]. Similar treatment of the

triacetates **11** gave a mixture of 1,2,3,4-tetra-*O*-acetyl-5-thio-α- and -β-D-ribopyranoses (**12a** and **12b**). Infrared evidence suggested that the α-anomer **12a** was in excess, and deacetylation gave 5-thio-D-ribopyranose (**1**). No indication of acyclic products was obtained in the acetolysis. Partial dedithioacetalation of acetylated aldose dithioacetals has been achieved by mercuric acetate-catalysed acetolysis, and, generally, one of the two possible diastereoisomeric acetylated hemithioacetals has been obtained in excess[11]. When the triacetates **11** were so treated, a mixture of tetra-acetates **12** was again obtained, but this time the β-anomer (**12b**) was in excess and could be crystallised out.

Unlike the monothioglycosides **2** and **3**, which reacted with sodium metaperiodate in the expected way (reducing three equivalents of periodate and releasing one equivalent of formic acid[1,2]), the dithioglycosides **4** underwent extensive over-oxidation (see Table I). This behaviour is not unexpected, since it is known[12] that acyclic dithioacetals also undergo similar over-oxidation.

TABLE I

PERIODATE OXIDATION[a] OF METHYL 1,5-DITHIO-α- AND -β-D-RIBOPYRANOSIDES (**4a** AND **4b**)

		Time (h)		
		5	*24*	*72*
4a	Periodate reduced[b]	2.4	4.5	6.0
	Acid released[b]	1.5	2.4	3.2
4b	Periodate reduced[b]	2.4	4.5	5.5
	Acid released[b]	1.4	2.3	3.3

[a]Followed by the thiosulphate method[13]. [b]Moles/mole.

EXPERIMENTAL

For general procedures, see Part I[1].

Methyl 1,5-dithio-α- and -β-D-ribopyranosides (**4a** *and* **4b**). — Conc. hydrochloric acid (4 ml) was added to a stirred suspension of 5-thio-D-ribopyranose (**1**) (0.70 g) in methanethiol (4 ml). After 40 min, an excess of conc. ammonia (sp. gr. 0.880) was added. The excess of ammonia and methanethiol was removed by evaporation, and the aqueous solution remaining was extracted continuously with ethyl acetate to give a gum (0.80 g). This was dissolved in water and chromatographed on a column (26 × 3 cm) of Dowex-1(HO^-) resin, by elution with water (220-ml fractions). Fraction 5 contained the α-anomer **4a** (0.43 g) which, after recrystallisation from ethyl acetate, had m.p. 67–69°, $[\alpha]_D$ +222° (*c* 0.5, methanol), R_F 0.60 (Found: C, 36.7; H, 6.1; S, 32.7. $C_6H_{12}O_3S_2$ calc.: C, 36.7; H, 6.2; S, 32.7%). Fractions 7 and 8 contained the β-anomer **4b** (0.29 g) which, after recrystallisation from ethyl acetate, had m.p. 112–114°, $[\alpha]_D$ −83° (*c* 0.3, methanol), R_F 0.62 (Found: C, 36.5; H, 6.3; S, 32.4%).

Although the dithioglycosides had similar R_F values, they could be distinguished by their response to the periodate–Schiff reagent; the α-anomer gave a blue colour and the β-anomer gave a green colour.

Desulphurisation of the glycosides **4**. — The α-glycoside **4a** (100 mg) was stirred under reflux in water–ethanol (8 ml, 1:4) containing a suspension of Raney nickel (1 ml) for 70 min. The mixture was filtered and evaporated to dryness. The residue was extracted with ethyl acetate and purified by distillation (120°/0.2 mmHg) to give 1,5-dideoxyribitol (R_F 0.56). This was heated in a sealed tube with conc. hydrochloric acid (0.25 ml) and 40% aqueous formaldehyde (0.25 ml) at 100° for 6 h. The mixture was then neutralised with potassium hydrogen carbonate and extracted continuously with ether. The concentrated extract was passed through a small column of silica gel and evaporated, and crystallisation of the residue from light petroleum gave 1,5-dideoxy-2,4-*O*-methyleneribitol (13 mg), m.p. and m.m.p. 93–95° (lit.[5], m.p. 94–95°).

The same compound (11 mg), m.p. and m.m.p. 93–95°, was obtained by similar treatment of the β-glycoside **4b** (100 mg).

The effect of acids on the dithioglycosides **4**. — (*a*) *Conc. hydrochloric acid.* Samples of each glycoside (5 mg) were separately dissolved in conc. hydrochloric acid (0.05 ml) at 0°. The solutions were allowed to reach room temperature and then kept for 90 min, during which time they became discoloured and gave off an odour of dimethyl disulphide. They were diluted with water, passed through columns of Dowex-1(AcO^-) resin, concentrated, and examined by paper chromatography. In each case, the main component was the starting material, but some anomerisation had taken place and small amounts of other products, including 5-thio-D-ribose (**1**) (R_F 0.30), were indicated.

(*b*) *0.2M Hydrochloric acid at 80°*. The appropriate weight of glycoside was dissolved in 0.2M hydrochloric acid, so that the solution was 23mM with respect to the glycoside. The solutions were kept at 80° in stoppered tubes. After 24 h, paper chromatography indicated the presence of starting material and the absence of hydrolysis products.

(*c*) *1.2M Hydrochloric acid at reflux*. Samples of each glycoside (10 mg) were refluxed in 1.2M hydrochloric acid (1 ml) for 1 h. The solutions became yellow and the odour of dimethyl disulphide was detected. Paper chromatography indicated that, although some unidentified decomposition products had been formed, the major component was the starting material. D-Ribose was the only product detected by paper chromatography after similar treatment of D-ribose dimethyl dithioacetal.

Attempted methanolysis of the dithioglycosides **4**. — Each dithioglycoside (10 mg) was refluxed in 1.2M methanolic hydrogen chloride for 2 h. The solutions remained colourless, although the odour of dimethyl disulphide was detected. Paper chromatography showed only the starting material in each case and traces of other products.

Similar treatment of D-ribose dimethyl dithioacetal gave four compounds, chromatographically identified as **3a**, **3b**, **5a**, and **5b**.

*Methyl 2,3,4-tri-*O*-acetyl-1,5-dithio-α- and -β-*D*-ribopyranosides* (**11a** *and* **11b**). —

The α-glycoside **4a** (23 mg) was acetylated in acetic anhydride–pyridine (1:1; 0.25 ml) for 18 h at room temperature. Work-up in the usual manner, with crystallisation from light petroleum, gave the α-triacetate **11a** (28 mg), m.p. 88–90°, $[\alpha]_D$ +286° (*c* 0.87, chloroform) [Found: C, 44.9; H, 5.8; S, 20.0%; *M* (mass spectroscopy), 322.0520. $C_{12}H_{18}O_6S_2$ calc.: C, 44.7; H, 5.6; S, 19.9%; *M*, 322.0544].

Similar treatment of the β-glycoside **4b** (45 mg) gave the β-triacetate **11b** (58 mg), m.p. 106–108°, $[\alpha]_D$ −24° (*c* 0.75, chloroform) (Found: C, 44.8; H, 5.4; S, 19.3%; *M*, 322.0508).

Acetolysis experiments. — (*a*) *In acetic anhydride–sulphuric acid.* Samples of each triacetate **11** (25 mg) were dissolved in acetic anhydride–sulphuric acid (0.25 ml; 9:1) and left for 1 h at room temperature. The deep red–brown solutions were diluted with dichloromethane and shaken with dilute, aqueous potassium hydrogen carbonate The dried dichloromethane solutions were evaporated to give syrups (17 mg). T.l.c. indicated the presence of the tetra-acetates (**12**) (α>β), and the infrared spectra of the syrups were very similar to that of the product of acetylation of 5-thio-D-ribose; no band at 1689 cm^{-1} (SAc) was observed. Deacetylation of the syrups with sodium methoxide in methanol at room temperature gave only 5-thio-D-ribose (**1**).

(*b*) *In acetic anhydride–acetic acid containing mercuric acetate.* The triacetate **11a** (60 mg) was dissolved in a solution of mercuric acetate (150 mg) in acetic anhydride (0.6 ml) and acetic acid (0.6 ml), and kept at 85° for 2 h. The cooled solution was added to an excess of aqueous potassium hydrogen carbonate. After the initial reaction had subsided, dichloromethane was added and the mixture was filtered. The dried dichloromethane extract gave a syrup (45 mg) on evaporation, from which 1,2,3,4-tetra-*O*-acetyl-5-thio-β-D-ribopyranose (**12b**) (13 mg), m.p. and m.m.p. 122–124° (lit.[1], 123–124°), was obtained on crystallisation from ethanol. T.l.c. of the mother liquors indicated the presence of the α-anomer **12a** in addition to more **12b**.

Similar treatment of **11b** (60 mg) gave the tetra-acetate **12b** (11 mg), m.p. 120–122°, m.m.p. 123–124°.

Experiments with methyl 1,5-dithio-β-D-xylopyranoside (by J. Harness). — Methyl 1,5-dithio-β-D-xylopyranoside, prepared as described[9] by Whistler and Rowell, had m.p. 120–121°, $[\alpha]_D$ −37° (*c* 1.93, methanol), R_F 0.64; lit.[9], m.p. 130°, $[\alpha]_D$ −49.5° (*c* 1.56, water).

(*a*) *Attempted hydrolysis.* The glycoside (50 mg) was dissolved in 0.5M hydrochloric acid (5 ml), and the solution was kept at 75° for 8 h. The solution was cooled, passed through Dowex-1(AcO^-) resin, and evaporated to dryness. Recrystallisation of the residue from ethyl acetate–benzene gave the starting material (19 mg), m.p. 114–115°, m.m.p. 115–116°. Paper chromatography of the mother liquors showed mainly starting material, with a possible trace of 5-thio-D-xylose.

(*b*) *Attempted methanolysis.* (*i*) Treatment of the glycoside (50 mg) as above but using 2M methanolic hydrogen chloride in a sealed tube, resulted in the recovery of starting material (24 mg), m.p. 117–118°, m.m.p. 117–118°. Paper chromatography revealed the presence of no other compounds in the mother liquors.

(*ii*) A slurry of Amberlite IR-120(H^+) resin (1 ml) in methanol (2 ml) containing the glycoside (36 mg) was stirred overnight at room temperature. The resin was filtered off, and the filtrate was evaporated to give a residue which crystallised from ethyl acetate–benzene to give the starting material (25 mg), m.p. and m.m.p. 120–121°.

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