Epimerisations Accompanying the Reductive Desulphurisation of some 5-*S*-Alkyl-5-thiopentose Dialkyl Dithioacetals

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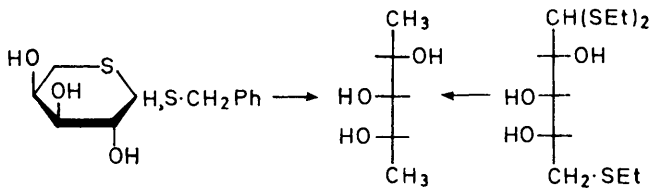
Reductive desulphurisation of some 5-*S*-alkyl-5-thiopentose dialkyl dithioacetals with Raney nickel was found to be followed by epimerisation, mainly at C-2 and C-4, of the resultant 1,5-dideoxypentitols. An alternative synthetic route to the 1,5-dideoxypentitols is described.

RECENTLY we reported the synthesis of the benzyl 1,5-dithio-α- and -β-arabinopyranosides (1a) and (1b).[1] Their structures were confirmed by their n.m.r. spectra but we attempted to provide additional evidence by subjecting them to reductive desulphurisation with Raney nickel. This gave a product which was indistinguishable on paper and thin-layer chromatography from that obtained by similar means from the known [2] 5-*S*-ethyl-5-thio-L-arabinose diethyl dithioacetal (2) and which we presumed to be 1,5-dideoxy-L-arabinitol (3). Unfortunately the product was not crystalline and we were unable to obtain a crystalline derivative. However, acetylation yielded a small amount of crystalline material which, though it gave the expected analytical figures, was devoid of optical activity. This lack of optical activity and the low yield suggested that the crystalline material might be the *ribo*- or *xylo*-isomer of

[1] J. Harness and N. A. Hughes, *Chem. Comm.*, 1971, 811.
[2] M. L. Wolfrom and T. E. Whiteley, *J. Org. Chem.*, 1962, **27**, 2109.

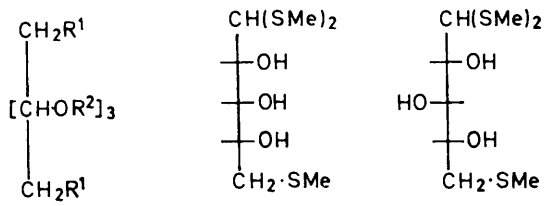
the expected triacetate (4A). G.l.c. of the acetylated material showed it to consist of three products, one major and two minor, and the crystalline triacetate was one of the minor products. It seemed likely that the major product was the L-*arabino*-triacetate (4A) and that the two minor products were the *ribo*- and *xylo*-isomers (4R) and (4X). This was confirmed, and all the peaks were identified by unambiguous synthesis of the three 1,5-dideoxypentitol triacetates (4).

The same synthetic route was used for all three compounds. The pentitols were treated with two equivalents of trityl chloride followed by an excess of benzoyl chloride. The resultant crystalline 2,3,4-tri-*O*-benzoyl-1,5-di-*O*-tritylpentitols (5) were treated briefly with acid to remove the trityl groups and then with toluene-*p*-sulphonyl chloride to give the crystalline disulphonates (6). The crystalline di-iodides (7) were obtained from the disulphonates (6) by displacement with sodium iodide in dimethylformamide or, in higher yield, by the recently reported [3] method employing lithium iodide–hexamethylphosphoric triamide complex in toluene.



(1a) α-anomer
(1b) β-anomer

(3) (2)



(4) R^1 = H, R^2 = Ac
(5) R^1 = $OCPh_3$, R^2 = Bz
(6) R^1 = OTs, R^2 = Bz
(7) R^1 = I, R^2 = Bz
(8) R^1 = H, R^2 = Bz

(9) (10)

A; L-*arabino*-
R; *ribo*-
X; *xylo*-

Hydrogenolysis of the di-iodides (7) with palladium–charcoal in the presence of sodium acetate gave the 2,3,4-tri-*O*-benzoyl-1,5-dideoxypentitols (8), of which only the *xylo*-isomer (8X) was crystalline. Zemplen debenzoylation gave the triols which, without further purification, were acetylated to give the triacetates (4). Only the *xylo*-isomer (4X) was crystalline, and this material was identical with the crystalline triacetate obtained earlier. The original three peaks, in order of increasing retention times, were assigned to the *ribo*- (4R), *arabino*- (4A), and *xylo*- (4X) triacetates.

Some of the structures (5)—(8) were confirmed by their n.m.r. spectra. Although only the spectrum of the *ribo*-di-iodide (7R) was amenable to a complete first-order analysis, the signals of the pentitol protons of the other compounds were often sufficiently well separated for integration to give the expected ratios (see Experimental section).

It was of interest to examine the reductive desulphurisation of *ribo*- and *xylo*-derivatives related to the dithioacetal (2). 5-*S*-Methyl-5-thio-D-ribose dimethyl dithioacetal (9) was available from earlier work in these laboratories.[4] Treatment of the known [5] 1,2-*O*-isopropylidene-5-*S*-methyl-5-thio-α-D-xylofuranose with methanethiol and hydrochloric acid gave 5-*S*-methyl-5-thio-D-xylose dimethyl dithioacetal (10). These compounds were desulphurised and the products were acetylated and subjected to g.l.c. analysis. The results, together with those from the *arabino*-derivatives (1a), (1b), and (2), are shown in Table 1. In each case the major product had the original configuration but the other two isomers were also present.

In order to determine whether the isomerisation accompanied the desulphurisation or was a subsequent reaction, the reaction of 5-*S*-ethyl-5-thio-L-arabinose diethyl dithioacetal (2) was followed by paper chromatography and g.l.c. The desulphurisation was found to be complete in 5 min at reflux temperature. Even after this short time the *ribo*- and *xylo*-products were detected in small amounts in the reaction mixture, though they increased in quantity as refluxing was continued (see Table 2). This result suggests that the isomerisation occurs after desulphurisation. The mechanism of the isomerisation or epimerisation is presumably an oxidation–reduction sequence. Raney nickel, in an atmosphere of hydrogen, has been used previously to catalyse the equilibration of substituted epimeric cyclohexanols, and the process is thought to involve initial dehydrogenation to a ketone.[6] An attempt to minimise the epimerisation by performing the desulphurisation at room temperature was unsuccessful. The desulphurisation of compound (2) under these conditions was found to be complete in 1 h, but after this time the *ribo*- and *xylo*-products were also present.

TABLE 1

Results of desulphurisation experiments

Compound	Yield (%) [a]	$[\alpha]_D$ [b]	Composition [c]	Yield (%) [d]
(1a)	86	+11°	80 : 9 : 11	5
(1b)	72	+7	75 : 9 : 16	5
(2)	77	+6 [e]	74 : 12 : 14	6
(9)	79		17 : 80 : 3	0
(10)	77		22 : 4 : 74	55

[b] Of dideoxypentitols. [b] *c* 2—4% in MeOH. [c] *arabino* : *ribo* : *xylo*. [d] Of *xylo*-triacetate (4X) isolated. [e] Lit.,[2] $[\alpha]_D$ +5·9°.

The results in Table 1 suggest that the epimerisation occurs faster at C-2 and C-4 than at C-3 in the 1,5-dideoxypentitols. In the desulphurisation of the *ribo*-compound (9) the major by-product has the *arabino*-configuration. The conversion *ribo* ⟶ *arabino* requires

[3] H. B. Sinclair, *Carbohydrate Res.*, 1970, **15**, 147.
[4] N. A. Hughes, R. Robson, and S. A. Saeed, *Chem. Comm.*, 1968, 1381.
[5] A. L. Raymond, *J. Biol. Chem.*, 1934, **107**, 85.
[6] R. J. Wicker, *J. Chem. Soc.*, 1956, 2165.

epimerisation at C-2 or C-4, whereas the *ribo* ⟶ *xylo* conversion requires epimerisation at C-3 or at C-2 and C-4. Similarly in the desulphurisation of the *xylo*-compound (10) the major by-product has the *arabino*-configuration, formed by epimerisation at C-2 or C-4; again formation of the minor by-product with the *ribo*-configuration requires epimerisation at C-3 or at C-2 and C-4. By contrast, in the desulphurisation of compounds (1a), (1b), and (2) with the *arabino*-configuration, both by-products (*ribo*- and *xylo*-) are formed in approximately the same yield by epimerisation at C-2 and C-4, respectively.

EXPERIMENTAL

Paper chromatography was performed on Whatman no. 1 paper in the solvent system n-butanol–water (86 : 14 v/v); compounds were detected with silver nitrate–potassium hydroxide.[7] Silica gel (Gelman, I.T.L.C. type SA) was used for t.l.c., and compounds were detected with iodine vapour. A column (2 m) of 15% polyethylene glycol succinate on Universal B (85—100 mesh) at 145° with nitrogen as carrier gas was used for g.l.c. with a Pye Series 104 Chromatograph. N.m.r. spectra were determined for solutions in deuteriochloroform with a Perkin-Elmer R10 60 MHz spectrometer, with tetramethylsilane as internal reference.

2,3,4-*Tri*-O-*benzoyl*-1,5-*di*-O-*tritylpentitols* (5).—The pentitol (1 g) was dissolved in pyridine (10 ml), and trityl chloride (3·8 g) was added. After 3 days at room temperature more pyridine (16 ml) and benzoyl chloride (4 ml) were added. After a further 2 days at room temperature the mixture was poured into ice–water. The product was extracted into dichloromethane and the extract was washed with dilute sulphuric acid, water, and dilute potassium hydrogen carbonate, dried, and evaporated. The crude product was recrystallised from ethanol or dichloromethane–ethanol. The L-arabino-*isomer* (5A) (35%) had m.p. 172—173°, $[\alpha]_D$ −0·5° (*c* 1·9 in $CHCl_3$) (Found: C, 80·8; H, 5·3. $C_{64}H_{52}O_8$ requires C, 81·0; H, 5·5%). The D-form [8] has m.p. 174—176°, $[\alpha]_D$ 4·5° (in EtOH). The *ribo*-isomer (5R) (67%) had m.p. 161—162° (lit.,[9] 161°) and the *xylo*-isomer (5X) (78%) m.p. 193—196° (lit.,[10] 197—198°).

2,3,4-*Tri*-O-*benzoyl*-1,5-*di*-O-p-*tolylsulphonylpentitols* (6).—Hydrogen bromide in acetic acid (45% w/v; 0·4 ml) was added to a solution of the trityl ether (5) (650 mg) in dichloromethane (8 ml) and glacial acetic acid (2 ml). After 1 min at room temperature the mixture was poured into an excess of potassium hydrogen carbonate solution. When carbon dioxide evolution had ceased the mixture was extracted with dichloromethane. The extract was dried and evaporated. The resultant crude 2,3,4-tri-*O*-benzoylpentitol was dissolved in pyridine (7 ml), and toluene-*p*-sulphonyl chloride (1·5 g) was added. After 60 h at room temperature the mixture was poured into ice–water and worked up with dichloromethane; the product was recrystallised from methanol or dichloromethane–methanol. [The *xylo*-isomer (6X) could be crystallised directly from the sulphonylation reaction mixture by adding methanol (30 ml).] The L-arabino-*isomer* (6A) (75%) had m.p. 116—117°, $[\alpha]_D$ −22·6° (*c* 3·2 in $CHCl_3$) (Found: C, 62·4; H, 4·6; S, 8·2. $C_{40}H_{36}O_{12}S_2$ requires C, 62·2; H, 4·7; S, 8·3%). The D-form [7] has m.p. 113—116°. The ribo-*isomer* (6R) (48%) had m.p. 160—161° (Found: C, 62·1; H, 4·75; S, 8·1%) and the xylo-*isomer* (6X) (60%) m.p. 165—168° (Found: C, 62·3; H, 4·8; S, 8·1%).

2,3,4-*Tri*-O-*benzoyl*-1,5-*dideoxy*-1,5-*di*-*iodopentitols* (7).—*Method A*. A solution of sodium iodide (0·15 g) in dimethylformamide (9 ml) was dried by distillation to a volume of 6 ml. The disulphonate (6) (0·22 g) was added and the solution was heated under reflux for 10 min and then evaporated to dryness. The residue was partitioned between dichloromethane and aqueous sodium thiosulphate. The extract was dried and evaporated to dryness and the product was crystallised from methanol.

Method B. Hexamethylphosphoric triamide (1 ml) was added to a suspension of lithium iodide monohydrate (0·18 g) in toluene (25 ml). Toluene (15 ml) was distilled from the resulting solution. The disulphonate (6) (0·12 g) was added and the solution was heated under reflux for 30 min. The product was isolated as in *A* but with toluene in place of dichloromethane. The L-arabino-*isomer* (7A) (*A* 29%; *B* 57%) had m.p. 149—151°, $[\alpha]_D$ −35° (*c* 1·6 in $CHCl_3$) (Found: C, 45·75; H, 3·4; I, 36·9. $C_{26}H_{22}O_6I_2$ requires C, 45·6; H, 3·2; I, 37·2%), τ 1·8—2·8 (m, aromatic H), 4·0—4·7 (3H, m, H-2, H-3, and H-4), and 6·2—6·7 (4H, m, H-1, H-1′, H-5, and H-5′). The ribo-*isomer* (7R) (*A* 39%; *B* 69%) had m.p. 81—83° (Found: C, 45·7; H, 3·3; I, 37·3%), τ 1·8—2·8 (m, aromatic H), 4·08 (1H, t, H-3), 4·41 (2H, oct, H-2 and H-4), 6·32 (2H, q, H-1 and H-5), and 6·51 (2H, q, H-1′ and H-5′), $J_{1,1'} = J_{5,5'} = 11·0$ Hz, $J_{1,2} = J_{4,5} = 4·4$ Hz, $J_{1',2} = J_{4,5'} = 6·8$ Hz, $J_{2,3} = J_{3,4} = 5·3$ Hz. The xylo-isomer (7X) (*A* 46%; *B* 63%) had m.p. 132—134° (Found: C, 45·7; H, 3·2; I, 36·9%), τ 1·8—2·8 (m, aromatic H), 3·81 (1H, t, $J_{2,3} = J_{3,4} = 5$ Hz, H-3), 4·52 (2H, q, width 16 Hz, H-2 and H-4), and 6·48 (4H, d, 5·5 Hz, H-1, H-1′, H-5, and H-5′).

2,3,4-*Tri*-O-*benzoyl*-1,5-*dideoxypentitols* (8).—Palladium–charcoal (28%; 40 mg) was added to a solution of the di-iodide (7) (100 mg) in a mixture of ethyl acetate and methanol containing sodium acetate (60 mg). After hydrogenolysis at atmospheric pressure the mixture was filtered and evaporated to dryness. The residue was partitioned between dichloromethane and aqueous sodium thiosulphate. The extract was dried and the solvent removed. Only the *xylo*-isomer (8X) was obtained in crystalline form (from light petroleum); the other two remained as syrups. The L-arabino-*isomer* (8A) (41%) had $[\alpha]_D$ −6° (*c* 1·6 in $CHCl_3$) (Found: C, 72·2; H, 5·9. $C_{26}H_{24}O_6$ requires C, 72·2; H, 5·6%), τ 1·8—2·7 (m, aromatic H), 4·1—4·5 (3H, m, H-2, H-3, and H-4), and 8·52 (6H, d, *J* 7 Hz, 2 × Me). The ribo-*isomer* (8R) (87%) (Found: C, 71·9; H, 5·9%) showed τ 1·8—2·7 (m, aromatic H), 4·1—4·5 (3H, m, H-2, H-3, and H-4), and 8·46 (6H, d, *J* 7 Hz, 2 × Me). The xylo-*isomer* (8X) (63%) had m.p. 134—136° (Found: C, 71·9; H, 5·6%), τ 1·8—2·7 (m, aromatic H), 4·2—4·6 (3H, m, H-2, H-3, and H-4), and 8·55 (6H, d, *J* 6 Hz, 2 × Me).

Samples of the benzoates (8) (15 mg) were dissolved in N-sodium methoxide (1 ml). After 1 h at 50°, the solutions were evaporated and partitioned between water and light petroleum. Evaporation of the aqueous fraction gave the crude triol, R_F 0·55, which was acetylated in the usual way

[7] W. E. Trevelyan, D. P. Procter, and J. S. Harrison, *Nature*, 1950, **166**, 444.

[8] J. Csaszar and V. Bruckner, *Ann. Univ. Sci. Budapest*, 1967, **9**, 49 (*Chem. Abs.*, 1968, **69**, 52,446u).

[9] D. A. Applegarth, Ph.D. Thesis, 1962, Newcastle upon Tyne.

[10] K. Anno, *J. Agric. Chem. Soc. Japan*, 1950, **23**, 441 (*Chem. Abs.*, 1952, **46**, 3495g).

(acetic anhydride–pyridine). Only the *xylo*-triacetate (4X) was crystalline (m.p. 124—125°) but all three gave single peaks on g.l.c. (typical retention times: *arabino*, 18; *ribo*, 16·5; *xylo*, 27 min).

5-S-*Methyl*-5-*thio*-D-*xylose Dimethyl Dithioacetal* (10).—A solution of 1,2-*O*-isopropylidene-5-*S*-methyl-5-thio-α-D-xylofuranose [5] (0·60 g) in acetic acid (3 ml) was cooled to 0°, and methanethiol (2 ml) and concentrated hydrochloric acid (1 ml) were added. The mixture was stirred at 0° for 75 min and then neutralised with ammonia (*d* 0·880). The mixture was evaporated and the residue was dissolved in water and continuously extracted with dichloromethane. The extract was dried and evaporated. Crystallisation of the residue from benzene gave the *dithioacetal* (10) (0·60 g), m.p. 105—106°, $[\alpha]_D$ +56° (*c* 1·3 in $CHCl_3$) (Found: C, 37·0; H, 7·0; S, 37·25. $C_8H_{18}O_3S_3$ requires C, 37·2; H, 7·0; S, 37·2%).

Preparation of Raney Nickel.—Sodium hydroxide (20%; 20 ml) was added slowly to a stirred suspension of nickel–aluminium alloy (40 g) in water (200 ml) at 40°, so that the temperature did not rise above 60°. After 2 h at 40° more sodium hydroxide (40%; 130 ml) was added and the stirred mixture was kept at 50° for 2 h. The white supernatant was discarded and the residue was washed by decantation (fifteen times with water and three times with ethanol). The nickel was kept under ethanol and used within 2 months.

Desulphurisation Experiments.—The general procedure was as follows. A mixture of the compound (1 part by weight) and Raney nickel (10 parts by volume) in 80% ethanol (100 parts by volume) was heated under reflux for 1 h. The mixture was filtered and evaporated to dryness. The residue was extracted with hot ethyl acetate and the extract was purified by bulb distillation at 120° and 0·1 mmHg. The distillates all gave single spots on paper chromatography (R_F 0·55) and t.l.c.

Samples of the dideoxypentitol containing distillates were acetylated (acetic anhydride–pyridine) for examination by g.l.c. In all cases, except that of the *ribo*-derivative (9), the crystalline 2,3,4-*tri*-O-*acetyl*-1,5-*dideoxyxylitol* (4X), m.p. 124—125° (from light petroleum) was isolated (Found: C, 53·5; H, 7·1. $C_{11}H_{18}O_6$ requires C, 53·6; H, 7·4%).

Table 1 gives the composition of the desulphurisation products as well as the yield of crystalline *xylo*-triacetate (4X) isolated.

Effect of Time on the Desulphurisation of 5-S-*Ethyl*-5-*thio*-L-*arabinose Diethyl Dithioacetal* (2).—The dithioacetal (2) (0·13 g) was desulphurised as just described. Samples were taken after 5, 15, 60, and 135 min, and immediately filtered. Each was examined by paper chromatography, which showed the desulphurisation to be complete after 5 min; thereafter no change was apparent. The samples were acetylated and examined by g.l.c. The results are shown in Table 2.

TABLE 2

Effect of time on the desulphurisation of the dithioacetal (2)

	Product composition (%)		
t/min	*arabino*	*ribo*	*xylo*
5	89	7	4
15	82	10	8
60	74	12	14
135	70	16	14

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