426. *Aspects of Stereochemistry. Part XI.* Isopropylidene Derivatives of* L-*Arabitol and Ribitol.*

By M. A. Bukhari, A. B. Foster, J. Lehmann, J. M. Webber, and J. H. Westwood.

The positions of the free hydroxyl groups in the di-*O*-isopropylidene derivatives of L-arabitol and ribitol have been established by reaction sequences based on benzoate exchange which involve treatment of the sulphonyl derivatives with sodium benzoate or sodium thiobenzoate in dimethylformamide. Thus, di-*O*-isopropylidene-L-arabitol has the 1-hydroxyl group unsubstituted. Di-*O*-isopropylideneribitol prepared by two methods is a mixture with the major component having a 1,2,3,4-distribution of the ketal rings, and the minor component has a 1,2,4,5-arrangement.

Treatment of certain carbohydrate primary and secondary *O*-sulphonates with sodium benzoate in dimethylformamide results in nucleophilic displacement to yield *O*-benzoates; inversion of configuration occurred with the secondary sulphonate.[1] In the preceding paper the reaction was applied as an alternative to methylation to locate the free hydroxyl group in 1,2:3,4-di-*O*-isopropylidene-L-rhamnitol and we now report further applications to the isopropylidene derivatives of L-arabitol and ribitol.

Although both arabitol and ribitol were observed by Speier[2] in 1895 to give di-*O*-isopropylidene derivatives, apparently there has been no subsequent report of structural investigations. When treated with a suspension of anhydrous copper sulphate in acetone containing sulphuric acid, L-arabitol gave a good yield of a liquid di-*O*-isopropylidene derivative. The crystalline *O*-toluene-*p*-sulphonate was readily converted by sodium benzoate in boiling dimethylformamide into an *O*-benzoyl-di-*O*-isopropylidenepentitol, the configuration of which was revealed when sequential application of saponification and acidic hydrolysis gave L-arabitol. Thus the free hydroxyl group in the di-*O*-isopropylidene-L-arabitol must be in a terminal position or at C-3; D- and L-arabitol are unique in that inversion of configuration at position 3 does not change the total configuration of the molecules.

In order to establish the precise location of the free hydroxyl group a variation of the benzoate exchange was introduced and evaluated for model compounds. When the 6-*O*-methanesulphonate or 6-*O*-toluene-*p*-sulphonate of 1,2:3,4-di-*O*-isopropylidene-α-D-galactose was treated with a boiling solution of sodium thiobenzoate (Ph·CO·SNa) in dimethylformamide, a good yield of 6-benzoylthio-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactose was obtained. No trace of 6-*O*-thiobenzoyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactose, arising from nucleophilic displacement by Ph·CS·O$^-$ could be detected. Reductive desulphuration of the thiobenzoate with Raney nickel gave 1,2:3,4-di-*O*-isopropylidene-α-D-fucose. Displacement of a secondary methanesulphonate by thiobenzoate has also been observed; thus, *cis*-5-methanesulphonyloxy-2-phenyl-1,3-dioxan yields *trans*-5-benzoylthio-2-phenyl-1,3-dioxan. Methanesulphonates were preferred to toluene-*p*-sulphonates in the thiobenzoate displacements since the course of the reaction could be followed by the rate of separation of sodium methanesulphonate, sodium thiobenzoate being freely soluble in dimethylformamide.

With sodium thiobenzoate in boiling dimethylformamide, the di-*O*-isopropylidene-*O*-toluene-*p*-sulphonyl-L-arabitol gave a thiobenzoate which when subjected in sequence to reductive desulphuration and acid hydrolysis gave 1-deoxy-L-arabitol identical with the product obtained[3] by reductive desulphuration of L-arabinose diethyl dithioacetal. Thus

* Part X, preceding paper.

[1] Reist, Goodman, and Baker, *J. Org. Chem.*, 1958, **80**, 5775; Reist, Spencer, and Baker, *ibid.*, 1959, **24**, 1618.

[2] Speier, *Ber.*, 1895, **28**, 2531.

[3] Zissis and Richtmyer, *J. Amer. Chem. Soc.*, 1954, **76**, 5515.

the original di-*O*-isopropylidene compound may be assigned the structure 2,3,4,5-di-*O*-isopropylidene-L-arabitol (1,2,3,4-di-*O*-isopropylidene-L-lyxitol). A 2,3:4,5-distribution of the ketal rings in this compound might be expected by analogy with the pattern of condensation established [4] for other polyhydric alcohol–acetone reactions since it would involve α and αT rings (in Barker and Bourne's terminology [5]). However, a different pattern of condensation appears to occur (see preceding paper). It is of interest that L-arabitol and L-arabinose diethyl dithioacetal condense in a similar manner with acetone.[6] Thus demercaptalation of 2,3,4,5-di-*O*-isopropylidene-L-arabinose diethyl dithioacetal and reduction of the resultant *aldehydo*-compound with sodium borohydride gave a di-*O*-isopropylidene derivative identical with that obtained by the condensation of L-arabitol with acetone.

The reaction of ribitol with acetone is of interest since, provided that 1,3-dioxolan derivatives are produced, α and αC rings, but not αT, ketal rings can be formed. There is no substantiated example of the formation of an αC-isopropylidene derivative in the reaction of acetone with polyhydric alcohols although certain acyclic *erythro*-1,2-diol derivatives do form isopropylidene derivatives.[7] Isopropylidene-hexitol derivatives which contain an αC-ketal ring can be obtained by indirect methods, *e.g.*, 1,2:4,5-di-*O*-isopropylidene-D-mannitol [8] {m. p. 43—45°, $[\alpha]_D$ −12° (*c* 1·7 in $CHCl_3$)} formed by reduction of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose with sodium borohydride.

Ribitol readily gave a di-*O*-isopropylidene derivative on reaction with acetone in the presence of hydrogen chloride or zinc chloride. Although the same product appeared to be formed in each case, as inferred from the close similarity of their infrared spectra, examination by vapour-phase chromatography revealed the presence in each product of two components in unequal proportion. The mixture of di-*O*-isopropylideneribitols gave a sharp-melting benzoate (*A*) (m. p. 73—74°, 50%) and *p*-phenylazobenzoate (m. p. 141—142°; 72%), but the methanesulphonate had a wide melting range (63—76°) and presumably was a mixture. When the crystalline methanesulphonate was treated with sodium benzoate and dimethylformamide a benzoate was obtained in moderate yield (43%) which was identical with benzoate *A*. Since benzoate *A* has the *ribo*-configuration, one component of the presumed mixture of methanesulphonates had undergone benzoate exchange without change in configuration and hence must have contained a primary methanesulphonate group. Thus benzoate *A* is a 1-*O*-benzoyl-2,3,4,5-di-*O*-isopropylideneribitol. When the benzoate, obtained by submitting the crude methanesulphonate to benzoate exchange, was subjected to sequential saponification, acidic hydrolysis, and acetylation and then examined by vapour-phase chromatography, two components were revealed with retention times similar to those of the penta-*O*-acetates of ribitol and xylitol, the former component predominating. Since the retention times of the penta-*O*-acetates of ribitol and arabitol are similar, the presence of the latter compound in the mixture of acetates cannot be ruled out, but in any case the amount must be small. The presence of penta-*O*-acetylxylitol requires that the mixed methanesulphonates contain a 1,2,4,5-di-*O*-isopropylidene-3-*O*-methanesulphonylribitol. Thus the presence of at least two components in the original di-*O*-isopropylideneribitol is confirmed. The 1,2,4,5-di-*O*-isopropylidene derivative probably has a 1,2:4,5-distribution of the cyclic ketal groups since any other arrangement would involve at least one 7-membered or larger ring. That this compound is the minor component in the mixture is surprising since it contains two α rings and might be expected [4] to be the favoured product. The structure of the 1,2,3,4-di-*O*-isopropylideribitol cannot be predicted with certainty since no analogous cases are known and the two most likely structures involving 1,2:3,4- and 1,3:2,4-distributions of

[4] Barker and Bourne, *Adv. Carbohydrate Chem.*, 1952, **7**, 137.
[5] Barker and Bourne, *J.*, 1952, 905.
[6] Bollenback and Underkofler, *J. Amer. Chem. Soc.*, 1950, **72**, 741.
[7] Hermans, *Z. phys. Chem.*, 1924, **113**, 337.
[8] Bukhari, Foster, Lehmann, and Webber, unpublished preparation.

the ketal rings contain sterically unfavourable features: the former contains a 1,3-dioxolan ring with *cis*-4,5-substituents and the latter a ring system related to *trans*-decalin but with two axial methyl groups.

The structures of the isopropylidene derivatives of ribitol are being further investigated.

The tendency of the *ribo*-1,2,3,4-tetrahydroxybutyl group to condense with two molecules of acetone was further exemplified by D-ribose diethyl dithioacetal, which gave a di-*O*-isopropylidene derivative under conditions similar to those employed for ribitol. The mercaptal groups were readily removed, to give 2,3,4,5-di-*O*-isopropylidene-*aldehydo*-D-ribose from which 1,2,3,4-di-*O*-isopropylidene L-ribitol was obtained by reduction with sodium borohydride and characterised as the benzoate.

Experimental

Vapour-phase chromatography was performed on a Pye argon instrument with ionisation detection and a column *ca.* 120 × 0·4 cm., packed with 10% silicone oil on 100—120 mesh Celite.

2,3,4,5-*Di*-O-*isopropylidene*-L-*arabitol*.—A mixture of L-arabitol (15·2 g.), anhydrous copper sulphate (12 g.), concentrated sulphuric acid (2 ml.), and acetone (300 ml.) was shaken at room temperature for 18 hr., then neutralised with concentrated aqueous ammonia and filtered. Concentration of the solution and distillation of the residue gave the product [2] (17·6 g., 76%), b. p. 74—80°/0·05 mm., $[\alpha]_D$ *ca.* +1° (*c* 1·2 in $CHCl_3$) (Found: C, 57·3; H, 8·45. Calc. for $C_{11}H_{20}O_5$: C, 56·9; H, 8·7%).

The *toluene*-p-*sulphonate*, prepared in the usual way, had m. p. 76—79°, $[\alpha]_D$ −16° (*c* 1·3 in $CHCl_3$) (Found: C, 55·7; H, 6·4; S, 8·4. $C_{18}H_{26}O_7S$ requires C, 55·95; H, 6·8; S, 8·3%); it decomposed on storage.

A solution of 2,3,4,5-di-*O*-isopropylidene-*aldehydo*-L-arabinose [6] (1·24 g.) in 50% aqueous methanol (20 ml.) containing sodium borohydride (0·35 g.) was stored at room temperature overnight and then continuously extracted with chloroform. Evaporation of the dried (Na_2SO_4) extract and distillation of the residue gave 2,3,4,5-di-*O*-isopropylidene-L-arabitol (0·84 g.), b. p. 125° (bath)/0·05 mm., which had an infrared spectrum (liquid film) indistinguishable from that of the product described above obtained by the reaction of L-arabitol with acetone. The toluene-*p*-sulphonate had m. p. 76—78° (from ethanol) alone or in admixture with the foregoing toluene-*p*-sulphonate and $[\alpha]_D$ −16° (*c* 1·4 in $CHCl_3$).

Benzoate Exchange Experiments.—(*a*) A solution of the foregoing toluene-*p*-sulphonate (2·1 g.) in dimethylformamide (50 ml.) was boiled in the presence of sodium benzoate (4 g.) for 6 hr. The mixture was poured into saturated aqueous sodium hydrogen carbonate (100 ml.) and extracted with chloroform (150 ml.). The extract was washed thrice with water, decolorised with charcoal, dried ($MgSO_4$), and concentrated. Distillation of the residue (1·6 g.) gave 1-O-*benzoyl*-2,3,4,5-*di*-O-*isopropylidene*-L-*arabitol* (1·25 g., 69%), b. p. 154°/0·05 mm., $[\alpha]_D$ −21° (*c* 0·8 in $CHCl_3$) (Found: C, 64·4; H, 7·4. $C_{18}H_{24}O_6$ requires C, 64·3; H, 7·2%).

A solution of the foregoing benzoate (1·0 g.) in water (30 ml.) and methanol (20 ml.) containing sodium hydroxide (6·5 g.) was heated on a boiling-water bath for 3 hr., then extracted continuously with ether for 3 hr. Concentration of the dried (Na_2SO_4) extract gave a residue (0·46 g.), the infrared spectrum (liquid film) of which was indistinguishable from that of 2,3,4,5-di-*O*-isopropylidene-L-arabitol. Treatment of the residue with boiling 60% acetic acid for 3 hr., and evaporation of the solution gave a product (0·374 g.) which had $\nu_{max.}$ (C=O) at *ca.* 1735 cm.$^{-1}$, probably owing to partial acetylation. A portion (0·1 g.) was treated with boiling methanol (2 ml.) containing 0·1N-methanolic sodium methoxide (1 drop) for 20 min. The hot solution was filtered and diluted with acetone to turbidity, to give L-arabitol (48 mg.), m. p. and mixed m. p. 101—102°, $[\alpha]_D$ −30° (*c* 0·4 in 5% aqueous ammonium molybdate [9]) and −131° (*c* 0·3 in acidified molybdate [9]).

(*b*) A solution of sodium thiobenzoate (4·16 g.) and 1,2:3,4-di-*O*-isopropylidene-6-*O*-toluene-*p*-sulphonyl-α-D-galactose (2·1 g.) in dimethylformamide (50 ml.) was boiled under reflux for 1 hr. The cooled solution was diluted with water (75 ml.) and extracted with chloroform (3 × 50 ml.). The combined extracts were washed with aqueous sodium hydrogen carbonate, then water, dried (Na_2SO_4), and concentrated. Distillation of the residue (1·78 g.) gave

[9] Richtmyer and Hudson, *J. Amer. Chem. Soc.*, 1951, **73**, 2249.

6-*benzoylthio*-6-*deoxy*-1,2:3,4-*di*-O-*isopropylidene*-α-D-*galactose* (1·63 g., 83%), b. p. 210—225° (bath)/0·05 mm., $[\alpha]_{5461}$ −39° (*c* 1·3 in $CHCl_3$) (Found: C, 59·9; H, 6·4; S, 8·6. $C_{19}H_{24}O_6S$ requires C, 60·0; H, 6·4; S, 8·4%).

Under essentially the same conditions the corresponding methanesulphonate (1·69 g.) also gave the thiobenzoate (1·61 g., 85%).

A solution of the foregoing thiobenzoate (1·61 g.) in ethanol (100 ml.) was boiled in the presence of Raney nickel (3·2 g.) for 3 hr. Filtration and concentration of the solution gave a residue (0·93 g.) with an infrared spectrum (liquid film) similar to that of 1,2:3,4-di-*O*-isopropylidene-α-D-fucose. Crystallisation of the residue from ethanol gave pure 1,2:3,4-di-*O*-isopropylidene-α-D-fucose (0·56 g.), m. p. and mixed m. p. 33—35°.

In essentially the same conditions, when *cis*-5-methanesulphonyloxy-2-phenyl-1,3-dioxan [8] (0·53 g.) was treated with sodium thiobenzoate (1·62 g.) in boiling dimethylformamide (20 ml.) for 15 min., trans-5-*benzoylthio*-2-*phenyl*-1,3-*dioxan* (0·47 g., 72%) was obtained with m. p. 87—88° (from ethanol) (Found: C, 68·0; H, 5·4; S, 10·6. $C_{17}H_{16}O_3S$ requires C, 68·0; H, 5·4; S, 10·65%).

(*c*) A solution of 2,3,4,5-di-*O*-isopropylidene-1-*O*-toluene-*p*-sulphonyl-L-arabitol (5·5 g.) and sodium thiobenzoate (10 g.) in dimethylformamide (100 ml.) was boiled under reflux for 3 hr., then worked up as described in (*b*). A portion (3·2 g.) of the crude product (4·53 g.) was distilled, to yield 1-*benzoylthio*-1-*deoxy*-2,3,4,5-*di*-O-*isopropylidene*-L-*arabitol* (1·8 g.), b. p. 156—160°/0·1 mm., $[\alpha]_D$ −40° (*c* 1·2 in $CHCl_3$) (Found: C, 61·3; H, 6·8. $C_{18}H_{24}O_5S$ requires C, 61·35; H, 6·9%).

When a solution of the foregoing thiobenzoate (2·11 g.) was boiled in ethanol (125 ml.) in the presence of Raney nickel [10] (5 ml.), then filtered and concentrated, a sulphur-containing residue (1·57 g.) was obtained. Further similar treatment with Raney nickel (30 ml.) and ethanol (150 ml.) gave a sulphur-free product (0·82 g.), presumably 1-deoxy-2,3,4,5-di-*O*-isopropylidene-L-arabitol, which was hydrolysed directly with boiling 0·1N-sulphuric acid (100 ml.) for 3 hr. Anions were removed from the hydrolysate by Amberlite resin IRA-400 (HO^- form), and subsequent concentration gave 1-deoxy-L-arabitol (0·28 g.), m. p. 130—131° (from methanol–ether) alone or in admixture with the authentic compound,[3,6] $[\alpha]_D$ +28° (*c* 0·4 in 5% aqueous ammonium molybdate [9]) and −17° (*c* 0·3 in acidified molybdate [9]).

(*d*) Treatment of di-*O*-isopropylideneribitol (2·5 g.) with methanesulphonyl chloride (2·5 ml.) in pyridine (15 ml.) at 0° in the usual way gave a crude product (3 g.) which crystallised from benzene–light petroleum (b. p. 60—80°), yielding mixed methanesulphonates, m. p. 63—76° (Found: S, 10·3. Calc. for $C_{12}H_{22}O_7S$: S, 10·3%). The m. p. range was not changed by repeated recrystallisation, and the product rapidly decomposed.

A solution of di-*O*-isopropylidene-*O*-methanesulphonylribitol (1·7 g.; m. p. 63—76°) in dimethylformamide (45 ml.) was boiled for 6 hr. in the presence of sodium benzoate (5 g.), then cooled and diluted with water (*ca.* 100 ml.). The mixture was extracted with chloroform (2 × 50 ml.), the combined extracts were washed with aqueous sodium hydrogen carbonate and then water, dried (Na_2SO_4), and evaporated. Distillation of the residue gave 1-*O*-benzoyl-2,3,4,5-di-*O*-isopropylideneribitol, b. p. 140—142°/0·1 mm. Crystallisation of the distillate from methanol gave a product (0·8 g., 43%), m. p. 72—73° alone or in admixture with the product obtained by benzoylation of di-*O*-isopropylideneribitol. The infrared spectra (in Nujol) of the two benzoates were indistinguishable.

In a second experiment the crude methanesulphonate, without recrystallisation, was subjected to benzoate exchange, and the benzoate (0·5 g.), instead of being distilled, was heated with sodium hydroxide (3 g.) in water (15 ml.) and methanol (10 ml.) for 3 hr. The mixture was diluted with water (40 ml.) and extracted with chloroform continuously overnight. The extract was concentrated and the residue was hydrolysed with boiling 50% acetic acid for 1·5 hr. Evaporation of the hydrolysate gave a residue which was acetylated with acetic anhydride and pyridine in the usual way. Examination of the product by vapour-phase chromatography at 175°/13 lb. per sq. in. revealed components with retention distances of 7·4 and 8·15 cm., and peak heights of 4·8 and 2·7, respectively. The penta-acetates of L-arabitol, ribitol, and xylitol had retention distances of 7·25, 7·2, and 8·2 cm., respectively.

Di-O-*isopropylideneribitol*.—(*a*) The products prepared by the reaction of ribitol with acetone in the presence of zinc chloride [11] or hydrogen chloride [2] had b. p. 155—160°/~12 mm.,

[10] Pavlic and Adkins, *J. Amer. Chem. Soc.*, 1947, **69**, 3039.
[11] Fischer and Taube, *Ber.*, 1927, **60**, 485.

and gave infrared spectra (liquid film) which were indistinguishable. Examination of these products by gas-phase chromatography at 175°/15 lb. per sq. in. gave two peaks with retention distances 2·8 and 3·7 cm. and peak heights in the ratio 2·3 : 1.

The di-*O*-isopropylidene compound (0·4 g.) with *p*-phenylazobenzoyl chloride (0·46 g.) and pyridine (5 ml.) in the usual way [12] gave a p-*phenylazobenzoate* (0·55 g., 72%), m. p. 141—142° (from acetone) (Found: C, 65·35; H, 6·5; N, 6·6. $C_{24}H_{28}N_2O_6$ requires C, 65·4; H, 6·4; N, 6·4%). Likewise with benzoyl chloride in pyridine a *benzoate* (50%) was obtained; this had m. p. 73—74° (from methanol) (Found: C, 64·0; H, 7·4. $C_{18}H_{24}O_6$ requires C, 64·3; H, 7·2%).

2,3,4,5-*Di*-O-*isopropylidene*-aldehydo-D-*ribose and its Derivatives*.—D-Ribose diethyl dithioacetal [13] (6 g.; m. p. 82—83°), anhydrous copper sulphate (8 g.), concentrated sulphuric acid (1·4 ml.), and acetone (220 ml.) were shaken at room temperature for 10 hr., then basified with aqueous ammonia. The filtered solution was evaporated, and a solution of the residue in chloroform was washed with water, aqueous sodium hydrogen carbonate, and water, dried (Na_2SO_4), and evaporated. Distillation of the residue gave 2,3,4,5-*di*-O-*isopropylidene*-D-*ribose diethyl dithioacetal* (6·1 g.), b. p. 125—135°/0·2 mm., $[\alpha]_D$ −53° (*c* 0·8 in $CHCl_3$) (Found: C, 53·4; H, 8·6; S, 18·9. $C_{15}H_{28}O_4S_2$ requires C, 53·6; H, 8·4; S, 19·0%).

A solution of the dithioacetal (3·5 g.) in acetone (120 ml.) and water (30 ml.) was stirred in the presence of cadmium carbonate (17 g.) and treated dropwise with a solution of mercuric chloride (17 g.) in acetone (60 ml.). After a further 15 hr. the filtered solution was diluted with 1% aqueous sodium carbonate (300 ml.) and extracted with chloroform (2 × 50 ml.). The combined extracts were washed with water (200 ml.), dried (Na_2SO_4), and concentrated. Distillation of the residue gave 2,3,4,5-*di*-O-*isopropylidene*-aldehydo-D-*ribose* (1·7 g.; 70%), b. p. 73—75°/0·1 mm., $[\alpha]_D$ −36° (*c* 0·6 in $CHCl_3$) (Found: C, 57·2; H, 7·6. $C_{11}H_{18}O_5$ requires C, 57·4; H, 7·9%).

A solution of the foregoing *aldehydo*-compound (0·25 g.) in 50% aqueous methanol (20 ml.) was treated with sodium borohydride at room temperature for 12 hr., then extracted continuously with chloroform. The extract was washed with water, dried ($CaSO_4$), and evaporated and the residue was distilled, to yield 2,3,4,5-*di*-O-*isopropylidene*-D-*ribitol* (81%), b. p. 155—160°/12 mm., $[\alpha]_D$ −8° (*c* 0·8 in $CHCl_3$) (Found: C, 56·9; H, 8·75. $C_{11}H_{20}O_5$ requires C, 56·9; H, 8·7%). The *benzoate* had m. p. 79—80°, $[\alpha]_D$ −32° (*c* 1·2 in $CHCl_3$) (Found: C, 64·3; H, 7·1. $C_{18}H_{24}O_6$ requires C, 64·3; H, 7·2%).

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CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

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[12] Baggett, Foster, Haines, and Stacey, *J.*, 1960, 3528.
[13] Kenner, Rodda, and Todd, *J.*, 1949, 1613.