425. *Aspects of Stereochemistry. Part X.* Isopropylidene Derivatives of* L-*Rhamnitol.*

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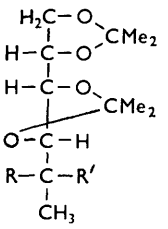
The condensation product of acetone with L-rhamnitol is shown to be 1,2:3,4-di-*O*-isopropylidene-L-rhamnitol which on graded hydrolysis affords the 3,4-*O*-isopropylidene derivative.

In certain cases, treatment of carbohydrate secondary sulphonates with sodium benzoate in dimethylformamide results in nucleophilic displacement of the sulphonate groups, affording benzoates with inverted configuration. The reaction, first described by Reist, Spencer, and Baker,[1] is of potential value in structural determination as an alternative to methylation. We now report an example of its use in this respect in the structural determination of 1,2:3,4-di-*O*-isopropylidene-L-rhamnitol.

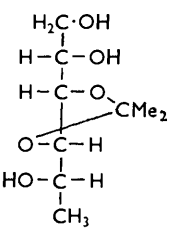
* Part IX, *J.*, 1961, 5011.

[1] Reist, Spencer, and Baker, *J. Org. Chem.*, 1959, **24**, 1618.

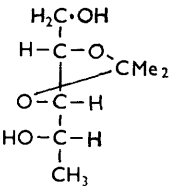
With acetone, concentrated sulphuric acid, and anhydrous copper sulphate, L-rhamnitol readily yielded a di-*O*-isopropylidene derivative (I). When a solution of the toluene-*p*-sulphonate of the latter compound in dimethylformamide was boiled in the presence of sodium benzoate for 6 hr. a moderate yield of a benzoate (II) was obtained which on saponification and subsequent acid hydrolysis gave 1-deoxy-L-glucitol (6-deoxy-D-gulitol), identified by comparison of its properties (m. p. 125—126°, $[\alpha]_D$ −3·9° in H_2O) with those



(I : R = OH, R′ = H)
(II : R = H, R′ = BzO)



(III)



(IV)

(m. p. 127°, $[\alpha]_D$ +3·97°) of authentic [2] 1-deoxy-D-glucitol. Only inversion of configuration at position 5 in the di-*O*-isopropylidene-L-rhamnitol could give rise to 1-deoxy-L-glucitol; hence the free hydroxyl group must have been located at that position with a consequent 1,2,3,4-distribution of the acetone residues. The benzoate was therefore 2-*O*-benzoyl-1-deoxy-3,4:5,6-di-*O*-isopropylidene-L-glucitol (II).

When a solution of the di-*O*-isopropylidene-L-rhamnitol in 70% acetic acid was kept at room temperature for 80 min., then neutralised, and fractionated on charcoal–Celite, a crystalline mono-*O*-isopropylidene compound (III) was obtained which was further characterised as the tri-*O*-*p*-phenylazobenzoate. The mono-*O*-isopropylidene compound rapidly consumed one mol. of periodate and hence contained one vicinal diol grouping. Reduction with borohydride of the carbohydrate product of the periodate oxidation gave a deoxy-*O*-isopropylidenepentitol (IV), characterised as the di-*p*-phenylazobenzoate. After application in sequence of acidic hydrolysis and acetylation to the deoxy-*O*-isopropylidenepentitol, 2,3,4,5-tetra-*O*-acetyl-1-deoxy-L-lyxitol was obtained; it was identified by comparison of its properties (m. p. 57—58°, $[\alpha]_D$ −47° in $CHCl_3$) with those (m. p. 58—59°, $[\alpha]_D$ +46·1° in $CHCl_3$) of the authentic D-compound.[3] Since one carbon atom was lost in the periodate oxidation of the mono-*O*-isopropylidene-L-rhamnitol the presence of a terminal vicinal diol grouping is revealed and since C-5 must be unsubstituted the isopropylidene group must span the 3,4-positions (III). The structure of the parent compound is therefore established as 1,2:3,4-di-*O*-isopropylidene-L-rhamnitol (I), that of the benzoate as 2-*O*-benzoyl-1-deoxy-3,4:5,6-di-*O*-isopropylidene-L-glucitol (II), and that of the pentitol derivative as 1-deoxy-3,4-*O*-isopropylidene-L-lyxitol (IV).

1,2:3,4-Di-*O*-isopropylidene-L-rhamnitol contains α and αT, but no αC, cyclic ketal groups (on Barker and Bourne's terminology [4]), and thus the reaction of L-rhamnitol with acetone conforms to the pattern established in numerous other cases.[5] However, unlike those in other compounds (*e.g.*, 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol [6]) which contain α and αT cyclic ketal groups, the isopropylidene groups in 1,2:3,4-di-*O*-isopropylidene-L-rhamnitol are not greatly different in their sensitivity towards acid. Thus the $[\alpha]_D$ of a solution of the di-*O*-isopropylidene compound in hydrochloric acid (pH 1·0) at room temperature changed from −15·6° to +8·2° in 275 min. with no break indicative

[2] Müller, and Reichstein, *Helv. Chim. Acta*, 1938, **21**, 251.
[3] Zissis and Richtmyer, *J. Amer. Chem. Soc.*, 1954, **76**, 5515.
[4] Barker and Bourne, *J.*, 1952, 905.
[5] Barker and Bourne, *Adv. Carbohydrate Chem.*, 1952, **7**, 137.
[6] Wiggins, *J.*, 1946, 13.

of a maximum concentration of the mono-*O*-isopropylidene compound. Further, analysis of the hydrolysate during this period revealed only small amounts of mono-*O*-isopropylidene derivative and, in fact, the best method of preparation of this compound was to allow the di-*O*-isopropylidene-L-rhamnitol to dissolve in hydrochloric acid (pH 1·0) (*ca.* 7 min.), then to neutralise the mixture, to recover unchanged starting material and mono-*O*-isopropylidene compound, and to repeat the acid treatment of the recovered material. By replication of this process a 59% yield of 3,4-*O*-isopropylidene-L-rhamnitol was obtained.

The physical constants (m. p. 62—63°, $[\alpha]_D$ *ca.* 0° in MeOH) of the di-*O*-isopropylidene-L-rhamnitol [7] obtained by treating 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-L-arabinose with methylmagnesium iodide {the D-analogue (m. p. 66—67°, $[\alpha]_D$ +1° ± 1·5° in MeOH), has also been prepared [8] by the Grignard route} are indicative of its non-identity with the 1,2:3,4-di-*O*-isopropylidene-L-rhamnitol (m. p. 64—66°, $[\alpha]_D$ −16° in MeOH) described herein. This being so, the structures of the di-*O*-isopropylidene-*aldehydo*-D- and L-arabinose cannot contain a 2,3:4,5-distribution of the cyclic ketal groups.

Experimental

Isopropylidenation of L-*Rhamnitol.*—A mixture of L-rhamnitol (18 g.), anhydrous copper sulphate (12 g.), concentrated sulphuric acid (2 ml.), and acetone (330 ml.) was shaken at room temperature for 16 hr., then basified with concentrated aqueous ammonia. The filtered solution was concentrated and the solid residue (24 g.) was recrystallised from benzene, to yield 1,2:3,4-di-*O*-isopropylidene-L-rhamnitol (17·5 g., 66%), m. p. 64—66°, $[\alpha]_D$ −16° (*c* 1·5 in MeOH), *ca.* 0° (*c* 2·5 in $CHCl_3$), $[\alpha]_{5461}$ −17° (*c* 2·2 in MeOH) (Found: C, 58·45; H, 8·9. Calc. for $C_{12}H_{22}O_5$: C, 58·55; H, 8·9%). Bollenback and Underkofler [7] record m. p. 62—64°, $[\alpha]_D$ 0° in MeOH, and Gätzi and Reichstein [8] record m. p. 66—67°, $[\alpha]_D$ +1° in MeOH for other di-*O*-isopropylidene derivatives, of undetermined structure, of L- and D-rhamnitol.

The conventional procedure gave the *toluene*-p-*sulphonate*, m. p. 83—84°, $[\alpha]_D$ −13° (*c* 2·0 in $CHCl_3$) (Found: C, 57·2; H, 6·9; S, 8·3. $C_{19}H_{28}O_7S$ requires C, 57·0; H, 7·0; S, 8·0%).

Benzoate Exchange of 1,2:3,4-*Di*-O-*isopropylidene*-5-O-*toluene*-p-*sulphonyl*-L-*rhamnitol.*—A solution of the toluene-*p*-sulphonate (7·36 g.) in dimethylformamide (185 ml) was boiled under reflux for 6 hr. in the presence of sodium benzoate (15 g.). The cooled mixture was diluted with water (185 ml.) and extracted with chloroform (*ca.* 200 ml.). The extract was washed with aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated and a solution of the residue in benzene was passed through alumina. The eluate was concentrated and the residue distilled, to yield 2-O-*benzoyl*-1-*deoxy*-3,4:5,6-*di*-O-*isopropylidene*-L-*glucitol* (2·53 g., 39%), b. p. 140°/0·5 mm., $[\alpha]_D$ −15° (*c* 1·6 in $CHCl_3$) (Found: C, 65·4; H, 7·5. $C_{19}H_{26}O_6$ requires C, 65·1; H, 7·4%).

The foregoing benzoate (2 g.) was treated on a boiling-water bath for 3 hr. with water (24 ml.) and methanol (16 ml.) containing sodium hydroxide (5·2 g.). The mixture was then extracted continuously overnight with ether. Evaporation of the dried (Na_2SO_4) ether layer and distillation of the residue gave 1-*deoxy*-3,4:5,6-*di*-O-*isopropylidene*-L-*glucitol* (0·96 g., 68%), b. p. 66—68°/0·2—0·3 mm., $[\alpha]_D$ −10° (*c* 3·0 in $CHCl_3$) (Found: C, 58·4; H, 8·95. $C_{12}H_{22}O_5$ requires C, 58·55; H, 8·9%).

A solution of the foregoing compound (0·68 g.) in 50% aqueous acetic acid (10 ml.) was boiled under reflux for 2 hr. and then evaporated under reduced pressure. The solid residue which after storage overnight *in vacuo* over sodium hydroxide had $[\alpha]_D$ −3·9° (*c* 1·6 in H_2O), was then recrystallised from methanol, to yield 1-deoxy-L-glucitol (0·16 g., 34%), m. p. 125—127° (Found: C, 43·8; H, 8·6. Calc. for $C_6H_{14}O_5$: C, 43·4; H, 8·4%). The infrared spectrum (in Nujol) was indistinguishable from that of authentic [2] 1-deoxy-D-glucitol (m. p. 127°).

Graded Acidic Hydrolysis of 1,2:3,4-*Di*-O-*isopropylidene*-L-*rhamnitol.*—(*a*) A solution of the di-*O*-isopropylidene compound (1·52 g.) in 70% acetic acid (75 ml.) was kept at room temperature for 80 min., then poured into an excess of saturated aqueous sodium carbonate. The mixture was extracted with chloroform (50 ml.) which removed mainly starting material (0·665 g.). Subsequent continuous extraction for 48 hr. with chloroform yielded a mixture (0·63 g.) of L-rhamnitol and 3,4-*O*-isopropylidene-L-rhamnitol. A solution of the mixture in

[7] Bollenback and Underkofler, *J. Amer. Chem. Soc.*, 1950, **72**, 741.
[8] Gätzi and Reichstein, *Helv. Chim. Acta*, 1938, **21**, 914.

dilute aqueous ammonia was added to a column (*ca.* 20 × 5 cm.) of charcoal–Celite,[9] and the column was eluted with the same solvent (200 ml.), yielding L-rhamnitol (97 mg.). Subsequent elution with 5% aqueous ethanol (1 l.) containing a small amount of ammonia gave crude mono-*O*-isopropylidene compound (0·21 g.). Recrystallisation from benzene–light petroleum (b. p. 60—80°) gave 3,4-O-*isopropylidene*-L-*rhamnitol* (0·12 g.), m. p. 77—78°. Further recrystallisation from benzene gave a product, m. p. 79—80°, $[\alpha]_D$ −24° (*c* 2·2 in H_2O) (Found: C, 52·4; H, 8·9. $C_9H_{18}O_5$ requires C, 52·4; H, 8·7%).

Omission of the ammonia from the solvents used in the charcoal–Celite chromatography resulted in hydrolysis of the isopropylidene compounds on the column, which was readily observed by paper chromatography with the organic phase of butanol–ethanol–water (4 : 1 : 5) and detection with silver nitrate [10] (R_F values: L-rhamnitol 0·34; mono-*O*-isopropylidene derivative 0·79; di-*O*-isopropylidene derivative not detected).

3,4-*O*-Isopropylidene-L-rhamnitol readily gave [11] a *tri*-p-*phenylazobenzoate*, m. p. 160—161° [from benzene–light petroleum (b. p. 60—80°)] (Found: C, 69·4; H, 5·2; N, 9·9. $C_{48}H_{42}N_6O_8$ requires C, 69·4; H, 5·1; N, 10·1%).

(*b*) The optical rotation of a 4% solution of 1,2:3,4-di-*O*-isopropylidene-L-rhamnitol in dilute hydrochloric acid (pH 1·0) was followed (see above). From a series of experiments the following appeared to be optimum conditions.

The di-*O*-isopropylidene derivative (24·6 g.) was finely powdered and shaken vigorously with dilute hydrochloric acid (600 ml.; pH 1·0) until an almost clear solution was obtained (*ca.* 7 min.). The solution was neutralised with aqueous sodium carbonate. Extraction of the mixture with chloroform (250 ml.) removed starting material (12·35 g.), and subsequent continuous extraction with ether removed the mono-*O*-isopropylidene compound with only traces of L-rhamnitol. The recovered starting material was rehydrolysed and the process repeated until recovered starting material was reduced to *ca.* 0·5 g. The combined ether extracts afforded crude product (21 g.) from which pure 3,4-*O*-isopropylidene-L-rhamnitol (12·2 g., 59%), m. p. 79—80°, was obtained by recrystallisation from benzene.

Periodate Oxidation of 3,4-O-*Isopropylidene*-L-*rhamnitol.*—(*a*) Cooled solutions of the isopropylidene compound (51 mg.) in water (1 ml.) and 0·25N-sodium metaperiodate (5 ml.) were mixed and the volume rapidly adjusted to 25 ml. Determination of oxidant consumption by a standard procedure [12] on aliquot parts withdrawn after 5 min. and 2 hr. revealed an uptake of 1·01 mol. in each case.

(*b*) A solution of 3,4-*O*-isopropylidene-L-rhamnitol (2 g.), sodium metaperiodate (5 g.), and sodium hydrogen carbonate (2·5 g.) in water (50 ml.) was stored at room temperature for 18 hr., then treated with saturated aqueous barium chloride until no further precipitation occurred. The filtered solution was treated with sodium borohydride (0·3 g.) and, after 18 hr. at room temperature, extracted continuously overnight with chloroform. Evaporation of the dried (Na_2SO_4) extract and distillation of the residue gave 1-*deoxy*-3,4-O-*isopropylidene*-L-*lyxitol* (1·08 g., 63%), b. p. 78—84°/0·1 mm., $[\alpha]_D$ +16° (*c* 2·7 in $CHCl_3$) (Found: C, 54·3; H, 9·2. $C_8H_{16}O_4$ requires C, 54·55; H, 9·1%); the *di*-p-*phenylazobenzoate* prepared in the usual way [11] had m. p. 130° (from ethanol) (Found: C, 68·3; H, 5·4; N, 9·5. $C_{32}H_{32}N_4O_6$ requires C, 67·6; H, 5·6; N, 9·9%).

A solution of 1-deoxy-3,4-*O*-isopropylidene-L-lyxitol (0·65 g.) in 50% aqueous acetic acid (30 ml.) was boiled under reflux for 3 hr., then evaporated to dryness under reduced pressure. Since the residue contained partially acetylated 1-deoxy-L-lyxitol as revealed by paper chromatography, acetylation of a portion (0·37 g.) was completed by using sodium acetate and acetic anhydride in the usual manner. Crystallisation of the crude product (0·6 g.) from chloroform–light petroleum (b. p. 40—60°) gave 2,3,4,5-tetra-*O*-acetyl-1-deoxy-L-lyxitol, m. p. 57—58°, $[\alpha]_D$ −47° (*c* 1·0 in $CHCl_3$) (Found: C, 51·3; H, 6·6. $C_{13}H_{20}O_8$ requires C, 51·3; H, 6·6%). Zissis and Richtmyer [3] record m. p. 58—59°, $[\alpha]_D$ +46·1° in $CHCl_3$, for the D-compound.

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[10] Trevelyan, Procter, and Harrison, *Nature*, 1950, **166**, 444.
[11] Baggett, Foster, Haines, and Stacey, *J.*, 1960, 3528.
[12] Jackson, *Org. Reactions*, 1944, **2**, 341.