909. *Ionophoresis of Carbohydrates. Part VII.** 2,5-*Di-O-methyl*-L-*rhamnose*: *its Ionophoresis and Conversion into* 6-*Deoxy*-2,5-*di-O-methyl*-L-*altrose.*

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A synthesis of 2,5-di-*O*-methyl-L-rhamnose is described. It is the first example of a sugar derivative the mobility of which in ionophoresis in borate buffer (pH 10) is due solely to complex formation of the aldehydo-form with borate ions. The conversion of 2,5-di-*O*-methyl-L-rhamnose into 6-deoxy-2,5-di-*O*-methyl-L-altrose is also described.

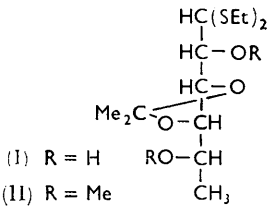
In order to rationalise the pattern of mobilities (M_G values) of a range of methylated sugars in ionophoresis in a borate buffer at pH 10, it has been suggested [1] that aldehydo-forms, in addition to pyranose and furanose structures, form complexes with borate ions.

* Part VI, *J.*, 1957, 4214.

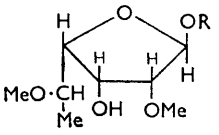
[1] Foster, *J.*, 1953, 982.

We now describe a synthesis of 2,5-di-*O*-methyl-L-rhamnose, the first example of a sugar derivative of which only the aldehydo-form gives rise to complexes with borate ions.

Treatment of L-rhamnose diethyl dithioacetal [2] with acetone, sulphuric acid, and anhydrous copper sulphate [3] afforded a mono-*O*-isopropylidene derivative (I) characterized as the di-*O*-*p*-phenylazobenzoate. From theoretical considerations,[4] acetone would be expected to condense with the 3,4-hydroxyl groups in L-rhamnose diethyl dithioacetal since they are αT (Barker and Bourne's nomenclature [5]). Proof of this was obtained as follows. Methylation of the *O*-isopropylidene derivative with dimethyl sulphate [6] gave 3,4-*O*-isopropylidene-2,5-di-*O*-methyl-L-rhamnose diethyl dithioacetal (II). Boiling a methanolic solution of this methyl ether with mercuric chloride caused demercaptalation with liberation of hydrogen chloride which catalysed methanolysis of the isopropylidene group and glycosidation of the sugar, affording crystalline methyl 2,5-di-*O*-methyl-α-L-rhamnofuranoside (III). The glycoside, which was characterized as the *p*-phenylazobenzoate, was allocated the α-configuration on the basis of its high negative rotation ($[\alpha]_D$ −110° in water); the β-glycoside was not detected. In the β-glycofuranoside, the



(I) R = H
(II) R = Me



(III) R = Me
(IV) R = H

1- and 2-methoxy-groups would be *cis*-disposed and the adverse non-bonded interaction associated with this steric arrangement probably accounts for the stereospecific formation of the α-glycoside which is free from such a steric effect. It is of interest that the isomers which predominate in the mixture of glycosides formed when erythrose and threose are separately treated with methanolic hydrogen chloride also have a *trans*-disposition of the 1-methoxyl and 2-hydroxyl group.[7] However, in the alternative isomers, these groups are *cis*-disposed and the intramolecular hydrogen bonding consequently possible could help to stabilise these isomers and this would reduce the stereospecificity of the glycosidation. Hydrogen bonding of this type cannot occur in the L-rhamnoside derivatives.

Acid hydrolyses the glycoside (III) to 2,5-di-*O*-methyl-α-L-rhamnofuranose (IV), the α-configuration being allocated on the basis of the mutarotational changes in water, $[\alpha]_D$ −61° (30 min.) ⟶ −41°. Sodium borohydride reduced the free sugar (IV) to 2,5-di-*O*-methyl-L-rhamnitol which consumed 1 mol. of periodate, giving products which when reduced with sodium borohydride and esterified afforded 2-*O*-methyl-1,3-di-*O*-*p*-phenylazobenzoylglycerol. Only a 2,5-distribution of methyl groups in the L-rhamnitol derivative permits formation of 2-*O*-methylglycerol in this reaction sequence. Determination of the structure of 2,5-di-*O*-methyl-L-rhamnitol also establishes the structures of all the preceding compounds (I)—(IV). Authentic 2-*O*-methyl-1,3-di-*O*-*p*-phenylazobenzoylglycerol was obtained from 2-methoxy-5-phenyl-1,3-dioxan [8] by acidic hydrolysis and subsequent esterification.

2,5-Di-*O*-methyl-L-rhamnose had M_G 0·20 on ionophoresis in a borate buffer pH 10. The sugar can exist only in furanose and aldehydo-forms in aqueous solution and, if hydration of the carbonyl group in the open-chain form is assumed, then, since terdentate

[2] Fischer, *Ber.*, 1894, **27**, 678.
[3] Curtis and Jones, *Canad. J. Chem.*, 1960, **38**, 890.
[4] Barker, Bourne, and Whiffen, *J.*, 1952, 3865; Mills, *Adv. Carbohydrate Chem.*, 1955, **10**, 1.
[5] Barker and Bourne, *J.*, 1952, 905.
[6] Glen, Myers, and Grant, *J.*, 1951, 2568.
[7] Baxter and Perlin, *Canad. J. Chem.*, 1960, **38**, 2217.
[8] Hill, Whelen, and Hibbert, *J. Amer. Chem. Soc.*, 1928, **50**, 2235.

complexes [9] are precluded, the pairs of hydroxyl groups available for borate complex formation are as follows: furanose form, *cis*- and *trans*-1,3; aldehydo-form, 3,4(αT), 1,3(β), and 1,4(γ). Complex formation with the furanose form can be ruled out because of the large O–O distances for the hydroxyl groups (*ca.* 3·5 Å for the *cis*-diol). Likewise a complex with the γ-hydroxyl groups in the open-chain form can be discounted since 1,4-diols do not react with borate ions.[10] The fact that 2,4-di-*O*-methyl derivatives of D-galactose [11] and D-glucose [1] have zero M_G values indicates that borate complex formation with carbonyl and a β-hydroxyl group does not occur since this structural feature is present in the aldehydo-forms of these compounds. This leaves only the αT hydroxyl groups in the open-chain form of 2,5-di-*O*-methyl-L-rhamnose for complex formation with borate ions. Frahn and Mills [10] have shown that borate ions form complexes more readily with αT than with αC or α hydroxyl groups (L-*threo*butane-2,3-diol M_G 0·51, *erythro*-isomer M_G 0·13, propane-1,2-diol M_G 0·16). Thus it may be predicted that 6-deoxy-2,5-di-*O*-methyl-L-altrose, which has the same possibilities for borate complex formation as 2,5-di-*O*-methyl-L-rhamnose (except that αC instead of αT hydroxyl groups are available in the aldehydo-form) would have an M_G value much lower than 0·2. The observed M_G value was zero.

6-Deoxy-2,5-di-*O*-methyl-L-altrose was synthesised as follows. The crystalline *O*-methanesulphonate of methyl 2,4-di-*O*-methyl-α-L-rhamnofuranoside with sodium benzoate in dimethylformamide gave methyl 3-*O*-benzoyl-6-deoxy-2,5-di-*O*-methyl-α-L-altrofuranoside. Nucleophilic displacement of sulphonyl groups with concomitant Walden inversion by this reagent has been described by Reist *et al.*[12] Saponification of the benzoate and acidic hydrolysis of the product gave 6-deoxy-2,5-di-*O*-methyl-L-altrose, which, although not crystalline, was homogeneous on paper chromatography and had the same R_F value as 2,5-di-*O*-methyl-L-rhamnose.

Experimental

3,4-O-*Isopropylidene*-L-*rhamnose Diethyl Dithioacetal.*—A mixture [3] of L-rhamnose diethyl dithioacetal [2] (30 g.; m. p. 135—137°), anhydrous copper sulphate (20 g.), concentrated sulphuric acid (3 ml.), and acetone (550 ml.) was shaken at room temperature for 6 hr. The acid was then neutralised with concentrated aqueous ammonia, and insoluble material was removed by filtration and washed with acetone. The combined filtrate and washings were concentrated, and the residue was dissolved in chloroform and washed with water, aqueous sodium hydrogen carbonate, and water. Evaporation of the dried ($MgSO_4$) solution and distillation of the residue gave the *product* (28 g., 81%), b. p. 148—152°/0·5 mm., $[\alpha]_D^{22}$ −31° (*c* 4·0 in $CHCl_3$), $[M]_D$ −96° (Found: C, 50·5; H, 8·1; S, 20·3. $C_{13}H_{26}O_4S_2$ requires C, 50·3; H, 8·4; S, 20·7%).

Treatment of this compound (1·55 g.) with *p*-phenylazobenzoyl chloride (2·67 g.) and pyridine (10 ml.) at 100° for 3 hr. and isolation of the product in the usual way [13] gave a 2,5-*di*-O-p-*phenylazobenzoate* (1·9 g., 62%) m. p. 118—119° [from benzene–light petroleum (b. p. 60—80°)] (Found: C, 64·7; H, 5·9; N, 7·5; S, 8·6. $C_{39}H_{42}N_4O_6S_2$ requires C, 64·5; H, 5·8; N, 7·7; S, 8·8%).

3,4-O-*Isopropylidene*-2,5-*di*-O-*methyl*-L-*rhamnose Diethyl Dithioacetal.*—A solution of 3,4-*O*-isopropylidene-L-rhamnose diethyl dithioacetal (4·61 g.) in acetone (7·5 ml.) was stirred vigorously with powdered sodium hydroxide [6] (3·2 g.) at 45—48° whilst dimethyl sulphate (4·2 ml.) was added during 30 min. The temperature of the mixture was then raised to 55—60° during 30 min. and maintained thereat for 3 hr. The cooled mixture was poured into water, and the aqueous solution was extracted several times with chloroform. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated and the residue was distilled, to

[9] Angyal and McHugh, *Chem. and Ind.*, 1956, 1147.
[10] Frahn and Mills, *Austral. J. Chem.*, 1959, **12**, 65.
[11] Lindberg and Swan, *Acta Chem. Scand.*, 1960, **14**, 1043.
[12] Reist, Spencer, and Baker, *J. Org. Chem.*, 1959, **24**, 1618.
[13] Baggett, Foster, Haines, and Stacey, *J.*, 1960, 3528.

yield the *product* (3·9 g., 78%) as a pale yellow oil, b. p. 118—122°/0·5 mm., $[\alpha]_D^{20}$ −34° (*c* 2·0 in $CHCl_3$), $[M]_D$ −115° (Found: C, 54·1; H, 9·1; S, 19·1. $C_{15}H_{30}O_4S_2$ requires C, 53·3; H, 8·9; S, 18·9%).

Methyl 2,5-*Di*-O-*methyl*-α-L-*rhamnofuranoside*.—3,4-*O*-Isopropylidene-2,5-di-*O*-methyl-L-rhamnose diethyl dithioacetal (5·4 g.) was boiled with mercuric chloride (11·6 g.) in dry methanol (95 ml.) under anhydrous conditions for 30 min., then filtered quickly, and the filtrate was evaporated. The residue was extracted with 10% aqueous sodium carbonate (200 ml.), and the extract was filtered and extracted with chloroform (4 × 100 ml.). The chloroform extracts were washed with water, dried ($MgSO_4$), and evaporated. Crystallization of the residue from ether–light petroleum (b. p. 40—60°) gave the *product* (2 g., 61%), m. p. 63—65°, b. p. 83—84°/0·5 mm., $[\alpha]_D^{20}$ −110° (*c* 1·5 in H_2O), $[M]_D$ −227° (Found: C, 52·25; H, 8·7. $C_9H_{18}O_5$ requires C, 52·4; H, 8·7%).

Esterification of the glycoside (0·2 g.) with pyridine (3 ml.) and *p*-phenylazobenzoyl chloride (0·265 g.) in the customary manner [13] gave the O-p-*phenylazobenzoate* (0·39 g.), m. p. 87° (from aqueous ethanol) (Found: C, 64·0; H, 6·2; N, 6·8. $C_{22}H_{26}N_2O_6$ requires C, 63·8; H, 6·3; N, 6·8%).

The glycoside, with methanesulphonyl chloride and pyridine in the usual way, gave the 3-O-*methanesulphonate* (58%), m. p. 36—37°, $[\alpha]_D$ −64° (*c* 1·2 in $CHCl_3$), $[M]_D$ −182° (Found: C, 42·2; H, 7·05; S, 11·2. $C_{10}H_{20}O_7S$ requires C, 42·3; H, 7·0; S, 11·3%).

2,5-*Di*-O-*methyl*-L-*rhamnose*.—A solution of methyl 2,5-di-*O*-methyl-α-L-rhamnofuranoside (1 g.) in 2N-hydrochloric acid (30 ml.) was kept at 100° for 2·5 hr., then neutralised with sodium hydrogen carbonate and extracted continuously with chloroform. The dried ($MgSO_4$) extract was concentrated and the residue recrystallized to yield 2,5-*di*-O-*methyl*-L-*rhamnose* (0·8 g., 84%), m. p. 94—95°, $[\alpha]_D$ −61° (30 min.) ⟶ −41° (equil.) (*c* 2·0 in H_2O), $[M]_D$ −117° ⟶ −79° (Found: C, 50·2; H, 8·6. $C_8H_{16}O_5$ requires C, 50·0; H, 8·3%), that reduced Fehling's solution and had M_G 0·20 on paper ionophoresis [1,14] in borate buffer of pH 10.

2,5-*Di*-O-*methyl*-L-*rhamnitol*.—A solution of 2,5-di-*O*-methyl-L-rhamnose (0·23 g.) and sodium borohydride (50 mg.) in water (15 ml.) was kept at room temperature for 8 hr., then neutralised with acetic acid to destroy the excess of reductant. The solution was basified with 20% aqueous sodium hydroxide (50 ml.) and continuously extracted with chloroform during 3 days. Concentration of the dried ($MgSO_4$) extract and recrystallization of the residue from acetone–ether gave the *product* (0·18 g., 78%), m. p. 71—72·5°, $[\alpha]_D$ +27° (*c* 2 in H_2O), $[M]_D$ +52° (Found: C, 49·55; H, 9·4. $C_8H_{18}O_5$ requires C, 49·5; H, 9·3%).

Periodate Oxidation of 2,5-*Di*-O-*methyl*-L-*rhamnitol*.—(*a*) By a standard method [15] the L-rhamnitol derivative was found to consume 1 mol. of periodate.

(*b*) A solution of 2,5-di-*O*-methyl-L-rhamnitol (0·2 g.), sodium metaperiodate (0·45 g.), and sodium hydrogen carbonate (0·17 g.) in water (5 ml.) was kept at room temperature for 5 hr. Iodate and periodate were precipitated by the addition of barium chloride, and sodium borohydride (100 mg.) was then added to the filtered solution. After 16 hr. the excess of reductant was destroyed with acetic acid and the solution, after basification with 20% aqueous sodium hydroxide (20 ml.), was continuously extracted with chloroform for 4 days. The dried ($MgSO_4$) extract was concentrated and the residue was treated with *p*-phenylazobenzoyl chloride (0·5 g.) and pyridine (4 ml.) at 100° for 3 hr. Working up in the usual way [13] yielded 2-*O*-methyl-1,3-di-*O*-*p*-phenylazobenzoylglycerol (0·38 g., 63%), m. p. 129° alone or in admixture with material described below. The infrared spectrum (Nujol mull) was indistinguishable from that of the authentic compound.

No trace of the *p*-phenylazobenzoate of the second reaction product, 2-methoxypropan-1-ol, was detected. Presumably the alcohol was lost by volatilization.

2-O-*Methyl*-1,3-O-p-*phenylazobenzoylglycerol*.—2-*O*-Methylglycerol [8] (0·1 g.) when esterified [13] with pyridine (4 ml.) and *p*-phenylazobenzoyl chloride (0·53 g.) gave the *diester* (0·49 g., 81%), m. p. 129—130° (from ethanol) (Found: C, 69·05; H, 5·3; N, 10·8. $C_{39}H_{26}N_4O_5$ requires C, 69·0; H, 5·0; N, 10·7%).

Methyl 6-*Deoxy*-2,5-*di*-O-*methyl*-α-L-*altrofuranoside*.—A solution of methyl 3-*O*-methanesulphonyl-2,5-di-*O*-methyl-α-L-rhamnofuranoside (1·5 g.) in dimethylformamide (64 ml.) was boiled under reflux in the presence of sodium benzoate (5·2 g.) for 6 hr., then poured into water and the solution extracted with chloroform. The extract was washed with aqueous sodium

[14] Foster, *Chem. and Ind.*, 1952, 1050.
[15] Jackson, *Org. Reactions*, 1944, **2**, 341.

hydrogen carbonate and with water, dried ($CaCl_2$), and evaporated. Distillation of the residue gave methyl 3-*O*-benzoyl-6-deoxy-2,5-di-*O*-methyl-α-L-altrofuranoside (0·95 g., 58%) contaminated with a small amount of starting material. The product had b. p. 124—126°/0·1 mm., $[\alpha]_D$ −105° (*c* 1·2 in $CHCl_3$).

A solution of this product (0·5 g.) in methanol (12 ml.) and water (18 ml.) containing potassium hydroxide (4 g.) was boiled under reflux for 3 hr., cooled, and extracted four times with chloroform (total vol. 100 ml.), and the combined extracts were washed with water and evaporated. The residue (0·27 g.) was distilled, to yield *methyl 6-deoxy-2,5-di-*O*-methyl-α-L-altrofuranoside*, b. p. 100—110°/0·1 mm., $[\alpha]_D$ −85° (*c* 2·0 in H_2O), $[M]_D$ −175° (Found: C, 52·7; H, 8·55. $C_9H_{18}O_5$ requires C, 52·4; H, 8·7%).

A solution of the glycoside (0·2 g.) in 2N-hydrochloric acid (10 ml.) was boiled under reflux for 3 hr., then neutralised and continuously extracted with chloroform. The extract was concentrated and a solution of the residue in water (50 ml.) was extracted with chloroform (2 × 40 ml.). Concentration of the aqueous solution gave 6-deoxy-2,5-di-*O*-methyl-L-altrose (90 mg.), $[\alpha]_D$ −16° (*c* 1·2 in H_2O). The compound failed to crystallize but appeared homogeneous on paper chromatography with the organic phase of a butanol–ethanol–water (4 : 1 : 5) solvent system; it had R_G 5·29 and R_{Rh} 2·17. On ionophoresis [14] in borate buffer pH 10 it had $M_G < 0·01$.

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