1359. *Boric Acid Derivatives as Reagents in Carbohydrate Chemistry. Part V.*[1] *The Interaction of Phenylboronic Acid with Methyl Pentopyranosides: Syntheses of* 3- *and* 2,4-*Substituted Ribose Derivatives*

By R. J. Ferrier and D. Prasad

Methyl β-L-arabinopyranoside and methyl α-D-lyxopyranoside condense smoothly with phenylboronic acid to give crystalline esters which are shown to possess 3,4- and 2,3-cyclic structures, respectively. From the reaction with methyl β-D-ribopyranoside a 3,4-cyclic product has been obtained in 90% yield which affords a convenient route to methyl ribopyranoside 3-esters. The phenylcarbamate has been employed in the synthesis of 2,4-di-*O*-methyl-D-ribose.

The results obtained to date in the investigation of the nature of the esters formed by condensing phenylboronic acid with glycosides show that six-membered 4,6-esters are produced initially from the methyl glucopyranosides, and that further reaction gives rise to seven-membered 2,3-pyroboronates.[1,2] The 2,3- and 4,6-sites are esterified with comparable facility in methyl α-D-mannopyranoside,[2] and with methyl galactopyranoside derivatives 3,4- or 4,6-esters are formed depending upon the nature of the C-1, C-2 groupings.[1] In the pentoside series only the xylosides have been investigated. With these the pyranosides react specifically at the 2,4-positions,[3] and the furanosides give 3,5-esters.[4] We now report on the nature of the phenylboronates of methyl β-L-arabino-, methyl α-D-lyxo-, and methyl β-D-ribo-pyranoside.

The ester obtained in 74% yield from the arabinoside on benzoylation and removal of the boronate grouping afforded methyl 2-*O*-benzoyl-β-L-arabinopyranoside which has been described and fully characterised by Oldham and Honeyman.[5,6] This establishes the structure of the initial ester as methyl β-L-arabinopyranoside 3,4-phenylboronate. From methyl α-D-lyxopyranoside a phenylboronate was isolated (71%) which, on acetylation and removal of the cyclic ester grouping, gave the same lyxoside acetate as was obtained by partial hydrolysis of methyl 4-*O*-acetyl-2,3-*O*-isopropylidene-α-D-lyxopyranoside prepared by acetylation of methyl 2,3-*O*-isopropylidene-α-D-lyxopyranoside.[7] The phenylboronate therefore has the 2,3-structure.

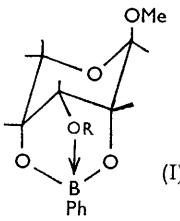
Despite the fact that the O–O distances of *cis* (a, e) and *trans* (e, e) vicinal diols on a normal pyranoid chair would be expected to be identical (~2·76 Å), a marked preference for *cis*-systems is exhibited by those condensing reagents which require the distance between reacting oxygen atoms to be reduced during cyclisations. (With a *cis*-diol, O–O approach causes ring flattening and a decrease in non-bonded interactions; with a *trans*-diol the opposite holds.[8]) Since the O–O distance in phenylboronic acid will be near 2·38 Å [1] this reagent would be expected to favour *cis*-diols and so form arabinoside 3,4- and lyxoside 2,3-cyclic boronates.

With methyl β-D-ribopyranoside, *cis*-vicinal diols are present at positions 2,3 and 3,4 but, in addition, the 2,4-diol is potentially available. Indeed, methyl β-D-ribopyranoside shows the specific interaction with phenylboronic acid (contained in chromatographic solvents) which characterises those pyranoid compounds possessing a *cis,cis*-triol structure,[9]

[1] Part IV, R. J. Ferrier, A. J. Hannaford, W. G. Overend, and B. C. Smith, *Carbohydrate Res.*, 1965, **1**, 38.
[2] R. J. Ferrier, *J.*, 1961, 2325.
[3] R. J. Ferrier, D. Prasad, A. Rudowski, and I. Sangster, *J.*, 1964, 3330.
[4] R. J. Ferrier, D. Prasad, and A. Rudowski, *J.*, 1965, 858.
[5] M. A. Oldham and J. Honeyman, *J.*, 1946, 986.
[6] J. Honeyman, *J.*, 1946, 990.
[7] P. W. Kent and P. F. V. Ward, *J.*, 1953, 416.
[8] S. J. Angyal and C. G. Macdonald, *J.*, 1952, 686.
[9] H. M. Wall, M.Sc. Thesis, University of London, 1964.

and which is believed to result from esterification of 1,3-related axial, axial hydroxyl groups.[10,11] This, together with the observation that the 2,4-diol in the methyl xylopyranosides is reactive,[3] led us to expect some riboside 2,4-ester. The glycoside gave a phenylboronate in 90% yield from which a crystalline monoacetate was obtained. Removal of the phenylboronic acid afforded a crystalline riboside acetate which did not reduce the periodate ion. It is therefore the 3-ester, and the phenylboronate has the 2,4-cyclic structure (I; R = H). Although this finding that the 2,4-diol is preferred to the vicinal diols is in agreement with the observations [12] that six-membered boronate rings are more stable than five-membered rings, it is suggested that the main stabilising influence in this case is co-ordination of O-3 to boron.

Acetone and phenylboronic acid have been found to react similarly with polyols which present more than one suitable diol,[1] and with the arabinoside and the lyxoside the analogy is extended. However, in the case of the ribopyranoside, a marked difference is found. Acetone in the presence of the acid catalyst, which is necessary for condensation to occur, forms acetals at the 2,3- and 3,4-sites, and also causes ring contraction with the formation of ribofuranoside derivatives.[13] No evidence of 2,4-ketal production was found. An ortho-ester of relevant significance has, however, been reported.[14] 1,2,4-*O*-Orthobenzoyl-α-D-ribopyranose is formed when 1,2-*O*-1′-benzyloxybenzylidene-α-D-ribopyranose is treated with very mild acid. It also is of interest as a precursor of 3-substituted ribose derivatives.



(I)

As an illustration of the application of phenylboronic acid in the preparation of ribose derivatives of biochemical significance the synthesis of 2,4-di-*O*-methyl-D-ribose has been undertaken. This ether has been prepared once previously from a methanolysis product of yeast, adenylic acid, but only in impure form.[15] Methyl β-D-ribopyranoside 2,4-phenylboronate (I; R = H) was treated with phenyl isocyanate to give the carbanilate (I; R = CO·NHPh) from which the cyclic ester was removed by prolonged treatment with propane-1,3-diol. Methylation of the product and reductive removal of the carbanilate ester grouping gave syrupy methyl 2,4-di-*O*-methyl-β-D-ribopyranoside. Hydrolysis of the glycoside afforded the free sugar which was resistant to periodate oxidation and is therefore the anticipated 2,4-dimethyl ether. Although an instance of phenylcarbamate migration during methylation has been reported,[16] this grouping is normally stable.[17]

Experimental

Optical rotations were measured in a 1-dm. tube at room temperature and within the concentration range 0·6—2%. Those of the boronates were measured in dry dioxan. N.m.r. spectra were recorded in carbon tetrachloride solution using tetramethylsilane as internal reference on the Varian A-60 instrument. The light petroleum fraction used throughout had b. p. 60—80°.

Methyl β-L-*Arabinoside* 3,4-*Phenylboronate*.—Methyl β-L-arabinopyranoside (8·1 g.; m. p. 168°; prepared by the method of Oldham and Honeyman,[5] who give m. p. 169—170°) was treated in boiling benzene (300 ml.) with triphenylboroxole (5·2 g., 0·33 mol.) and water (0·9 ml., 1 mol.) was collected in a Dean and Stark head. Removal of the solvent afforded a syrup which crystallised on treatment with benzene–light petroleum. Recrystallisation from this solvent gave the *arabinoside boronate* (9·3 g., 74%), m. p. 73—74°, $[\alpha]_D$ +117° (Found: C, 56·8; H, 6·3; B, 4·4; OMe, 12·0. $C_{12}H_{15}BO_5$ requires C, 57·6; H, 6·0; B, 4·3; OMe, 12·4%).

[10] R. J. Ferrier, W. G. Overend, G. A. Rafferty, H. M. Wall, and N. R. Williams, *Proc. Chem. Soc.*, 1963, 133.
[11] E. J. Bourne, E. M. Lees, and H. Weigel, *J. Chromatog.*, 1963, **11**, 253.
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[14] H. G. Fletcher and R. K. Ness, *J. Amer. Chem. Soc.*, 1955, **77**, 5337.
[15] P. A. Levene and S. A. Harris, *J. Biol. Chem.*, 1933, **101**, 419.
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[17] P. J. Garegg, *Acta Chem. Scand.*, 1962, **16**, 1849.

Methyl 2-O-*Benzoyl*-β-L-*arabinopyranoside*.—The foregoing arabinoside boronate (3·0 g.) was treated in dry pyridine (25 ml.) at 0° with benzoyl chloride (1·8 ml.) for 1 hr. The precipitated pyridine hydrochloride and the pyridine were removed, and the residue was extracted with hot dry benzene. Evaporation of the benzene gave a syrup (4·0 g., 94%), $[\alpha]_D$ +184° which showed no infrared hydroxyl absorption. Ethylene glycol (0·6 ml.) was added to the benzoate (1·25 g.) and was then removed by distillation at reduced pressure. The residue, on extraction with ethanol, removal of the solvent, and treatment with aqueous ethanol, gave the arabinoside 2-benzoate (0·5 g., 53%), m. p. 146—147°, $[\alpha]_D$ +201° (Me_2CO). Oldham and Honeyman [5] report m. p. 146—147°, $[\alpha]_D$ +257° (Me_2CO) for this compound, but a sample prepared by us from methyl 2,3-*O*-isopropylidene-β-L-arabinopyranoside had m. p. 145—146°, $[\alpha]_D$ +200° (Me_2CO). The infrared spectra of the two samples were identical and their mixed melting point showed no depression.

Methyl α-D-*Lyxopyranoside* 2,3-*Phenylboronate*.—Methyl α-D-lyxopyranoside [1·93 g.; m. p. 106—108° (lit.,[7] 108—109°)] was treated with triphenylboroxole as above and afforded a syrup which crystallised with difficulty from benzene–light petroleum at 0°. Recrystallisation from this solvent gave the *lyxoside phenylboronate* (2·1 g., 71%), m. p. 66—69°, $[\alpha]_D$ +36° (Found: C, 57·6; H, 6·2; B, 4·2; OMe, 11·9%).

Methyl 4-O-*Acetyl*-α-D-*lyxopyranoside* 2,3-*Phenylboronate*.—The boronate (0·52 g.) was acetylated with acetyl chloride (0·4 ml.) in pyridine solution (20 ml.) during 3 hr. at 0°. The pyridine hydrochloride and the solvent were removed and the residue was extracted with hot benzene. Evaporation of the benzene left a syrup which was distilled [140—145° (bath temp.)/0·005 mm.] to give the syrupy *acetylated boronate* (0·56 g., 91%), $[\alpha]_D$ +13° (Found: C, 56·4; H, 6·0; B, 3·4; OMe, 11·1. $C_{14}H_{17}BO_6$ requires C, 57·6; H, 5·8; B, 3·7; OMe, 10·6%). It showed insignificant hydroxyl absorption in the infrared region.

Methyl 4-O-*Acetyl*-α-D-*lyxopyranoside*.—(*a*) *From the phenylboronate*. The boronate (0·38 g.) was dissolved in acetone and propane-1,3-diol (1·5 ml.) was added. (This reagent is to be preferred to ethylene glycol since six-membered boronate rings are more stable than five-membered.[3]) Removal of the volatile components left a syrup which gave a positive boron test and so a further portion of propane-1,3-diol (1·5 ml.) was added and again removed by distillation. Crystalline *methyl* 4-O-*acetyl*-α-D-*lyxopyranoside* was obtained from ethyl acetate–light petroleum (0·14 g., 53%), m. p. 111—112°, $[\alpha]_D$ +51° ($CHCl_3$) (Found: C, 47·2; H, 6·9; OMe, 15·3. $C_8H_{14}O_6$ requires C,46·6; H, 6·8; OMe, 15·0%).

(*b*) *From methyl* 2,3-O-*isopropylidene*-α-D-*lyxopyranoside*. Acetylation of the ketal (1·4 g.) with acetic anhydride in pyridine solution and distillation of the product gave syrupy *methyl* 4-O-*acetyl*-2,3-O-*isopropylidene*-α-D-*lyxopyranoside* (1·2 g., 70%), $[\alpha]_D$ +26° ($CHCl_3$) (Found: C, 53·4; H, 7·2; OMe, 11·1. $C_{11}H_{18}O_6$ requires C, 53·6; H, 7·4; OMe, 12·6%). The acetate (1·0 g.) was heated under reflux with aqueous acetic acid (25 ml., 0·1%) for 3·5 hr. when it was shown by thin-layer chromatography that hydrolysis of the ketal ring was complete. Removal of the solvent left the 4-acetate (0·83 g., 99%) which on recrystallisation from ethyl acetate–light petroleum had m. p. 111—112°, $[\alpha]_D$ +51° ($CHCl_3$). The infrared spectra of the two samples were identical and their mixed melting point showed no depression.

Methyl β-D-*Ribopyranoside* 2,4-*Phenylboronate*.—The riboside {4·3 g., m. p. 81—82°, $[\alpha]_D$ −104° (H_2O); Jackson and Hudson [18] give m. p. 83°, $[\alpha]_D$ −105° (H_2O)} was treated in the normal manner with triphenylboroxole. On concentration of the benzene solution the product precipitated as a gel which was removed and crystallised from benzene–light petroleum to give the *riboside phenylboronate* (5·9 g., 90%), m. p. 149—150°, $[\alpha]_D$ −113° (Found: C, 57·5; H, 6·5; B, 4·2; OMe, 12·1%).

Methyl 3-O-*Acetyl*-β-D-*ribopyranoside* 2,4-*Phenylboronate*.—The boronate (4·0 g.) was acetylated under normal conditions and after distillation [140—145° (bath temp.)/0·05 mm.] crystallised readily on trituration with light petroleum. Recrystallisation from this solvent afforded the *acetylated boronate* (3·2 g., 69%), m. p. 82—83°, $[\alpha]_D$ −118° (Found: C, 58·3; H, 5·7; B, 3·9; OMe, 10·6%).

Methyl 3-O-*Acetyl*-β-D-*ribopyranoside*.—The acetylated boronate (1·8 g.) was treated with propane-1,3-diol (3 ml. then 4 ml.) as before, and the boron-free residue, on crystallisation from ethyl acetate–light petroleum, afforded the *riboside acetate* (0·6 g., 48%), m. p. 112—113°, $[\alpha]_D$ −143° ($CHCl_3$) (Found: C, 46·7; H, 6·8; OMe, 15·2%).

Methyl β-D-*Ribopyranoside* 2,4-*Phenylboronate* 3-N-*Phenylcarbamate*.—The riboside boronate

[18] E. L. Jackson and C. S. Hudson, *J. Amer. Chem. Soc.*, 1941, **63**, 1229.

(1·3 g.) was dissolved in dry benzene (80 ml.), phenyl isocyanate (0·6 ml.) was added, and the solution heated under reflux for 12 hr. Evaporation of the solvent and removal of final traces of phenyl isocyanate under high vacuum left a solid which, on recrystallisation from benzene–light petroleum, yielded the *boronate carbanilate* (0·5 g.) m. p. 163—164·5°, $[\alpha]_D$ −94° (Found: C, 62·1; H, 5·5; B, 2·8; OMe, 8·2. $C_{19}H_{20}BNO_6$ requires C, 61·8; H, 5·4; B, 2·9; OMe, 8·4%). Further treatment of the non-crystalline fraction with phenyl isocyanate afforded a second crop (1·0 g; total yield 79%).

Methyl 2,4-*Di*-O-*methyl*-β-D-*ribopyranoside* 3-N-*Methyl*-N-*phenylcarbamate*.—The boronate carbanilate (0·95 g.) was dissolved in acetone (5 ml.) and propane-1,3-diol (3 ml.) and the solution was heated under reflux for 10 hr. Volatile components were removed by distillation and the process was repeated. The pale yellow residue (0·75 g., 103%), $[\alpha]_D$ −81° ($CHCl_3$) was chromatographically pure on silica plates and was free from boron. N.m.r. spectroscopy revealed that it contained phenyl, methoxyl, and riboside ring protons in the correct proportions, but that it was slightly contaminated, probably with oxidation products of the propane-1,3-diol. Methylation of the carbanilate (0·75 g.) was carried out in dry dimethylformamide (30 ml.) with methyl iodide (6 ml.) and silver oxide (8 g.) in the presence of Hi-Drite (2 g.). The course of reaction was followed by thin-layer chromatography and after 16 hr. was complete. After removal of the solids and the solvent, the pale yellow syrupy product was dissolved in methylene dichloride and washed with water. After drying ($MgSO_4$) and brief treatment with decolourising charcoal, the solvent was removed to give a syrup (0·79 g.) which crystallised partially on trituration with light petroleum. Recrystallisation from light petroleum–ethyl acetate gave the *methylated ester* (0·24 g.) m. p. 86—86·5°, $[\alpha]_D$ −48° ($CHCl_3$) (Found: C, 59·3; H, 7·2; N, 4·5; OMe, 27·9. $C_{16}H_{23}NO_6$ requires C, 59·1; H, 7·1; N, 4·3; OMe, 28·6%). A second portion of the fully substituted product (0·07 g., total 34%) was obtained with the aid of a column of silica gel.

Methyl 2,4-*Di*-O-*methyl*-β-D-*ribopyranoside*.—The methylated carbanilate (0·21 g.) was heated under reflux in dry tetrahydrofuran (15 ml.) with lithium aluminium hydride (0·1 g.), and the reduction was followed by thin-layer chromatography. After 4·5 hr. the excess hydride was destroyed with moist ethanol and then water. Phosphoric acid was added to pH 7 and the solids and solvent were removed. Distillation of the residue [70—80° (bath temp.)/0·01 mm.] gave a syrup (0·08 g., 65%), $[\alpha]_D$ −80° ($CHCl_3$) which was shown to be chromatographically pure on silica plates. N.m.r. spectroscopy confirmed the presence of three methoxy-groups in the compound (methoxyl protons : all other protons, 9 : 7; methoxyl protons : anomeric porton, 9 : 1).

2,4-*Di*-O-*methyl*-D-*ribose*.—The syrupy glycoside (0·05 g.) was heated under reflux in 50% aqueous ethanol in the presence of a small amount of cation-exchange resin [IR-120(H^+)] for 10 hr. After removal of the resin, brief treatment with decolourising charcoal and evaporation of the solvent, 2,4-*di*-O-*methyl*-D-*ribose* (0·032 g., 69%), $[\alpha]_D$ −35° ($CHCl_3$) was obtained. R_{Ribose} Values [in butan-1-ol–ethanol–water (4 : 1 : 5); upper phase] were: 2,4-di-*O*-methylribose, 2·18; 2,3-di-*O*-methylxylose, 2·70; 2,4-di-*O*-methylxylose, 2·50.

2,4-*Di*-O-*methyl*-N-*phenyl*-D-*ribosylamine*.—The free sugar (0·032 g.) was dissolved in ethanol (5 ml.) and heated under reflux with pure aniline (0·033 g.) in an atmosphere of nitrogen for 3·5 hr. Removal of the volatile components and crystallisation from ethyl acetate–light petroleum gave the *methylated ribosylamine*, m. p. 128—129°, $[\alpha]_D$ +184° ($CHCl_3$) (Found: C, 61·1; H, 7·3; N, 6·0. $C_{13}H_{19}NO_4$ requires C, 61·7; H, 7·5; N, 5·5%).

Periodate Oxidations.—Methyl 3-*O*-acetyl-β-D-ribopyranoside and 2,4-di-*O*-methyl-D-ribose were oxidised respectively in aqueous and aqueous ethanolic (3 : 1) solutions, and reduced 0·12 and 0·10 mol. of the reagent in the times required for complete oxidation of methyl α-D-glucopyranoside. The reactions were followed spectrophotometrically.[19]

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Department of Chemistry, Birkbeck College, University of London,
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[19] G. O. Aspinall and R. J. Ferrier, *Chem. and Ind.*, 1957, 1216.