630. *Boric Acid Derivatives as Reagents in Carbohydrate Chemistry. Part II.*[1] *The Interaction of Phenylboronic Acid with Methyl Xylopyranosides.*

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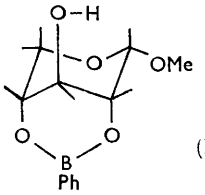
Phenylboronic acid reacts with methyl α- and β-xylopyranoside to give crystalline 2,4-cyclic esters. The free hydroxyl groups in these products have been esterified, and a simple, non-destructive method for the removal of phenylboronic acid from the resulting esters has been developed; in this way, methyl xyloside 3-acetate, 3-benzoate, and 3-*N*-phenylcarbamate have been prepared. By use of the protecting phenylboronate grouping, 3-*O*-methyl- and 2,4-di-*O*-methyl-D-xylose and their methyl glycosides have been synthesised.

Phenylboronic acid, when incorporated into chromatographic solvents, enhances the mobilities of cyclic carbohydrate derivatives which possess a 1,3-diaxial diol system.[2,3] The methyl D-xylopyranosides contain such a system when the rings are in the 1C conformation (and the ring oxygen atom is suitably disposed to stabilise a cyclic ester [2]); however, neither showed interaction with the acid during chromatography,[4] so that under these conditions the stable C1 conformation is not inverted. Sulphonated phenylboronic acid at pH 6·5 also shows no interaction with the β-glycoside during electrophoresis.[5] When, however, the two xylosides were treated with phenylboronic acid under dehydrating conditions, water was eliminated, and, after its removal, the crystalline methyl xyloside 2,4-phenylboronates (I) and (II) were obtained.

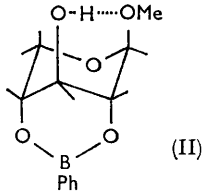
The structures were established by the determination of the bonding of the hydroxyl groupings within the molecules. In dilute carbon tetrachloride solution when intermolecular bonding is eliminated, the O–H stretching frequency of a hydroxyl system can be related to the type of intramolecular hydrogen bond in which the alcoholic function is

[1] Ferrier, *J.*, 1961, 2325, to be taken as Part I.
[2] Ferrier, Overend, Rafferty, Wall, and Williams, *Proc. Chem. Soc.*, 1963, 133.
[3] Bourne, Lees, and Weigel, *J. Chromatog.*, 1963, **11**, 253.
[4] Wall, M.Sc. Thesis, University of London, 1964.
[5] Garegg and Lindberg, *Acta Chem. Scand.*, 1961, **15**, 1913.

involved, and in this way configurations and conformations of substances related to carbohydrates have been studied [6] and the assignment of configuration to branched-chain sugar derivatives has been made.[2] The infrared spectra showed that the hydroxyl grouping of compound (I) was free from intramolecular hydrogen bonding (O–H stretch 3623 cm.$^{-1}$),[7]



(I)



(II)

while that of compound (II) was involved in a six-membered ring and was therefore axial and strongly bonded to another axial oxygen [2] (O–H stretch 3512 cm.$^{-1}$). Only in the case of the 2,4-esters would these frequencies have been observed; all other esters would have been expected to show frequencies near 3600 cm.$^{-1}$.[8] Furthermore, the conformation of the pyranoid ring of compound (I) must be 1C as shown, since the only attainable boat-form (B3) would permit a hydrogen bond with the ring oxygen atom.[9] The evidence available does not allow a clear choice to be made between the 1C and B3 modifications in the case of compound (II), but the determined stretching frequency is in such good agreement with those found in other carbohydrate systems having axial hydroxyl–axial oxygen interactions,[2] that the chair-form is favoured.

Boronate rings on carbohydrates have been shown to be stable to esterifying conditions,[1] and compounds (I) and (II) were converted to the acetyl and benzoyl derivatives. The lower reactivity in the esterification of non-bonded hydroxyl groups [10] was exemplified during benzoylations. Esterification in pyridine with benzoyl chloride—conditions which normally cause smooth benzoylation—resulted, in the case of the α-ester, in the isolation of starting material (19%) with only moderate yields of product (37%). Satisfactory substitution occurred in high-temperature experiments with benzoic anhydride.

Brown and Zweifel [11] removed butylboronic acid from cyclic boronate esters by adding excess of ethylene glycol and separating ethylene glycol butylboronate by distillation. Although this method has been applied successfully by us to the liberation of carbohydrate derivatives from their boronate esters, we have preferred to add molar proportions of propane-1,3-diol to solutions of the esters and to isolate the carbohydrate component by crystallisation, after evaporation of the solvent and extraction of the propanediol boronate with light petroleum. (In some cases, precipitation of the carbohydrate component occurred spontaneously on addition of the diol.) In one instance when the product was non-crystalline, evaporation of the solvent and extraction of the residue with light petroleum caused the removal of 95% of the phenylboronic acid originally present, so the utility of the procedure is not necessarily dependent on crystallisation. Propane-1,3-diol is to be preferred to ethylene glycol for this purpose since six-membered borate [12,13] and boronate [14] cyclic esters are more stable than the cyclic esters formed from 1,2-diols. The crystalline mono-acetates and -benzoates of both methyl xylopyranosides were obtained in high yield by application of this method, so that phenylboronic acid, since it can be attached and removed under extremely mild conditions, is demonstrated to be an attractive

[6] Foster, Harrison, Lehmann, and Webber, *J.*, 1963, 4471, and previous Papers in the series.
[7] Cole and Jefferies, *J.*, 1956, 4391; Dalton, Meakins, Robinson, and Zaharia, *J.*, 1962, 1566.
[8] Kuhn, *J. Amer. Chem. Soc.*, 1952, **74**, 2492; Brimacombe, Foster, Stacey, and Whiffen, *Tetrahedron*, 1958, **4**, 351.
[9] Barker, Brimacombe, Foster, Whiffen, and Zweifel, *Tetrahedron*, 1959, **7**, 10.
[10] Buck, Foster, Perry, and Webber, *J.*, 1963, 4171.
[11] Brown and Zweifel, *J. Org. Chem.*, 1962, **27**, 4708.
[12] Dale, *J.*, 1961, 922.
[13] Hubert, Hartigay, and Dale, *J.*, 1961, 931.
[14] Finch and Lockhart, *J.*, 1962, 3723; Bowie and Musgrave, *J.*, 1963, 3945.

protecting group. All the mono-esters were resistant to oxidation by the periodate ion, and therefore bore the substituent at C-3.

Six-membered boron-containing rings of the type present in compounds (I) and (II) have not been reported previously in the carbohydrate series, although Bell [15] found evidence for a 2,4-borate ester amongst the products of the reaction between boric acid and methyl β-D-glucopyranoside. In more simple systems, such rings are, however, well known; *cis*-cyclohexane-1,3-diol has been separated from the *trans*-isomer by the use of trihexyl borate [12] and of butylboronic acid,[11] the method depending upon the fact that only the *cis*-compound forms cyclic esters.

Methylation of methyl β-D-xylopyranoside 2,4-phenylboronate with methyl iodide and silver oxide in dimethylformamide solution gave a syrup which, on distillation, yielded crystalline methyl 3-*O*-methyl-β-D-xylopyranoside 2,4-phenylboronate, in 18% yield, and an oil which has not been further examined. The cause of the unsatisfactory yields obtained during this and other [1] methylations is under investigation. Crystalline methyl 3-*O*-methyl-β-D-xylopyranoside was isolated with the aid of propane-1,3-diol; it gave 3-*O*-methyl-D-xylose on acidic hydrolysis. A convenient synthetic route to 2,4-di-*O*-methyl-D-xylose followed from the isolation of methyl β-D-xylopyranoside 3-*N*-phenylcarbamate; this was smoothly converted into methyl 2,4-di-*O*-methyl-β-D-xylopyranoside 3-*N*-methyl-*N*-phenylcarbamate, which was then de-esterified by reduction with lithium aluminium hydride to give methyl 2,4-di-*O*-methyl-β-D-xylopyranoside, which on hydrolysis gave the free sugar. Carbanilates of glycerol 1,2-phenylboronate and galactitol 1,3:4,6-bisphenylboronate have previously been reported.[16] Other routes to 2,4-di-*O*-methyl-D-xylose have been developed,[17] but all, at some stage, involve a selective reaction, and are therefore to be avoided.

Experimental

The benzene and light petroleum (b. p. 60—80°) used were dried over sodium wire. Dioxan was dried by distillation from lithium aluminium hydride, acetone by rolling with potassium carbonate and distillation from "Hi-Drite," and dimethylformamide with "Hi-Drite" followed by distillation from barium oxide. Specific rotations were measured in a 1-dm. tube at room temperature at concentrations in the range 0·8—1·2%; dry dioxan was the solvent used, unless otherwise stated.

The high-resolution infrared spectra were measured at room temperature on carbon tetrachloride solutions of concentration 0·003—0·005M, using the Unicam S.P. 700 spectrophotometer.

Methyl β-D-*Xylopyranoside* 2,4-*Phenylboronate*.—Methyl β-D-xylopyranoside (16·8 g.) was treated in boiling benzene (550 ml.) with triphenylboroxole (10·6 g., 0·33 mol.); water (1·8 ml., 1·0 mol.) was collected in a Dean and Stark head. Removal of the main part of the benzene and addition of light petroleum caused the crystallisation of the *product* (22·7 g., 89%), m. p. 85—86° (from light petroleum), $[\alpha]_D$ −104° (Found: C, 58·1; H, 6·3; B, 4·3; OMe, 12·2. $C_{12}H_{15}BO_5$ requires C, 57·6; H, 6·0; B, 4·3; OMe, 12·4%).

Methyl α-D-*Xylopyranoside* 2,4-*Phenylboronate*.—Methyl α-D-xylopyranoside (0·18 g., prepared by the method of Hudson [18]) was treated as above with triphenylboroxole (0·11 g., 0·33 mol.) to give a crystalline product (0·2 g., 73%). Recrystallisation from benzene gave the *product*, m. p. 175—176°, $[\alpha]_D$ +10° (Found: C, 57·4; H, 5·7; B, 4·3; OMe, 12·3%). Almost quantitative yields were obtained when the synthesis was repeated after a method for isolating large quantities of methyl α-D-xylopyranoside became available.[19]

Acetylation and Benzoylation of Methyl Xyloside Phenylboronates.—Both acetyl chloride and acetic anhydride in pyridine solution at room temperature were found to be suitable acetylating reagents; yields of the required acetates, after vacuum distillation followed by crystallisation,

[15] Bell, *J.*, 1935, 175.
[16] Lees, Ph.D. Thesis, University of London, 1963.
[17] (*a*) Robertson and Speedie, *J.*, 1934, 824; (*b*) Barker, Hirst, and Jones, *J.*, 1946, 783; (*c*) Wintersteiner and Klingsberg, *J. Amer. Chem. Soc.*, 1949, **71**, 939; (*d*) Dalley and McIlroy, *J.*, 1949, 555.
[18] Hudson, *J. Amer. Chem. Soc.*, 1925, **47**, 265.
[19] Ferrier, Prasad, and Rudowski, unpublished results.

were *ca.* 60 and 80%, respectively. Benzoyl chloride in pyridine solution caused satisfactory esterification in the case of the β-glycoside (60% yield), but only 37% of product was isolated from the reaction with the α-isomer. Thus, an alternative method of benzoylation was adopted; methyl α-D-xyloside 2,4-phenylboronate (5·0 g.) was heated with benzoic anhydride (4·6 g., 1·02 mol.) and pyridine (3·0 ml.) at 95° for 2 hr. The addition of dry ether (10 ml.) to the reaction mixture caused the precipitation of *methyl* 3-O-*benzoyl*-α-D-*xylopyranoside* 2,4-*phenylboronate*. Further quantities (total 5·3 g., 75%) were obtained from the mother liquors after removal of the solvent and sublimation of the benzoic acid formed. The acetylated and benzoylated phenylboronates were recrystallised from light petroleum. Details of the products are given in Table 1.

TABLE 1.

Acetylated and benzoylated phenylboronates.

Compound *	M. p.	$[\alpha]_D$	Found (%) C	H	B	OMe	Formula	Required (%) C	H	B	OMe
A	119—121°	+13°	58·2	5·9	3·7	10·8	$C_{14}H_{17}BO_6$	57·6	5·8	3·7	10·6
B	122—123	−127	57·4	5·9	3·7	10·3					
C	138—140	+18	64·7	5·2	3·2	8·8	$C_{19}H_{19}BO_6$	64·4	5·4	3·1	8·8
D	99—100	−82	64·6	5·4	3·2	9·0					

* Compounds: A, *methyl*-3-O-*acetyl*-α-D-*xylopyranoside* 2,4-*phenylboronate*; B, *methyl* 3-O-*acetyl*-β-D-*xylopyranoside* 2,4-*phenylboronate*; C, *methyl* 3-O-*benzoyl*-α-D-*xylopyranoside* 2,4-*phenylboronate*; D, *methyl* 3-O-*benzoyl*-β-D-*xylopyranoside* 2,4-*phenylboronate*.

Removal of the Phenylboronic Acid from Esters A—D.—The fully substituted ester was dissolved in dry acetone and propane-1,3-diol (1 mol.) added. Evaporation of the solution to dryness and extraction of the propanediol phenylboronate with light petroleum left a solid residue which was recrystallised from ethyl acetate–light petroleum. The yields given in Table 2 refer to experiments in which *ca.* 4 g. of the ester was used.

TABLE 2.

Products from the removal of boronic acid from esters A—D.

Compound *	M. p.	$[\alpha]_D$	Yield (%)	Found (%) C	H	OMe	Formula	Required (%) C	H	OMe
A′	123—125°	+150°	90	46·0	6·8	15·1	$C_8H_{14}O_6$	46·6	6·8	15·0
B′	115—116	−49	86	46·0	6·8	14·6				
C′	139—141	+111	85	58·7	5·8	11·5	$C_{13}H_{16}O_6$	58·2	6·0	11·6
D′	138—139	−15	89	57·9	6·1	11·9				

* Compounds: A′, *methyl*-3-O-*acetyl*-α-D-*xylopyranoside*; B′, *methyl* 3-O-*acetyl*-β-D-*xylopyranoside*; C′, *methyl* 3-O-*benzoyl*-α-D-*xylopyranoside*; D′, *methyl* 3-O-*benzoyl*-β-D-*xylopyranoside*.

Attempted Periodate Oxidation of the Xyloside 3-*Esters.*—The reactions were carried out in 0·015M-sodium metaperiodate in 50% aqueous ethanol, and esters A′—D′ were found to be stable under conditions in which methyl α-D-glucopyranoside reduced the expected 2 mol. of periodate. The consumption of periodate was followed spectrophotometrically.[20]

Methyl 3-O-*Methyl*-β-D-*xylopyranoside* 2,4-*Phenylboronate.*—Methyl β-D-xylopyranoside 2,4-phenylboronate (10·0 g.) was dissolved in dry dimethylformamide (120 ml.) in the presence of methyl iodide (15 ml.) and " Hi-Drite " (7 g.). Silver oxide (25 g.) was added during 10 hr., and the reaction mixture was stirred for a further 10 hr. After the addition of dry benzene (50 ml.) and removal of the solids and solvents, a syrup remained which, on distillation, gave a heavy oil (3·4 g.), b. p. 120—125°/0·1 mm., which partially solidified. Recrystallisation of the solid portion from light petroleum gave the *product* (1·8 g.) which was further purified by sublimation (1·6 g.), m. p. 82—84°, $[\alpha]_D$ −114° (Found: C, 59·1; H, 6·4; B, 4·2; OMe, 23·0. $C_{13}H_{17}BO_5$ requires C, 59·1; H, 6·4; B, 4·1; OMe, 23·5%). Further quantities (0·4 g.; total 18%) were obtained by sublimation from the non-crystalline fractions.

Methyl 3-O-*Methyl*-β-D-*xylopyranoside.*—The above methylated boronate (1·0 g.) was dissolved in dry acetone (30 ml.) and propane-1,3-diol (0·29 g., 1·0 mol.) was added. Removal of the solvent left a syrup which, on trituration with light petroleum, gave a solid (0·52 g., 77%);

[20] Aspinall and Ferrier, *Chem. and Ind.*, 1957, 1216.

this gave the *monomethyl-glycoside* (0·3 g.), m. p. 106—107° (from ethyl acetate–light petroleum), $[\alpha]_D$ −66° (in water) (Found: C, 46·8; H, 7·8; OMe, 34·2. $C_7H_{14}O_5$ requires C, 47·2; H, 7·9; OMe, 34·8%).

3-O-*Methyl*-D-*xylose*.—The above glycoside was heated under reflux in water in the presence of the ion-exchange resin IR 120 (H^+). The free sugar was crystallised from ethyl acetate–methanol and had m. p. 97—98°, $[\alpha]_D$ +39° (3 min.) ⟶ +14·7° [90 min. in water (const.)]. The derived 3-*O*-methyl-*N*-phenyl-D-xylosamine had m. p. 133—134°.

Methyl β-D-*Xylopyranoside* 2,4-*Phenylboronate* 3-N-*Phenylcarbamate*.—Methyl β-D-xylopyranoside 2,4-phenylboronate (1·0 g.) was dissolved in dry benzene (25 ml.), phenyl isocyanate (0·43 ml., 1·0 mol.) was added, and the solution heated under reflux for 6 hr. The solvent was evaporated under reduced pressure, the final traces of volatile material being removed at 0·1 mm. Trituration of the residual syrup with light petroleum–benzene gave a solid which, on recrystallisation from the same solvent, yielded the *boronate carbanilate* (0·97 g., 65%), m. p. 146—147°, $[\alpha]_D$ −90° (Found: C, 61·7; H, 5·25; B, 3·0; N, 3·85; OMe, 8·2. $C_{19}H_{20}BNO_6$ requires C, 61·8; H, 5·4; B, 2·9; N, 3·8; OMe, 8·4%).

Methyl β-D-*Xylopyranoside* 3-N-*Phenylcarbamate*.—Propane-1,3-diol (0·65 g., 1·0 mol.) was added to a solution of the above boronate carbanilate (3·16 g.) in acetone. Evaporation of the solvent left a solid (2·3 g.) which, on recrystallisation from ethyl acetate–light petroleum, gave the *xyloside* 3-*carbanilate* (1·95 g., 80%), m. p. 147—149°, $[\alpha]_D$ −6° (Found: C, 55·0; H, 6·2; N, 4·6; OMe, 10·6. $C_{13}H_{17}NO_6$ requires C, 55·1; H, 6·0; N, 4·9; OMe, 10·9%).

Methyl 2,4-*Di*-O-*methyl*-β-D-*xylopyranoside* 3-N-*Methyl*-N-*phenylcarbamate*.—The above xyloside 3-carbanilate (1·44 g.) was methylated in dimethylformamide (45 ml.), using methyl iodide (6 ml.), silver oxide (10 g.), and " Hi-Drite " (3 g.). Removal of the solids and solvent gave a syrupy residue which was extracted with chloroform. The extract was washed with water, dried, and treated with decolourising charcoal; after filtration and evaporation of the chloroform, the remaining syrup crystallised spontaneously. Recrystallisation from benzene–light petroleum gave the methylated carbanilate (1·1 g., 69%), m. p. 88—89°, $[\alpha]_D$ −24° (Found: C, 58·9; H, 7·1; N, 4·3; OMe, 28·7. $C_{16}H_{23}NO_6$ requires C, 59·1; H, 7·1; N, 4·3; OMe, 28·6%). *N*-Methylation must have occurred, since the infrared spectrum showed an absence of N–H absorptions and the nuclear magnetic resonance spectrum the presence of four methyl groupings in the molecule.

Methyl 2,4-*Di*-O-*methyl*-β-D-*xylopyranoside*.—The above carbanilate (0·9 g.) was treated, in boiling tetrahydrofuran (40 ml.), with lithium aluminium hydride (0·5 g.) for 3·5 hr. The excess of the hydride was destroyed by dropwise addition of moist ethanol and then water. Neutralisation was then effected by addition of dilute phosphoric acid, solids were removed, the solvent was dried, and, after its removal, a crystalline product was obtained. Recrystallisation from light petroleum gave the dimethyl-xyloside (0·35 g., 64%), m. p. 77—78°, $[\alpha]_D$ −79° (in chloroform). This m. p. corroborates a previous finding [17c] and differs markedly from the values of 60—61° quoted by other authors.[17a,d] Dimorphism may be responsible for these discrepancies, since our specific rotation does not disagree with those quoted for the lower-melting samples.

2,4-*Di*-O-*methyl*-D-*xylose*.—The above glycoside was heated under reflux in aqueous alcohol and then in water in the presence of a cation-exchange resin (H form). The free sugar, after recrystallisation from ethyl acetate–light petroleum, had m. p. 108—109°, $[\alpha]_D$ +22° (const. in water). The derived 2,4-di-*O*-methyl-*N*-phenyl-D-xylosamine had m. p. 159—160°, $[\alpha]_D$ −80°.

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