1360. *Boric Acid Derivatives as Reagents in Carbohydrate Chemistry. Part VI.*[1] *Phenylboronic Acid as a Protecting Group in Disaccharide Synthesis*

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Phenylboronic acid is demonstrated to be a suitable protecting reagent for use in disaccharide syntheses. 3-*O*-β-D-Glucopyransoyl-D-xylose and 3-*O*-α- and -β-D-xylopyranosyl-D-xylose have been prepared by glycosylation, under modified Koenigs–Knorr conditions, of benzyl β-D-xylopyranoside 2,4-phenylboronate.

Since carbohydrate phenylboronates are stable under esterifying conditions, and since the boronate groupings can be readily removed under neutral conditions,[1-3] these derivatives can be used in the syntheses of partially and specifically substituted sugars. Of particular interest are those phenylboronates formed from diols which cannot be protected by acetal- or ketal-ring formation; thus, the 2,4-cyclic derivatives of xylo- and ribopyranosides offer suitable means of preparing 3-*O*-substituted xyloses [2] and riboses.[1] We now report the synthesis of 3-*O*-glycosylxyloses from benzyl β-D-xylopyranoside 2,4-phenylboronate.

Benzyl α-D-xylopyranoside gave a crystalline phenylboronate which was shown by infrared spectroscopy to contain an unsubstituted hydroxyl group which was not intramolecularly hydrogen-bonded; the ester therefore possessed the 2,4-cyclic structure.[2] Reaction of this compound with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in the presence of silver carbonate and Hi-Drite (Hi-Drite Ltd.) under a variety of conditions did not give an isolable product containing both glucose and xylose, and we were led to suspect that the water formed under these conditions was causing hydrolysis of the boronate grouping. With the aim of carrying out the condensation strictly in the absence of water the mercuric cyanide–nitromethane modification [4] of the Koenigs–Knorr reaction [5] was adopted. Thin-layer chromatography (t.l.c.) showed that reaction occurred at room temperature and that apparently one major product was formed. When, however, this product was isolated by application of column chromatography, it was found to give glucose without xylose on acidic hydrolysis. Since tetra-*O*-acetyl-α-D-glucosyl bromide is known to react with mercuric cyanide in nitromethane under the conditions employed for the attempted condensation to give a mixture from which 3,4,6-tri-*O*-acetyl-1,2-*O*-1′-cyanoethylidene-α-D-glucopyranose and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl cyanide have been isolated,[6] it seems most likely that the product detected by t.l.c. was a cyano-derivative.

When the hydrogen atom of a hydroxyl group takes part in intramolecular hydrogen-bonding the nucleophilic character of the oxygen is enhanced.[7] It was anticipated therefore that benzyl β-D-xylopyranoside 2,4-phenylboronate, in which the unsubstituted hydroxyl group is strongly bonded to O-1 (O–H stretching frequency [2] 3512 cm.$^{-1}$), would be more reactive than the α-isomer in the Koenigs–Knorr reaction, and so the tetra-*O*-acetyl-α-D-glucosyl bromide–mercuric cyanide–nitromethane condensation was repeated using the β-anomer. T.l.c. showed that one main product was formed, and this was obtained in crystalline form on removal of the solids and the solvent. Infrared spectroscopy showed it to be devoid of hydroxyl groups and to contain acetyl and phenylboronate esters. On complete hydrolysis it gave glucose and xylose. Catalytic deacetylation with sodium methoxide was inhibited by phenylboronates (presumably the methoxide co-ordinates

[1] Part V, preceding Paper.
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[3] R. J. Ferrier, D. Prasad, and A. Rudowski, *J.*, 1965, 858.
[4] B. Helferich and K. Weis, *Chem. Ber.*, 1956, **89**, 314.
[5] W. Koenigs and E. Knorr, *Ber.*, 1901, **34**, 957.
[6] B. Coxon and H. G. Fletcher, *J. Amer. Chem. Soc.*, 1963, **85**, 2637.
[7] K. W. Buck, A. B. Foster, A. R. Perry, and J. M. Webber, *J.*, 1963, 4171.

with boron) so that the boronate protecting group was removed first. Addition of propane-1,3-diol to the crystalline product followed by its distillation [2] afforded crystalline benzyl 3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-β-D-xylopyranoside which was then smoothly deacetylated to give the disaccharide benzyl glycoside. Hydrogenolysis of this afforded the reducing disaccharide which, on hydrolysis, gave glucose and xylose, and which was characterised by preparation of its phenylosazone and by chromatographic comparison with an authentic sample. This compound has been prepared previously by enzymic methods,[8] as has the α-anomer,[9] which must have been produced to some extent during the present condensation but was not detected.

The anomeric 3-*O*-xylopyranosylxyloses are both known. The α-isomer has been isolated from the products of reversion of xylose,[10] and the β-(" rhodymenaboise ") prepared by enzymolysis of a pentosan,[11] by the action of a transferase,[12] and also by a Koenigs–Knorr synthesis involving the use of 5-*O*-benzoyl-2,4-*O*-benzylidene-D-xylose dimethyl acetal.[13] Both disaccharides have now been isolated from the condensation between 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide and benzyl β-D-xylopyranoside 2,4-phenylboronate. The reaction product was purified on a column of silica gel and the phenylboronate protecting group was removed with the aid of propane-1,3-diol, whereupon a small amount of crystalline benzyl 3-*O*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-β-D-xylopyranoside was obtained. Removal of the remaining protecting groups from this compound afforded crystalline 3-*O*-β-D-xylopyranosyl-D-xylose. Deacetylation of the purified mother-liquors gave crystalline benzyl 3-*O*-(α-D-xylopyranosyl)-β-D-xyloside in high yield, and this on hydrogenolysis gave the α-disaccharide.

Although β-glycosides are generally formed from tetra-*O*-acetyl-α-D-glucosyl and -xylosyl bromide under normal Koenigs–Knorr conditions, the mercuric cyanide–nitromethane modification is known to result in mixtures of anomers.[14] It is believed that the isolation of derivatives of the α- and β-xylosylxyloses in 25% and 4% yield, respectively, and of the β-glucosylxylose in 29% yield, reflects only the ease of isolation of these compounds. These yields compare favourably with those normally obtained from Koenigs–Knorr reactions involving a secondary hydroxyl group on a cyclic sugar derivative [15] which is partially protected by more conventional groups.

Experimental

Optical rotations were measured in a 1-dm. tube at room temperature and within the concentration range 0·7—1·8%. 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. Infrared spectra were measured at room temperature in carbon tetrachloride solution (0·004M) on the Unicam S.P. 700 spectrophotometer. The light petroleum used throughout had b. p. 60—80°.

Benzyl α-D-Xylopyranoside 2,4-Phenylboronate.—Benzyl α-D-xylopyranoside {3·3 g.; m. p. 127—128°, $[\alpha]_D$ +138° (H_2O); prepared by the method of Ballou *et al.*[16] who give m. p. 127—128·5°, $[\alpha]_D$ +139° (H_2O)} was treated with triphenylboroxole (1·43 g., 0·33 mol.) in boiling benzene. Removal of the liberated water and then the solvent left a syrup which crystallised from benzene–light petroleum to give the *α-glycoside boronate* (4·05 g., 93%), m. p. 152—153°, $[\alpha]_D$ −4°, O–H stretching frequency 3620 cm.$^{-1}$ (Found: C, 66·2; H, 5·9; B, 3·5. $C_{18}H_{19}BO_5$ requires C, 66·3; H, 5·8; B, 3·3%).

[8] (*a*) S. A. Barker, E. J. Bourne, G. C. Hewitt, and M. Stacey, *J.*, 1957, 3541; (*b*) F. B. Anderson and D. J. Manners, *Biochem. J.*, 1959, **71**, 407; (*c*) W. A. M. Duncan, D. J. Manners, and J. L. Thompson, *Biochem. J.*, 1959, **73**, 295.

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[15] E. J. C. Curtis and J. K. N. Jones, *Canad. J. Chem.*, 1959, **37**, 358.

[16] C. E. Ballou, S. Roseman, and K. P. Link, *J. Amer. Chem. Soc.*, 1951, **73**, 1140.

Benzyl β-D-*Xylopyranoside* 2,4-*Phenylboronate.*—The β-glycoside {m. p. 115—117°, $[\alpha]_D$ −74° (EtOH); prepared by the Koenigs–Knorr method; Ballou *et al.*[16] give m. p. 113—115°, $[\alpha]_D$ −72° (EtOH)} was converted by the same route into the β-*glycoside boronate* in 91% yield. It had m. p. 77—78°, $[\alpha]_D$ −144°, O–H stretching frequency 3512 cm.$^{-1}$ (Found: C, 66·3; H, 5·7; B, 3·4%).

Benzyl 3-O-(2,3,4,6-*Tetra*-O-*acetyl*-β-D-*glucopyranosyl*)-β-D-*xylopyranoside* 2,4-*Phenylboronate.*—Benzyl β-D-xylopyranoside 2,4-phenylboronate (3·58 g.) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (5·4 g., 1·2 mol.) were dissolved in anhydrous nitromethane (60 ml.), mercuric cyanide (1·39 g., 0·5 mol.) was added, and the mixture was shaken for 6 hr. T.l.c. showed that the reaction was complete in this time and that one major product [R_F 0·6; silica gel plates, methylene dichloride–ethyl acetate (1 : 1)] had been formed. The initial boronate and the glycosyl bromide had R_F 0·1 and 0·8, respectively, in this solvent. The solids and the solvent were removed, and the residual syrup was extracted with warm, dry benzene. Evaporation of the benzene left a clear syrup which deposited impure crystals from ethyl acetate–light petroleum when left at 0°. Recrystallisation from this solvent gave the *fully substituted disaccharide derivative* (0·85 g.), m. p. 151—152°, $[\alpha]_D$ −97° (Found: C, 58·3; H, 5·5; B, 1·8. $C_{32}H_{37}BO_{14}$ requires C, 58·6; H, 5·6; B, 1·6%). Further quantities of this product (0·88 g., total 1·73 g., 24%) were obtained by fractionating the mother-liquors on a column of silica gel (eluted with methylene dichloride containing increasing amounts of ethyl acetate). A subsequent fraction (1·13 g.), m. p. 120—140°, could not be purified by crystallisation but, after removal of the phenylboronic acid in it, the partially substituted disaccharide acetate (see below) was obtained (0·28 g.). The total isolated yield of β-disaccharide derivatives was 29%.

Benzyl 3-O-(2,3,4,6-*Tetra*-O-*acetyl*-β-D-*glucopyranosyl*)-β-D-*xylopyranoside.*—The fully substituted derivative (1·14 g.) was dissolved in acetone (15 ml.) and propane-1,3-diol (2·5 ml.) was added. The acetone was removed at the water-pump and the propanediol and its phenylboronate were removed by distillation at 0·01 mm. The residue was extracted with hot ethyl acetate and the extract taken to dryness to leave a syrup which crystallised on trituration with light petroleum. Recrystallisation from ethyl acetate–light petroleum afforded the *glycoside acetate* (0·73 g., 74%), m. p. 145—145·5°, $[\alpha]_D$ −22° ($CHCl_3$) (Found: C, 55·1; H, 5·9. $C_{26}H_{34}O_{14}$ requires C, 54·7; H, 6·0%).

When the fully substituted disaccharide derivative was treated with catalytic amounts of methanolic sodium methoxide, deacetylation did not occur on standing overnight. Concentration of the solution afforded instead crystalline benzyl 3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-β-D-xylopyranoside. That the phenylboronic acid was responsible for this inhibition was shown in independent experiments with inositol hexa-acetate. The addition of a molar quantity of phenylboronic acid to a methanolic solution of the acetate prevented catalytic deacetylation which otherwise occurred rapidly.

Benzyl 3-O-(β-D-*Glucopyranosyl*)-β-D-*xylopyranoside.*—The tetra-acetate (0·5 g.) was dissolved in dry methanol (40 ml.) and treated with 0·1N-sodium methoxide solution (3·5 ml.) for 1 hr. at room temperature. The sodium ions were removed with cation-exchange resin, and evaporation gave the *disaccharide glycoside* which was crystallised from ethyl acetate–methanol (0·29 g., 83%), m. p. 169—170·5°, $[\alpha]_D$ −59° (EtOH) (Found: C, 54·1; H, 6·5. $C_{18}H_{26}O_{10}$ requires C, 53·7; H, 6·5%).

3-O-β-D-*Glucopyranosyl*-D-*xylose.*—The glycoside (0·29 g.) was dissolved in ethanol (30 ml.) and shaken in an atmosphere of hydrogen in the presence of 5% palladised charcoal until hydrogen (1·0 mol.) had been consumed. T.l.c. indicated that at this stage hydrogenolysis was complete. Removal of the catalyst and the solvent afforded the reducing disaccharide (0·19 g., 83%), $[\alpha]_D$ −3° (H_2O). Barker *et al.*[8a] report $[\alpha]_D$ −0·6°, and Duncan *et al.*[8c] −6·4° for this compound. The disaccharide could not be induced to crystallise. From it a phenylosazone was prepared, m. p. 204—206° (lit., 205—206°,[8c] 213—215° [8a]). The disaccharide was indistinguishable from an authentic sample on paper chromatograms run in acidic and in basic solvents, and on acidic hydrolysis it gave xylose and glucose in equal quantities (visual estimation).

Condensation of 2,3,4-*Tri*-O-*acetyl*-α-D-*xylopyranosyl Bromide with Benzyl* β-D-*Xylopyranoside* 2,4-*Phenylboronate.*—The boronate (3·5 g.) and the glycosyl bromide (4·5 g., 1·2 mol.) were dissolved in anhydrous nitromethane (45 ml.) and shaken with mercuric cyanide (1·4 g., 0·5 mol.) at room temperature for 3·5 hr. T.l.c. revealed that only traces of starting materials remained [R_F 0 and 0·9; silica gel plates run in methylene dichloride–ethyl acetate (7 : 3)] and that two products which ran as elongated spots (R_F 0·1 and 0·4) had been formed. The solids and solvent

were removed, the residue was extracted with hot, dry benzene, and the extract was taken to dryness to leave a syrup (7·0 g.) which was fractionated on a column of silica gel using methylene dichloride–ethyl acetate (7 : 3) as solvent. Only the fraction (3·6 g.) containing the component with R_F 0·4 was examined further, and it was found to contain boron.

Benzyl 3-O-(2,3,4-*Tri*-O-*acetyl*-β-D-*xylopyranosyl*)-β-D-*xylopyranoside*.—Removal of boron from the syrupy fraction was accomplished as before with the aid of propane-1,3-diol, and from the resultant mixture a crystalline product (0·3 g.) was obtained on trituration with ethyl acetate–light petroleum. Recrystallisation from this solvent gave *benzyl* 3-O-(2,3,4-*tri*-O-*acetyl*-β-D-*xylopyranosyl*)-β-D-*xylopyranoside* (0·2 g.), m. p. 173—174·5°, $[\alpha]_D$ +47° ($CHCl_3$) (Found: C, 55·0; H, 6·0. $C_{23}H_{30}O_{12}$ requires C, 55·4; H, 6·1%). N.m.r. spectroscopy revealed the presence of 30 protons, three acetyl groups, and one benzyl group.

3-O-β-D-*Xylopyranosyl*-D-*xylose*.—The acetylated compound (0·18 g.) was de-esterified with sodium methoxide and the product (0·11 g., 85%) was obtained as a glass $[\alpha]_D$ +43° (MeOH) which was chromatographically pure (t.l.c.). The benzyl glycoside (0·095 g.) was hydrogenolysed in ethanolic solution using 5% palladised charcoal as catalyst to give a product which deposited the β-linked disaccharide (0·015 g.) on treatment with methanol. The crystalline product had m. p. 188—190°, $[\alpha]_D$ −23° (H_2O, const.) {lit.,[13] m. p. 192—193°, $[\alpha]_D$ −22° (H_2O, const.)}.

Benzyl 3-O-(α-D-*Xylopyranosyl*)-β-D-*xylopyranoside*.—The non-crystalline material remaining after removal of benzyl 3-*O*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-β-D-xylopyranoside contained traces of boron and was therefore given a second treatment with propane-1,3-diol, and a portion (2·1 g.) was then refractionated by chromatography on silica gel. The central fraction (1·06 g.) was retained and was shown to exhibit hydroxyl, acetyl, and phenyl infrared absorptions. Deacetylation of this syrup (0·85 g.) afforded a solid (0·52 g., 81%; 25% based on starting materials) which, on recrystallisation from methanol, gave the *α-linked disaccharide glycoside*, m. p. 215—217°, $[\alpha]_D$ +57° (H_2O) (Found: C, 55·0; H, 6·4. $C_{17}H_{24}O_9$ requires C, 54·8; H, 6·4%).

3-O-α-D-*Xylopyranosyl*-D-*xylose*.—The glycoside (0·1 g.) was hydrogenolysed as before and gave, after crystallisation from methanol, the β-linked disaccharide (0·05 g.), m. p. 179—180°, $[\alpha]_D$ +106° (H_2O, 5 mins.) ⟶ +116° (75 mins., const.). Ball and Jones [10] give m. p. 178°, $[\alpha]_D$ +106° (H_2O, 5 mins.) ⟶ +118° (75 mins., const.) for this disaccharide.

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