Improvements in the synthesis of xylobiose (4-*O*-β-D--xylopyranosyl-D-xylopyranose)

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Dedicated to Professor R. L. Whistler, in honour of his 65th birthday

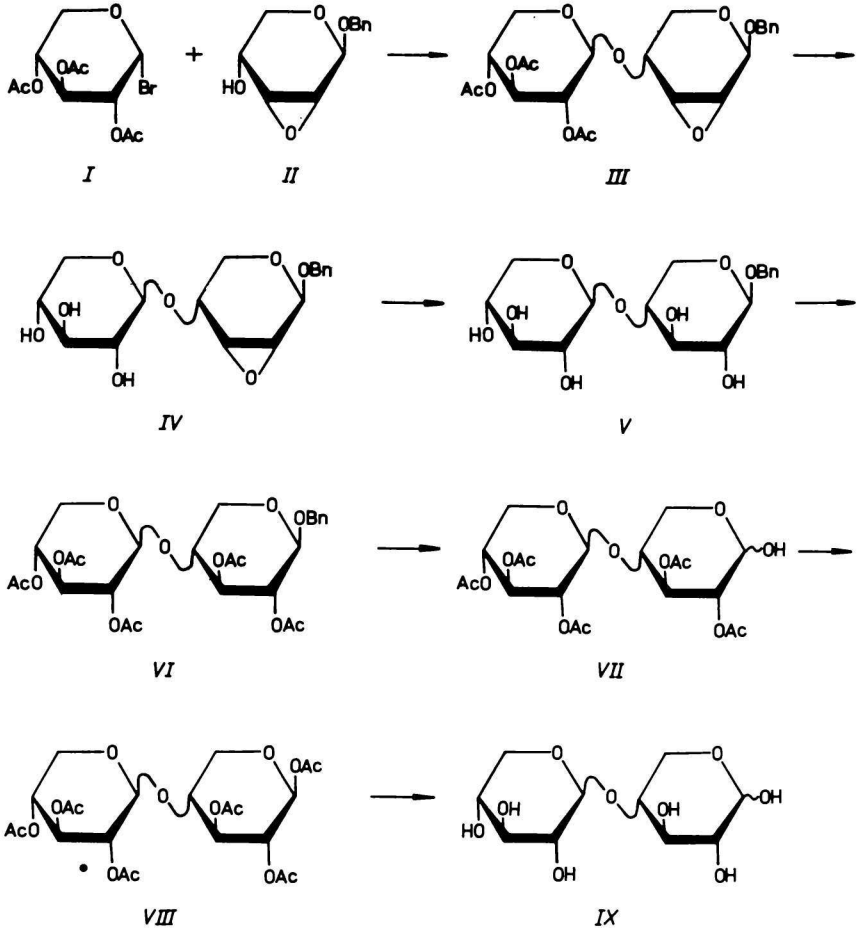
Reaction of 2,3,4-tri-*O*-acetyl-1-bromo-1-deoxy-α-D-xylopyranose with benzyl 2,3-anhydro-β-D-ribopyranoside followed by deacetylation gave benzyl 2,3-anhydro-4-*O*-(β-D-xylopyranosyl)-β-D-ribopyranoside (*IV*) in 62% overall yield. Opening of the anhydro ring in *IV* by alkaline hydrolysis and following acetylation yielded crystalline benzyl per-*O*-acetyl-β-xylobioside (*VI*); catalytic hydrogenolysis and acetylation then gave xylobiose per-*O*-acetate. Deacetylation of the β-acetate afforded xylobiose.

Бензил-2,3-ангидро-4-*O*-(β-D-ксилопиранозил)-β-D-рибопиранозид (*IV*) был получен, с выходом 62%, конденсацией 2,3,4-три-*O*-ацетил-1--бром-1-дезокси-α-D-ксилопиранозы с бензил-2,3-ангидро-β-D-рибопиранозидом и последующим деацетилированием. Раскрытием ангидро--кольца в *IV* при щелочном гидролизе и ацетилированием был получен кристаллический бензил-пер-*O*-ацетил-β-ксилобиозид (*VI*), из которого после каталитического гидрогенолиза и ацетилирования был обнаружен пер-*O*-ацетат ксилобиозы. Деацетилированием β-ацетата была получена ксилобиоза.

Xylobiose (4-*O*-β-D-xylopyranosyl-D-xylopyranose) and its higher homologues were isolated from the products of partial hydrolysis of plant polysaccharides [1]. This procedure of isolation is impractical for large-scale preparation of the substance since it requires separation by chromatography of complex mixtures [2—4]. Neither the chemical syntheses described so far make larger amounts of xylobiose or its derivatives readily available. Some of the conversions involved in the procedures [5—7] do not give good yields of the products and the recently described synthesis is tedious as it uses intermediates which are obtainable only with difficulty [6]. The procedure developed by *Aspinall* and *Ross* [7] is based on ready-to-make starting compounds. It takes advantage of the stereoselective [8] nucleophilic opening of the anhydro ring in alkyl β-D-ribopyranosides resulting in the formation of the corresponding derivative of D-xylose in high yield. The critical

step here was the condensation of 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide with benzyl 2,3-anhydro-β-D-ribopyranoside. After separation of the condensation products by chromatography the key intermediate of the synthesis namely benzyl 2,3-anhydro-4-*O*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-β-D-ribopyranoside was obtained in a yield of only 23% [7].

The synthesis of higher homologues of xylobiose (xylodextrins) and aldooligouronic acids related to (4-*O*-methylglucurono)xylans required larger amount of xylobiose per-*O*-acetate. In the work described herein the known synthesis [7] has been modified in several ways (Scheme 1) and the wanted product *VIII* was obtained in good overall yield.



Scheme 1

The condensation of the bromosugar *I* [9] with benzyl 2,3-anhydro--β-D-ribopyranoside (*II*) [10] was carried out in acetonitrile in the presence of mercuric cyanide under the conditions of the Koenigs—Knorr synthesis of glycosides as modified by *Helferich* [11]. Chromatography of the crude reaction product yielded the known crystalline substance *III* in 47% yield. Owing to the poor separation of *III* from the reaction by-products, the formation of which could not be prevented by altering the reaction conditions, a portion of *III* could not be recovered without rechromatographing the mother liquors.

Deacetylation of *III* gave virtually a theoretical yield of the hitherto unknown, crystalline benzyl 2,3-anhydro-4-*O*-β-D-xylopyranosyl-β-D-ribopyranoside (*IV*). Its extremely poor solubility in common organic solvents made it possible to further improve the conversion *II* → *IV*, while the isolation of the intermediate *III* could be omitted. The reaction mixture of the condensation of *I* with *II* was worked up and the crude reaction product was deacetylated (Zemplén). The oligosaccharide *IV* crystallized without chromatography in 58% yield, which is a 2.5-fold yield of the key step of the synthesis of xylobiose, compared to that obtained by the original authors [7]. Preparative chromatography of the mother liquors gave but a small amount of *IV* (~4% of the theory) indicating that virtually all *IV* present in the deacetylated crude product crystallized.

The next two steps leading to benzyl β-xylobioside per-*O*-acetate *VI* were most conveniently performed without the isolation of the intermediate *V* The anhydro ring in *IV* was opened by alkaline hydrolysis with aqueous potassium hydroxide at elevated temperature and the crude product was acetylated in pyridine with an excess of acetic anhydride. In this way, the hitherto unknown, crystalline glycoside *VI* was obtained in 80% yield, again without chromatography.

Catalytical hydrogenolysis of *VI* followed by acetylation of *VII* under the conditions known to give predominantly β-acetates [12—14] yielded α,β-xylobiose per-*O*-acetate. The β-per-*O*-acetate *VIII* crystallized in ~70% yield and was, according to its physical constants, identical with the substance obtained by the conversion of xylobiose of natural origin. Its deacetylation gave then xylobiose, the specific optical rotation of which was in excellent agreement with the reported values.

Experimental

Melting points were determined on a Kofler hot-stage. Optical rotations were measured with a Perkin—Elmer automatic polarimeter, Model 141. Thin-layer chromatography (t.l.c.) on Silica gel G (Merck, A.G., Darmstadt) and preparative chromatography on columns of dry-packed silica gel (Merck, A.G., Darmstadt, prod. No. 9385) which, prior to packing was equilibrated with 40% (v/w) of the mobile phase, instead of the recommended [15] 10%, was performed with *A*. carbon tetrachloride—acetone 5 : 1, *B*. carbon tetrachlo-

ride—acetone 10 : 1, *C*. benzene—acetone 8 : 1, *D*. chloroform—methanol 8 1, and *E*. chloroform—methanol 3.5 : 1. Detection was effected by spraying with 5% (v/v) sulfuric acid in ethanol and heating until permanent char spots were visible. The purity of xylobiose was checked by chromatography on commercial, cellulose coated aluminium foils (Lucefol, Lachema, Brno) with ethyl acetate—acetic acid—water 18 : 7 8 mixture as the mobile phase. In this case the detection was performed by spraying with anilinium hydrogen phthalate and heating at 100°C. The solutions in organic solvents were dried with anhydrous sodium sulfate and concentrated at 40°C/2 kPa.

Benzyl 2,3-anhydro-4-O-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)-β-D-ribopyranoside (III)

To a stirred mixture of benzyl 2,3-anhydro-β-D-ribopyranoside (*II*, 2.75 g, 0.0124 mol) and mercuric cyanide (4.6 g, 0.0182 mol) in dry acetonitrile (30 ml) was added 2,3,4-tri-*O*-acetyl-1-bromo-1-deoxy-α-D-xylopyranose (*I*, 5.5 g, 0.0162 mol). The mixture was stirred at room temperature and with the exclusion of atmospheric moisture for 1 h and t.l.c. (solvent *A* and *B*) then showed that *I* has reacted completely and that only traces of unreacted *II* were present. The mixture contained mainly the product *III* (R_f 0.4, solvent *A*), together with the product of hydrolysis of *I*. Some reaction by-products, probably the α-isomer of *III* and the trehalose type derivatives of xylobiose, were also present. After concentration, the residue was partitioned between benzene and aqueous 1 M potassium bromide solution, to remove the mercuric salts. The benzene solution was processed in the usual manner and the crude product was chromatographed on silica gel to give a fraction containing mainly *III*. Crystallization from ethanol—isopropyl ether gave *III* (2.8 g, 47% based on *II*), melting at 131—133°C. Ref. [7], m.p. 131—132°C. Repeated chromatography of the mother liquors gave further amount of *III*.

Benzyl 2,3-anhydro-4-O-(β-D-xylopyranosyl)-β-D-ribopyranoside (IV)

a) Methanolic 1 M sodium methoxide (2 ml) was added to a solution of *III* (5 g) in dry methanol (200 ml) and the reaction mixture was left at room temperature for 30 min, after which time t.l.c. (solvent *D*) showed that the reaction was complete. After neutralization with Ionenaustauscher V (Merck, A.G., Darmstadt) and usual work-up the product *IV* (R_f 0.6, 3.4 g, 93%) was crystallized from ethanol. Recrystallization from the same solvent afforded material melting at 203.5—204.5°C, $[\alpha]_D^{22}$ −31.7° (*c* 1, pyridine).

For $C_{17}H_{22}O_8$ (354.35) calculated: 57.62% C, 6.26% H; found: 57.53% C, 6.35% H.

b) Aqueous 10% potassium hydroxide was added (50—60°C) to strong alkalinity to a solution of *III* (crude product prepared from 20 g of *II*, from which mercuric salts had been removed as described above) in ethanol (600 ml). Compound *IV* separated almost immediately in crystalline form. The product was filtered after 30 min at 0°C and recrystallized from water to give 15.63 g of pure *IV* The combined mother liquors, after deionization with Ionenaustauscher V, afforded a second crop of *IV* (2.9 g, total yield obtained without chromatography, 58.2%), and a further amount of the same material (1.3 g, total yield 62.3%) was obtained after chromatography of the residual mother liquor.

Benzyl 2,3-di-O-acetyl-4-O-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)-β-D-xylopyranoside (VI)

A vigorously stirred suspension of *IV* (13 g) in 10% aqueous potassium hydroxide was heated at 105—110°C with the exclusion of atmospheric carbon dioxide. A clear, colourless solution was obtained after 3—4 h and t.l.c. (solvent *D*) then showed that the starting material was no more present. The solution was cooled (0°C), neutralized with carbon dioxide (pH 7.5) and concentrated, and the residue was evaporated several times with toluene to remove as much water as possible. After addition of pyridine (50 ml) and acetic anhydride (100 ml, portionwise) the mixture was left at room temperature for 18 h. Only traces of components other than *VI* (R_f 0.5, solvent *B*) were then present, as shown by t.l.c. The excess of the acetylating agent was destroyed by portionwise addition of methanol and, after concentration to dryness, the crude product was partitioned between chloroform and water. The chloroform extract was processed in the usual manner and crystallization from ethanol gave 17.1 g (80%) of chromatographically pure *VI* melting at 125—127°C. A portion, when recrystallized from the same solvent melted at 126—127°C and had $[\alpha]_D^{22}$ − 104.7° (*c* 1.28, chloroform).

For $C_{27}H_{34}O_{14}$ (582.54) calculated: 55.66% C, 5.88% H; found: 55.89% C, 5.91% H.

1,2,3-Tri-O-acetyl-4-O-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)-β-D-xylopyranose (VIII)

A solution of *VI* (15.2 g) in a mixture of acetone—ethanol (1 1, 200 ml) containing 5% palladium-on-charcoal catalyst (1.5 g) was vigorously stirred under hydrogen at room temperature and atmospheric pressure until t.l.c. (solvent *B*) showed complete conversion of the starting material to the product (R_f 0.1). After filtration and concentration the solution of the residue in a minimum amount of hot toluene was added at 100°C to a stirred mixture of toluene (10 ml), acetic anhydride (10 ml), and anhydrous sodium acetate (2.5 g). After 1 h t.l.c. showed that the reaction was complete and the mixture was poured into an excess of aqueous, saturated solution of sodium hydrogen carbonate. When the hydrolysis of the excess of acetic anhydride was complete the mixture was partitioned between water and chloroform and the dried chloroform solution was concentrated. Crystallization from ethanol gave 8.8 g of *VIII* melting at 152—154°C, and a second crop of the same material (0.9 g, total yield based on the amount of *VI*, 69.8%) slowly crystallized (from ether) from the concentrated mother liquors. Recrystallization of a portion from ethanol afforded the analytical sample having m.p. 153—155°C. Ref. [16, 17], m.p. 154—156°C for β-xylobiose per-*O*-acetate obtained by conversion of xylobiose isolated from a natural source. Ref. [6], m.p. 155°C for the same substance obtained by synthesis.

4-O-β-D-Xylopyranosyl-D-xylopyranose (IX)

The per-*O*-acetate *VIII* (1 g) was dissolved in anhydrous methanol (50 ml) and methanolic 1 M sodium methoxide was added until the solution was strongly alkaline. After 1 h at room temperature t.l.c. (solvent *E*) showed that the reaction was complete and that one product (R_f 0.1) was formed. A half volume of the solvent was removed and the

remaining solution was percolated through a small layer of silica gel which was then washed with a little methanol. The neutral filtrate was concentrated and the residue was crystallized from ethanol containing a few drops of water. The thus obtained xylobiose (400 mg, 75%) showed m.p. 183—187°C and $[\alpha]_D^{22}$ −35.5°→ −23° (3 h). Recrystallization from the same solvent gave material melting at 184.5—186°C and having $[\alpha]_D^{22}$ −33.0°→ −23° (*c* 1, water). Preparations of xylobiose, synthetic and those isolated from natural sources, show [18] m.p. 185—190°C and $[\alpha]_D$ (equil.) −20°—−30° (in water).

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