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Note

Oxidation of methyl α- and β-D-xylopyranoside and a xylan with bromine in the presence of borate

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Glycosiduloses are intermediates in the biosynthesis[1,2] and chemical synthesis[3,4] of other sugars. Introduction of keto groups into the units of polysaccharides provides useful starting materials for their further modification. Methyl α- and β-D-*erythro*-pentopyranosid-3-uloses have been prepared by the oxidation of the anomeric methyl D-xylopyranosides with methyl sulfoxide–acetic anhydride in the presence of phenylboronic acid[5]. By treatment of methyl α- and β-D-xylopyranosides with *Acetobacter suboxydans*, the corresponding 4-uloses were obtained[6].

When glycosides and polysaccharides are treated with aqueous bromine, secondary alcohol groups are oxidised to keto groups. Studies with hexopyranosides[7] have shown that hydroxyl, methoxyl, and glycosyl groups in *syn*-diaxial relation to an axial hydrogen obstruct oxidation of the secondary alcohol at that position. Thus, the aglycon group of an α-glycopyranoside residue in the $^4C_1$ conformation protects an axial H-3 from attack by bromine.

Hydrated glycosulose residues in aqueous solution contain vicinal *cis*-hydroxyl groups, which readily form complexes with borate. Further oxidation of glycosulose residues to dicarboxylic acids can therefore be minimised by performing the oxidation in the presence of borate[8]. The present investigation was undertaken to study the regioselectivity of the oxidation of xylopyranosides with bromine and to devise a method for preparing pentopyranosid-4-uloses.

Methyl α- (**1**) and β-D-xylopyranoside (**2**) were oxidised with 0.2M bromine at pH 7 in the presence of sodium metaborate. Conventional removal of boric acid as methyl borate by repeated reaction with methanol at pH 5 may cause some degradation of the pentosiduloses, and residual borate was therefore removed by chromatography on Sephadex G-10 on which borate is retarded, presumably by

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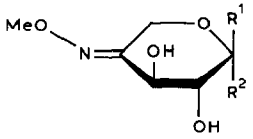
complex formation with the glycerol residues[9]. Most of the sodium bromide was also removed by this procedure. The optimal yield of pentopyranosiduloses (75%, g.l.c.) from methyl α-D-xylopyranoside was obtained at a molar ratio of bromine to xyloside of 10:3. In the absence of borate, the optimum yield (45%) was obtained at a molar ratio of bromine to xyloside of 8:3. The higher molar ratio required in the presence of borate is presumably attributable to complex formation between bromine and borate. T.l.c. of the methoximated products from **1** and **2** revealed the presence of one main product from each reaction, which were isolated and characterised as the *O*-methyloxime (**3**) of methyl β-L-*threo*-pentopyranosid-4-ulose and the corresponding α anomer (**4**). The ^{13}C-n.m.r. data for **3** and **4** were in good agreement with those given by Schnarr and Szarek[6], and established that **3** and **4** adopt the (*E*) conformation. The yields of isolated **3** and **4** (41 and 47%, respectively) were lower than those determined by g.l.c. Traces of other methoximated pentopyranosiduloses were also obtained from **1** and **2**, but were not isolated pure. The ^{1}H-n.m.r. spectra suggested that 2-uloses were present. Demethoximation[7] of a fraction obtained from **2**, followed by reduction and sugar analysis[10], revealed the presence of arabinitol (lyxitol), ribitol, and xylitol, indicating that methyl β-D-*erythro*-pentopyranosid-3-ulose was present in this mixture. The yield of 2- and 3-uloses from **1** and **2** was <5% (g.l.c.), but the yields rose to ~10% when the reactions were performed in the absence of borate.



3 R^1 = H, R^2 = OMe
4 R^1 = OMe, R^2 = H

The xylan was obtained from retted jute sticks and contained D-xylose (89%), L-rhamnose (1%), D-galactose and D-glucose (traces), and 4-*O*-methyl-D-glucuronic acid residues (10%) linked to position 2 of the xylose residues[11,12]. Oxidation of the xylan with 0.2M bromine (4, 6, and 8 mmol of Br_2/g of xylan) in the presence of sodium metaborate yielded the oxidised xylans OX 1–3 (Table I). Sugar analysis of reduced OX 1–3 revealed the presence of xylitol, arabinitol (lyxitol), and ribitol, indicating that oxidation had occurred at C-2 or C-3. No oxidation of the 4-*O*-methyl-D-glucuronic acid residues was detected, since 4-*O*-methylglucitol was the only hexitol found in the sugar analyses of the carboxyl-reduced[13] oxidised xylans.

Signals of similar intensities at δ 94.7 and 96.3 in the ^{13}C-n.m.r. spectra of OX 1–3 were assigned to the hydrated forms of pentopyranosid-2- and -3-ulose residues; no signals in the carbonyl region could be detected. The proportion (Table I) of pentopyranosidulose residues in OX 1–3 was determined by comparing

TABLE I

PROPERTIES OF THE OXIDISED XYLANS **1–3**

Sample	*Bromine (mmol/g of xylan)*	*Yield (%)*	$[\alpha]^{20}_{578}$ *(degrees)*	*Carbonyl groups per xylose residue*	*Carboxyl groups per xylose residue*
OX1	4	42	−37.9	0.19	0.01
OX2	6	42	−30.3	0.24	0.04
OX3	8	41	−19.8	0.36	0.06

the integrated signals of the hydrated and anomeric carbons (δ 99–103). *O*-Methyloximation of OX 1–3 was incomplete. Their contents of carboxylic acid were determined by titration (Table I).

It has been proposed[14] that the rate-determining step in the oxidation of secondary alcohols with bromine involves hydride-transfer from carbon. The oxidation of methyl hexopyranosides is stereospecific; oxidation at ring carbons where the hydrogen is axial is hindered by a bulky, β-diaxially related substituent. Another regioselective effect is observed in the oxidation of the methyl xylopyranosides. Preferential oxidation at C-4 is presumably promoted by the absence of a ring-substituent at C-5. The xylosyl residues of the (1→4)-β-D-xylan have no axial ring-substituents and oxidation occurs at both C-2 or C-3.

EXPERIMENTAL

General methods. — Melting points are uncorrected. Solutions were concentrated under reduced pressure below 40°. Optical rotations were measured with a Perkin–Elmer Model 141 polarimeter. N.m.r. spectra (external Me_4Si) were recorded for solutions in D_2O at 30° using a Jeol FX 90 Q Fourier-transform spectrometer with 16K data points (8K zero-filling) and a spectral width of 5 kHz. Integrations were performed with inverse gated decoupling, using a 45° pulse angle, a pulse delay of 4 s, and a pulse repetition time of 4.8 s. T.l.c. and column chromatography were performed on silica gels F_{254} and 60 G (10–40 μm) (Merck), respectively. G.l.c. was performed on a Packard 427 instrument. Peak areas were measured with an Autolab minigrator. Quantitative analysis of the methyl pentopyranosiduloses was performed on CP-Sil 5 glass-capillary columns (25 m × 0.3 cm) at 130→330° (6°/min). Detector responses were determined only for the trimethylsilylated **1** (1.0) and the trimethylsilylated methyloxime of **3** (0.7), and were relative to that of trimethylsilylated methyl α-D-glucopyranoside. The detector responses of isomers were assumed to be similar. For sugar analysis, separations of alditol acetates were performed on OV-275 glass-capillary columns (25 m × 0.3 cm) at 140→200° (4°/min). For g.l.c.-m.s., a Finnigan 4021 instrument was used. The e.i. spectra were obtained at 70 eV and the helium flow rate was 25 mL/min.

Oxidations with bromine. — (*a*) *In the absence of borate.* To solutions of

methyl α-D-xylopyranoside (100 mg, 0.61 mmol) in water (10 mL) was added 0.2M bromine (2–14 mL, 0.4–2.8 mmol). The pH was maintained at 7.0 by automatic titration with M sodium hydroxide using a Metrohm 300B pH-meter. When the oxidant had been consumed, the pH was adjusted to 5.0 and each reaction mixture was concentrated to 5.0 mL. Methoxylamine hydrochloride (0.10 g) was added, the pH was adjusted to 4.0 with 2M sodium hydroxide, and each mixture was kept at 50° and pH 4. After 2.5 h, the pH was adjusted to 7.0 and the volume to 25.0 mL. Methyl α-D-glucopyranoside (3 mg) was added to 3.0-mL samples, which were then concentrated to dryness, and the residues were trimethylsilylated and analysed by g.l.c.

(*b*) *In the presence of borate.* To solutions of methyl α-D-xylopyranoside (100 mg, 0.61 mmol) and sodium metaborate (1.0 g, 7.2 mmol), adjusted to pH 7, 0.2M bromine (2–14 mL, 0.4–2.8 mmol) was added. The pH was maintained at 7.0 by automatic titration with 0.1M sodium metaborate. When the oxidant had been consumed, the pH was adjusted to 5, the mixture was concentrated to dryness, and methanol was repeatedly evaporated from the residue maintaining the pH at 5. When all borate was removed, as tested by curcumine paper (Merck), the product mixtures were methoximated, and samples for g.l.c. were prepared as in (*a*).

(*c*) A solution of methyl α-D-xylopyranoside (1.00 g, 6 mmol) and sodium metaborate (10 g, 72 mmol) in water (20 mL) was adjusted to pH 7. 0.2M Bromine (100 mL, 20 mmol) was added, and the reaction was performed as in (*b*). After 15–20 h, the pH was adjusted to 5.0, the mixture was concentrated to dryness, and methanol was evaporated repeatedly from the residue keeping the pH at 5.0. Residual borate and most of the inorganic salts were removed by passing a solution of the residue in water (20 mL) through a column (3 × 90 cm) of Sephadex G10, and eluting with water at 0.3 mL/min. The eluate was monitored on the basis of refractive index, optical rotation, and reactions with silver nitrate and curcumine paper. Sugar-containing fractions were combined and concentrated to ~10 mL, and each residue was methoximated as described in (*a*). The pH of the resulting mixture was adjusted to 7.0, and the mixture was concentrated to dryness. Elution of the residue from a column (2.5 × 45 cm) of silica gel 60G with light petroleum (b.p. 60–80°)–ethyl acetate (1:3) yielded methyl β-L-*threo*-pentopyranosid-4-ulose *O*-methyloxime (**3**, 413 mg), isolated as a syrup, $[\alpha]_{578}^{25}$ +106° (*c* 0.6, water). N.m.r. data (D_2O): ^1H, δ 4.89 (d, $J_{1,2}$ 3.3 Hz, H-1), 3.72 (dd, $J_{2,3}$ 9.2 Hz, H-2), 4.46 (d, H-3), 4.80 (d, $J_{5,5'}$ 14.8 Hz, H-5), 4.11 (d, H-5'), 3.89 (s, N-OMe), 3.47 (s, OMe); ^{13}C, δ 100.8 (C-1), 74.0 (C-2), 70.2 (C-3), 156.8 (C-4), 55.8 (C-5), 63.2 (N-OCH_3), 57.2 (OCH_3). Mass spectrum: *m/z* 73 (100%), 335 (0.7), 320 (2), 275 (1), 246 (2), 245 (5), 244 (22), 230 (1), 217 (1), 214 (2), 204 (4).

Anal. Calc. for $C_7H_{13}NO_5$: C, 44.0; H, 6.8; N, 7.3. Found: C, 44.0; H, 6.7; N, 7.0.

(*d*) Methyl β-D-xylopyranoside (1.00 g) was oxidised with bromine in the presence of borate, and the products were methoximated as in (*c*) to give methyl α-L-*threo*-pentopyranosid-4-ulose *O*-methyloxime (**4**, 466 mg), m.p. 66°, $[\alpha]_{578}^{25}$

$-108°$ (*c* 0.5, water). N.m.r. data (D_2O): δ 4.66 (d, $J_{1,2}$ 4.6 Hz, H-1), 3.57 (dd, $J_{2,3}$ 8.3 Hz, H-2), 4.37 (d, H-3), 4.70 (d, $J_{5,5'}$ 16.5 Hz, H-5), 4.35 (d, H-5'), 3.89 (s, N-OMe), 3.49 (s, OMe); ^{13}C, δ 104.9 (C-1), 75.8 (C-2), 71.3 (C-3), 157.5 (C-4), 58.4 (C-5), 63.3 ($N\text{-}OCH_3$), 57.5 (OCH_3). Mass spectrum: *m/z* 73 (100%), 335 (0.8), 320 (2), 275 (1), 246 (2), 245 (4), 244 (17), 230 (1), 214 (1), 204 (3), 203 (1).

Anal. Found: C, 43.7; H, 6.7; N, 7.2.

(*e*) To solutions of the xylan (500 mg) and sodium metaborate (5 g) in water (20 mL) was added 0.2M bromine (10, 15, or 20 mL). The oxidations were performed as in (*b*) for 9–10 h. The pH was adjusted to 5, and each mixture was dialysed against distilled water (4 × 4 L). The borate-free (curcumine paper) solutions were freeze-dried to give the oxidised xylans OX 1–3 (Table I).

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