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Note

Synthesis of methyl α- and β-D-gulopyranosiduronic acids

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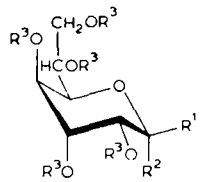
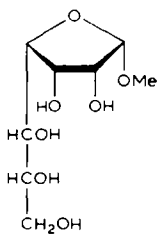
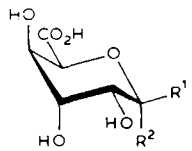
The synthesis of glycosides of uronic acids by catalytic air-oxidation of glycosides of the corresponding aldoses has been reviewed by Heyns and Paulsen[1]. Methyl α- and β-D-gulopyranosiduronic acids, required for a study of lanthanide-induced shifts in the n.m.r. spectra of carbohydrates, may be prepared as their ammonium salts by catalytic air-oxidation of the corresponding, neutral methyl gulosides[2]. However, since the methyl α- and β-D-gulosides were not readily available, we now report the preparation of the uronic acid glycosides from D-*glycero*-D-*gulo*-heptose (**1**),



1 R^1, R^2 = H, OH ; R^3 = H
2 R^1 = OMe ; R^2 = R^3 = H
3 R^2 = OMe ; R^1 = R^3 = H





5 R^1 = H ; R^2 = OMe
6 R^1 = OMe ; R^2 = H

which is readily obtainable[3] from D-glucose by the cyanohydrin synthesis. Methyl glycosidation of **1** in the presence of Amberlite IR-120 (H^+) resin[4] gave crystalline methyl D-*glycero*-β-D-*gulo*-heptopyranoside (**2**). The α anomer **3** was isolated by chromatography, which also gave crystalline methyl D-*glycero*-α-D-*gulo*-heptofuranoside[5] (**4**).

The resonance at 82.2 p.p.m. in the ^{13}C-n.m.r. spectrum of **4**, not obtained crystalline hitherto, is characteristic of C-4 in a furanoside ring[6] (*cf.* 65–70 p.p.m. for pyranosides).

When **3** was subjected to lanthanide-induced shift experiments, it was concluded that the Eu^{3+}–carbohydrate complex must be very similar to that formed with methyl α-D-gulopyranoside[7]. The signals for H-1, H-5, and OMe were shifted downfield, whereas that for H-2 was shifted upfield, thus indicating that complexation involved the *ax–eq–ax* sequence of O-1, O-2, and O-3.

The $J_{4,5}$ value (H-4*eq*,H-5*ax*) in the ^1H-n.m.r. spectra of the guloside derivatives is ~1 Hz, in contrast to the value of ~3.5 Hz usually observed for ^3J *ax–eq* coupling (*e.g.*, for $J_{2,3}$ and $J_{1\alpha,2}$). This is due to the antiperiplanar relationship of H-4 and the ring oxygen. A similar, small coupling-constant is observed between H-2 (eq) and H-1 (ax) in methyl β-D-mannopyranoside. It has been suggested[8] that H-1 in the α-guloside shows a long-range coupling to H-3 because of a planar W-arrangement. However, the extra splitting of the H-1 signal disappears when the signals for H-2 and H-3 are shifted away from each other, that for H-1 then becomes a clear, first-order doublet (see Fig. 1 in Ref. 7). The extra splitting of the signal for H-1 is therefore due to virtual coupling.

Oxidation of **2** or **3** with one mol of sodium metaperiodate gave the corresponding methyl α- and β-D-*gulo*-hexodialdo-1,5-pyranosides[9]. Further oxidation with bromine (1.2 mol) in the presence of strontium carbonate[10] gave methyl α- (**5**) or β-D-gulopyranosiduronic acid (**6**), isolated as their strontium salts. When a larger proportion of bromine was used, oxidation of the secondary hydroxyl groups occurred.

EXPERIMENTAL

General. – Melting points are uncorrected. Concentrations were performed at reduced pressure below 50°. T.l.c. was performed on silica gel G (Merck) with *A*, 1-butanol–pyridine–water (10:3:3); and *B*, 1-butanol–acetic acid–water (2:1:1). N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) or D_2O [internal sodium 3-(trimethylsilyl)propane-1-sulphonate] with a Jeol FX-100 instrument at 25.1 (^{13}C) and 99.8 MHz (^1H), respectively. Assignments of the ^1H-n.m.r. spectra were made after various double-resonance experiments.

Methyl D-*glycero*-α- (**3**) *and* -β-D-*guloheptopyranoside* (**2**). — A mixture of D-*glycero*-D-*gulo*-heptose[3] (2 g), methanol (100 ml), and Amberlite IR-120(H^+) resin (4 g, washed with methanol and dried) was stirred and boiled under reflux for 10 h. The heptose dissolved after 2 h and the reaction was monitored by t.l.c. (solvent *A*). After 10 h, three spots were seen at R_F 0.30, 0.39, and 0.47. The resin was collected,

and washed with methanol, and the combined filtrate and washings were concentrated. The syrupy residue (2.4 g) crystallised from ethanol, and the product (0.97 g) was purified by two further crystallisations from ethanol, to give **2**, m.p. 172°, $[\alpha]_D$ (−69° (*c* 1, water), R_F 0.39; lit.[11] m.p. 170°, $[\alpha]_D$ −74.6° (water). ^{1}H-N.m.r. data (D_2O): δ 3.52 (s, 3 H, OMe) and 4.54 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1).

The syrupy glycoside mixture remaining after crystallisation of **2** was eluted from a column (3.5 × 60 cm) of Dowex-1 X8 (HO^-) resin[5] (200–400 mesh) with CO_2-free water at 14 ml/h. Fractions (7 ml) were collected, and the separation was followed polarimetrically and by t.l.c. (solvent *A*).

Fractions 44–47, which were dextrorotatory, were combined and concentrated. The residue, R_F 0.30, was crystallised from ethanol–2-propanol, to give **3**, m.p. 105–106°, $[\alpha]_D$ +103° (*c* 1, water); lit.[11] m.p. 106–107°, $[\alpha]_D$ +111.5° (water). ^{1}H-N.m.r. data (D_2O): δ 3.39 (s, 3 H, OMe) and 4.78 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1).

Fractions 51–62 were levorotatory and contained **2**, R_F 0.39.

Fractions 73–88, which were dextrorotatory, were combined and concentrated. The residue, R_F 0.47, was crystallised from ethanol, to give methyl D-*glycero*-α-D-*gulo*-heptofuranoside[5] (**4**), m.p. 93–95°. ^{1}H-N.m.r. data (D_2O): δ 3.43 (s, 3 H, OMe) and 4.92 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-1).

Methyl α- (**5**) *and β-*D-*gulopyranosiduronic acid* (**6**). — To a solution of **2** (3 g) in water (150 ml) at 0° was added, dropwise, 0.09M sodium metaperiodate (165 ml) at <5°. The mixture was stirred for 1 h and then kept at 3° for 16 h. Barium carbonate (equivalent to the original periodate) was added and the mixture was stirred for 1 h, and then filtered, deionised with IR MB-1 resin, and concentrated. Formaldehyde was removed from the residue by repeated evaporation of ethanol therefrom, to give methyl β-D-*gulo*-hexodialdo-1,5-pyranoside (2.3 g, 88%), $[\alpha]_D$ −69° (*c* 2, water); lit.[9] $[\alpha]_D$ −71° (water).

The dialdehyde (1 g) was dissolved in water (100 ml), strontium carbonate (1.4 g) was added, and the mixture was cooled to 0°. After the addition of bromine (0.32 ml), the mixture was shaken in the dark until the bromine dissolved, and then kept in the dark at room temperature for 85 h. Excess of bromine was removed by aeration, to give a solution that was slightly reducing towards Fehling's solution. Bromine ions were removed by stirring with silver carbonate (5 g), and the mixture was filtered, passed through a column of Amberlite IR-120(H^+) resin, and concentrated, to give a syrup that contained one major component, R_F 0.24 (t.l.c., solvent *B*). An aqueous solution of the syrup was adjusted to pH 8 with 0.1M NaOH and kept thereat for 30 min to change any lactones into the sodium salts. The solution was then eluted from a column (2 × 60 cm) of Dowex-1 X8 (AcO^-) resin (200–400 mesh) with a linear gradient (0.2→2M) of acetic acid at 7 ml/h. Fractions (3.5 ml) were monitored by the phenol–sulphuric acid reagent[13] and t.l.c. (solvent *B*). The fractions (154–180) containing **6** were combined and freeze-dried. An aqueous solution of the product (0.34 g) was neutralised (to pH 6) with 0.1M NaOH and then freeze-dried, to give **6**. ^{1}H-N.m.r. data (D_2O): δ 4.60 (d, 1 H, $J_{1,2}$ 8.3, H-1) and 3.58 (s, 3 H, OMe).

Oxidation of **3**, as described above for **2**, and purification by chromatography

gave a product, R_F 0.28, which was converted into the sodium salt **5**. ^{1}H-N.m.r. data (D_2O): δ 5.16 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1) and 3.38 (s, 3 H, OMe).

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