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Note

Selective sulphation of the axial hydroxyl group in methyl 2-acetamido-6-O-acetyl-2-deoxy-α-D-galactopyranoside with sulphur trioxide-pyridine

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It is well known that HO-4 (axial in the *C1* conformation) in α-D-galactopyranose derivatives is especially difficult to esterify with sulphur trioxide–pyridine[1], benzoyl chloride–pyridine[2], and sulphonyl chloride–pyridine[3]. Secondary, axial hydroxyl groups of carbohydrates usually undergo acylation less rapidly than the equatorial isomers[2,4,5]. An exception to this rule is now reported, namely, the selective sulphation of HO-4 of methyl 2-acetamido-6-*O*-acetyl-2-deoxy-α-D-galactopyranoside (**1**) with sulphur trioxide–pyridine. In contrast, both HO-3 and HO-4 were esterified with methanesulphonyl chloride–pyridine.

Proof of the location of the sulphate at position 4 was obtained as follows: (*a*) elemental and sulphate analyses indicated a monosulphate; (*b*) a 3,4-cyclic sulphate structure was ruled out by the broad, strong i.r. absorption at ~3450 cm^{-1} attributable to a free hydroxyl group; (*c*) the i.r. absorption at 860 cm^{-1}, which is consistent with an axial sulphate group. 3-Sulphates of D-galactose show i.r. absorption at 810–832 cm^{-1} for C–O–S, in spite of the variations due to sample phases, substituents, etc.[6,7]. It is known that an axial sulphate group in the free-acid form migrates to a vicinal, equatorial OH group, and that an equatorial sulphate group does not migrate. This has been demonstrated[8] with the chondroitin sulphates and the related oligosaccharides, by storage at elevated temperature *in vacuo* over phosphorus pentoxide. Similar treatment of **3** resulted in a change of C–O–S absorption from 860 to 820 cm^{-1} as shown in Fig. 1.

The axial sulphate group at position 4 in the 2-acetamido-2-deoxy-β-D-galactopyranosyl moiety of chondroitin 4-sulphate has been established[9].

EXPERIMENTAL

N.m.r. spectra were recorded at 60 MHz, with a Varian A-60 spectrometer and tetramethylsilane as internal standard, for solutions in chloroform-*d* and sodium 4,4-dimethyl-4-silapentane-1-sulphonate for solutions in D_2O. I.r. spectra were recorded with a Shimadzu AR-6 spectrometer, and specific rotations were measured with a Yanagimoto direct-reading polarimeter. Melting points are uncorrected.

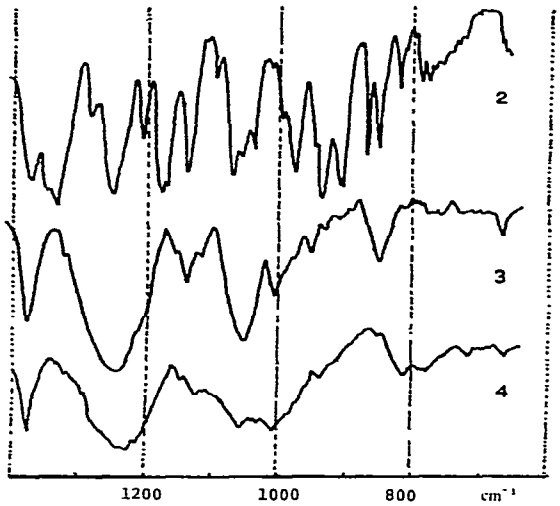

Fig. 1. I.r. spectra (KBr) of **2**, **3**, and the sulphate-migrated product (**4**) of **3**.

*Methyl 2-acetamido-6-O-acetyl-2-deoxy-α-*D*-galactopyranoside* (**1**). — Methyl 2-acetamido-6-*O*-acetyl-2-deoxy-3,4-*O*-isopropylidene-α-D-galactopyranoside[10] (7 g) was dissolved in 95% ethanol (42 ml), and 0.43% hydrochloric acid in 95% ethanol (42 ml) was added. The mixture was thoroughly shaken and kept at room temperature for 22 h. Excess of silver oxide was slowly added to the reaction mixture with vigorous shaking, and the pH was adjusted to 5.0–5.2. The mixture was immediately filtered and concentrated *in vacuo*. The resulting syrup crystallized from 95% ethanol to give **1** as needles (3.8 g, 62%), m.p. 189–190.5°, $[\alpha]_D^{26}$ +155° (*c* 1, water). I.r. data: ν_{max}^{Nujol} 3450 (OH,NH), 1750 (OAc), 1630 cm^{-1} (NAc). N.m.r. data (D_2O): δ 2.05 (*s*, 3 protons, NAc), 2.13 (*s*, 3 protons, OAc), 3.38 (*s*, 3 protons, OMe), 4.82 (*d*, 1 proton, $J_{1,2}$ 3.2 Hz, H-1).

Anal. Calc. for $C_{11}H_{19}NO_7$: C, 47.65; H, 6.91; N, 5.05. Found: C, 47.74; H, 7.01; N, 5.14.

*Methyl 2-acetamido-6-O-acetyl-2-deoxy-3,4-di-O-methanesulphonyl-α-*D*-galacto-pyranoside* (**2**). — Compound **1** (0.5 g) was allowed to react with methanesulphonyl chloride (1 ml) in dry pyridine (20 ml) at 0° for 2 days, according to the conventional procedure[11]. Recrystallization of the product from methanol gave **2** (0.5 g, 64%), m.p. 185–186°, $[\alpha]_D^{15}$ +105° (*c* 1, chloroform). I.r. data: ν_{max}^{Nujol} 3250 (NH), 1730 (OAc), 1640 (NAc), 1350 and 1180 (S=O), 870 (axial C–O–S), 850 cm^{-1} (equatorial C–O–S)[12]*. N.m.r. data (chloroform-*d*): δ 2.03 (*s*, 3 protons, NAc), 2.10 (*s*, 3 protons, OAc), 3.13 (*s*, 3 protons, SMe), 3.22 (*s*, 3 protons, SMe), 3.42 (*s*, 3 protons, OMe), 5.23 (*d*, 1 proton, $J_{1,2}$ 3.0 Hz, H-1), 5.90 (*d*, 1 proton, HN).

*The C–O–S absorptions of sulphonates lie at higher wave-numbers (by 10–40 cm^{-1}) than those of sulphates.

Anal. Calc. for $C_{13}H_{23}NO_{11}S_2$: C, 36.02; H, 5.35; N, 3.20. S, 14.40. Found: C, 36.32; H, 5.40; N, 3.37; S, 14.61.

Methyl 2-acetamido-6-O-acetyl-2-deoxy-α-D-galactopyranoside 4-sulphate (3). — Compound **1** (1 g) was dissolved in dry pyridine (30 ml), sulphur trioxide–pyridine complex[13] (1.4 g) was added, and the mixture was kept at room temperature overnight. Cold water (10 ml) was added to the reaction mixture, the pH was immediately adjusted to 7.4 with saturated, aqueous barium hydroxide, and the solution was concentrated *in vacuo* at 30°. A solution of the syrupy residue in water (50 ml) was adjusted to pH 7.0 with dilute sulphuric acid and then centrifuged, and the supernatant solution was concentrated *in vacuo*. To the syrupy residue were added ethanol (50 ml) and ether (50 ml) to give **3** (1.3 g, 67.9%), m.p. 220–221° (dec.), $[\alpha]_D^{26}$ +74° (*c* 1.0, water). I.r. data: ν_{max}^{Nujol} 3450 (OH), 3300 (NH), 1750 (OAc), 1630 (NAc), 1240 (S=O), 860 cm^{-1} (axial C–O–S). There was no absorption at ~820 cm^{-1}. N.m.r. data (D_2O): δ 2.05 (*s*, 3 protons, NAc), 2.13 (*s*, 3 protons, OAc), 3.38 (*s*, 3 protons, OMe), 4.83 (*d*, 1 proton, $J_{1,2}$ 3.2 Hz, H-1).

Anal. Calc. for $C_{11}H_{18}BaNO_{10}S \cdot 0.5H_2O$: C, 29.82; H, 4.55; N, 3.16. Found: C, 29.62; H, 4.86; N, 2.95.

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