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Preliminary communication

Synthesis of heparin saccharides. Part II[1]. Synthesis and stereochemical aspects of anomeric methyl (benzyl 2,3-di-*O*-benzyl-L-idopyranosid)uronates

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The sequence of the hexopyranosyl residues of 2-amino-2-deoxy-D-glucose and D-glucuronic[2] and L-iduronic acids[3], and the configuration of their glycosidic linkage, in the heteropolysaccharide chain of heparins of different origins[4] could not, until now, be completely established.

In order to contribute to knowledge of the anomeric configuration and the conformation of the hexopyranosyluronic residues in the heparin chain, the anomers of methyl (benzyl 2,3-di-*O*-benzyl-L-idopyranosid)uronate, and the corresponding D-gluco-pyranosiduronates, have now been synthesized as model reference-compounds.

The starting material was 3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-idofuranose* (1), m.p. 86–87°; $[\alpha]_D^{25}$ −61° (*c* 0.44, chloroform); it was prepared by treatment of 3-*O*-benzyl-1,2-*O*-isopropylidene-5,6-di-*O*-*p*-tolylsulfonyl-α-D-glucofuranose[5] with anhydrous potassium acetate in acetic anhydride, followed by deacetylation, and removal of the isopropylidene protecting group by treatment with aqueous acetic acid. A facile, intramolecular condensation occurred during this solvolytic process, and 1,6-anhydro-3-*O*-benzyl-β-L-idopyranose (3) [m.p. 155–156°; $[\alpha]_D^{25}$ +67.3° (*c* 0.21, ethyl acetate)] was obtained.

In order to avoid formation of the anhydro sugar 3, the hydroxyl group on C-6 of 1 was protected with a *p*-nitrobenzoyl group, giving 2; m.p. 93–94°; $[\alpha]_D^{25}$ −52.5° (*c* 0.68, chloroform).

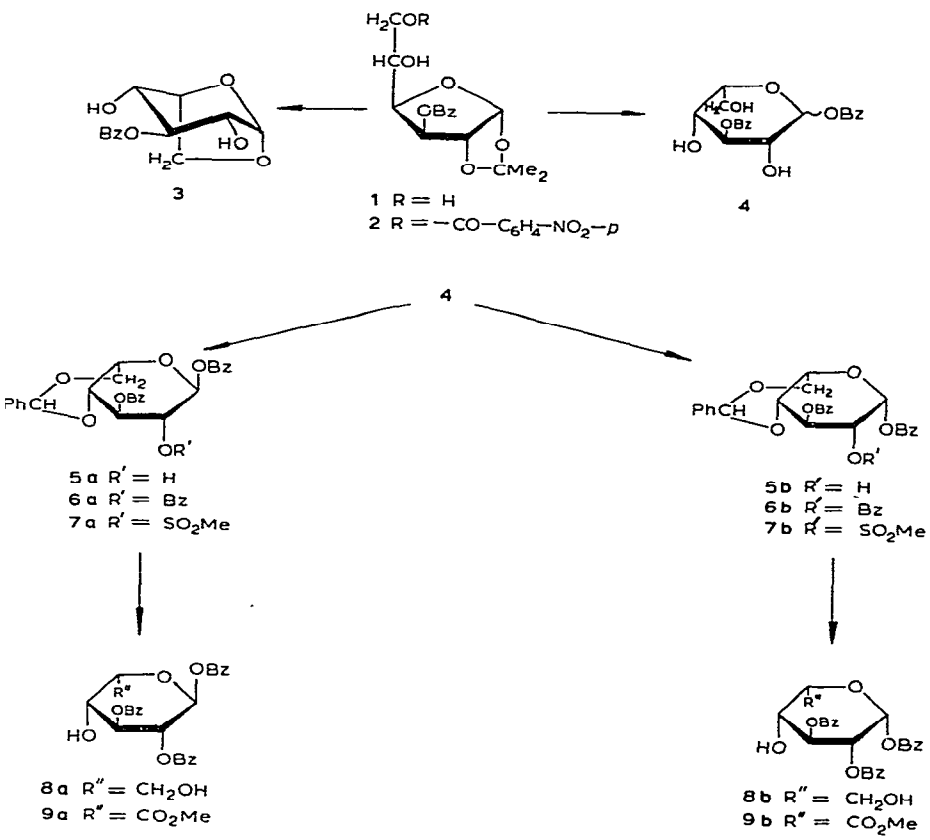
The acetal grouping was removed from 2 by acid hydrolysis, and the product was treated with benzyl alcohol containing hydrogen chloride; then the *p*-nitrobenzoyl protecting group was removed, and the benzyl glycosides (4) were converted into their 4,6-benzylidene acetals (5). The anomeric mixture 5 was resolved by column chromatography on silica gel, to give 5a, m.p. 109°, $[\alpha]_D^{25}$ −91.2° (*c* 0.16, chloroform); and 5b, m.p. 151°, $[\alpha]_D^{25}$ +72.2° (*c* 0.70, chloroform).

*Satisfactory microanalytical data were obtained for all new compounds.

Reaction of the 2-hydroxyl group of compounds **5a** and **5b** with benzyl chloride–potassium hydroxide gave the corresponding benzyl ethers: **6a**, m.p. 145–146°, $[\alpha]_D^{25}$ −80.2° (*c* 0.2, chloroform); and **6b**, syrup, $[\alpha]_D^{25}$ +47.2° (*c* 0.39, chloroform). Removal of the benzylidene protecting groups with aqueous acetic acid at 100° then afforded the anomeric benzyl 2,3-di-*O*-benzyl-L-idopyranosides, **8a** [m.p. 71–72°; $[\alpha]_D^{25}$ −58.7° (*c* 0.74, chloroform)] and **8b** [amorphous; $[\alpha]_D^{25}$ +91.8° (*c* 0.58, chloroform)].

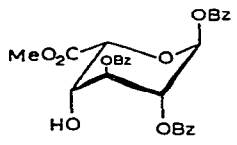
Compounds **8a** and **8b** were oxidized with oxygen in aqueous *p*-dioxane in the presence of platinum catalyst[6] (15–20 h, at pH 7.5–8.1), and the resulting uronic acids[7] were esterified with diazomethane. The α-L anomer (**9a**) had m.p. 65–66°, $[\alpha]_D^{25}$ −29.5° (*c* 0.72, chloroform); n.m.r. data (benzene-d_6): δ 5.15 (broad s, H-1, $J_{1,2} \approx J_{1,3}$ 0.5–1.5 Hz), 4.95 (d, H-5, $J_{4,5}$ 1.6 Hz), ~4.25 (overlapped signal, H-4), 3.81 (ddd, H-3, $J_{1,3}$ 0.5–1.5 Hz; $J_{2,3} \approx J_{3,4}$ ~3.3 Hz), 3.65 (d, C-4-OH, $J_{OH,4}$ 11.6 Hz), and 3.57 p.p.m. (ddd, H-2, $J_{1,2}$ 0.5–1.5 Hz; $J_{2,3}$ ~3.3 Hz; $J_{2,4}$ <1.0 Hz). The β-L anomer (**9b**) was amorphous, and had $[\alpha]_D^{25}$ +113.6° (*c* 0.12, chloroform); n.m.r. data (benzene-d_6): δ 4.87 (d, H-1, $J_{1,2}$ 1.2 Hz), ~4.55 (overlapped signal, H-5), ~4.2 (overlapped signal, H-4), 3.83 (dd, H-3, $J_{2,3} \approx J_{3,4}$ ~3.5 Hz), and 3.58 p.p.m. (ddd, H-2, $J_{1,2}$ 1.2 Hz; $J_{2,3}$ ~3.5 Hz; $J_{2,4} \leqslant 1.0$ Hz).

Proton magnetic resonance data indicated that, in solution, the L-idopyranosiduronates **9a** and **9b** adopt the *1C* (L) conformation almost exclusively[8]. In this

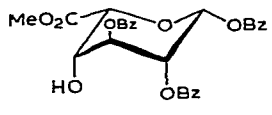


conformation, the (large) benzyloxy groups are axially, whereas the 5-alkoxycarbonyl groups are equatorially, oriented[9].

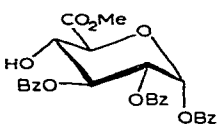
For comparative studies, the corresponding, anomeric methyl (benzyl 2,3-di-*O*-benzyl-D-glucopyranosid)uronates **10a** and **10b** were also synthesized, by a route previously described[10]. The α-D anomer (**10a**) had m.p. 56–57°; $[\alpha]_D^{25}$ +68.1° (*c* 0.21, chloroform); n.m.r. data (benzene-d_6); δ 4.94 (d, H-1, $J_{1,2}$ 3.5 Hz), 4.46 (d, H-5, $J_{4,5}$ 9.0 Hz), 3.95–



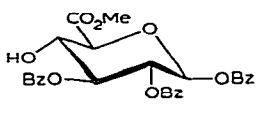
9a



9b



10a



10b

4.17 (H-3 and H-4), and 3.50 p.p.m. (m, H-2, $J_{1,2} + J_{2,3}$ 13.0 Hz). The β-D anomer (**10b**) had m.p. 82–83°, $[\alpha]_D^{25}$ −46.3° (*c* 0.22, chloroform); n.m.r. data (benzene-d_6): δ 4.37 (d, H-1, $J_{1,2}$ 7.5 Hz), 4.02 (dd, H-4, $J_{3,4}$ ~8.0 Hz; $J_{4,5}$ 9.6 Hz), 3.69 (d, H-5, $J_{4,5}$ 9.6 Hz), 3.57 (dd, H-2 or H-3, $J_{2,3}$ ~9.0 Hz), 3.49 (dd, H-2 or H-3), and 2.73 p.p.m. (d, C-4-OH, $J_{OH,4}$ ~3.0 Hz).

The magnitude of the coupling constants supports the *trans*-diaxial arrangement of the ring protons H-2 to H-5, and is consistent with the formulation of the α-D (**10a**) and β-D (**10b**) anomers in the *C1* (D) conformation. In this spatial arrangement, the (large) benzyloxy groups on C-2 and C-3, as well as the 5-alkoxycarbonyl groups, are equatorially oriented.

The effect of sulfonylation on molecular rotation has been reported to be insignificant[11]. The 2-*O*-(methylsulfonyl) derivatives **7a** [m.p. 123–124°; $[\alpha]_D^{25}$ −94.5° (*c* 0.46, chloroform)] and **7b** [syrup; $[\alpha]_D^{25}$ +26.9° (*c* 0.44, chloroform)] were synthesized in order to examine the effect of the methylsulfonyl group on the molecular rotation. The results clearly showed that this group causes a negative shift in the molecular rotation, the β-L anomer showing a significantly larger shift (**7b**: M_D +14,166; **5b**: M_D +31,371) than the α-L anomer (**7a**: M_D −49,764; **5a**: M_D −39,626).

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