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Note

Crystalline glycosyl halides derived from 4-*O*-methyl-D-glucuronic acid*

PAVOL KOVÁČ AND RADOSLAV PALOVČÍK
Institute of Chemistry, Slovak Academy of Sciences, 809 33 Bratislava (Czechoslovakia)
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4-*O*-Methyl-D-glucuronic acid is a constituent of numerous aldobiouronic acids isolated from depolymerization products of plant polysaccharides: it is quite abundant in (4-*O*-methylglucurono)xylans, the main hemicellulose component of hardwoods[2]. Although partial hydrolysis (acidic or enzymic) of certain polysaccharides gives the 4-*O*-methyl-D-glucuronic acid–aldose-type aldobiouronic acids, their preparation by this approach requires tedious separation by chromatography and the substances are rarely obtained in an appreciable quantity. Chemical synthesis of these aldobiouronic acids requires glycosyl halides derived from 4-*O*-methyl-D-glucuronic acid. Only one compound of this class, namely, syrupy methyl 2,3-di-*O*-acetyl-1-bromo-1-deoxy-4-*O*-methyl-α-D-glucopyranuronate, is known in the literature[3]. We now describe the conversion of crystalline methyl 1,2,3-tri-*O*-acetyl-4-*O*-methyl-β-D-glucopyranuronate[4] (**1**) into two crystalline glycosyl halides that are potential intermediates in the synthesis of 4-*O*-methyl-D-glucuronic acid-containing oligosaccharides.

It has previously been shown[5] that, when treated with dihalogenomethyl methyl ethers in the presence of a catalytic amount of boron trifluoride etherate, 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronate gives the corresponding β-halides in a stereospecific reaction. When **1** was treated in this way with dichloromethyl methyl ether, an excellent yield of crystalline β-chloride **2** was obtained. The p.m.r. spectrum of the crude **2** showed that the conversion was complete (absence of the starting acetate **1**) and confirmed the stereospecificity of the reaction [absence of the downfield doublet of H-1 (α-D) at δ 6.24 (Table I)]. The crystalline α-glycosyl chloride **3** was obtained in a very good yield by treatment of **1** (or an anomeric mixture of 1-acetates) with dichloromethyl methyl ether in the presence of a catalytic amount of zinc chloride. The same compound, albeit in a somewhat lower yield, was obtained by using anhydrous aluminium chloride in absolute chloroform as the reagent[6].

Crystalline α-glycosyl halides **5** and **6** were obtained from **4** by treatment with dichloromethyl methyl ether in the presence of zinc chloride and hydrogen bromide in

*Synthesis and Reactions of Uronic Acid Derivatives: Part XIV. For Part XIII, see Ref. 1.

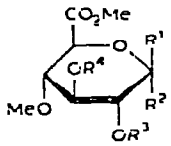
TABLE I

P.M.R. DATA[a] FOR 2-6

Compound	Chemical shifts[b] (δ)									Coupling constants (Hz)			
	H-1	H-2	H-3	H-4	H-5	OMe	OAc		Aromatic	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
2	5.41d	4.88——5.30m		3.81t	4.10d	3.45; 3.85	2.10	2.08	— —	~7.5	[c]	~9.0	9.7
3	6.24d	4.94q	5.54t	3.66t	4.48d	3.43; 3.83	2.11	2.08	— —	3.8	10.0	8.8	10.3
4	6.82d	5.57q	6.06t	4.08t	4.54d	3.48; 3.87	—	—	7.75——8.60m	3.5	10.0	9.0	9.6
5	6.44d	5.39q	6.02t	3.98t	4.64d	3.45; 3.88	—	—	8.0——8.30m	3.8	10.0	9.0	9.7
6	6.74d	5.24q	6.03t	4.01t	4.62d	3.45; 3.88	—	—	8.0——8.30m	3.8	10.1	9.2	9.8

[a]Deuteriochloroform; sweep width, 100 Hz. [b]Observed multiplicities: d, doublet; t, triplet; q, quartet; m, multiplet. [c]First-order coupling constants were not observed.

glacial acetic acid, respectively. The hitherto unknown *p*-nitrobenzoate **4** is readily obtainable by standard *p*-nitrobenzoylation of the known[7], crystalline methyl 4-*O*-methyl-D-glucopyranuronate.



NBz = *p*-nitrobenzoyl

	R^1	R^2	R^3	R^4
1	OAc	H	Ac	Ac
2	Cl	H	Ac	Ac
3	H	Cl	Ac	Ac
4	H	ONBz	NBz	NBz
5	H	Cl	NBz	NBz
6	H	Br	NBz	NBz

EXPERIMENTAL

M.p.s. were determined on a Kofler hot-stage. Optical rotations were measured with a Perkin–Elmer automatic polarimeter Model 141. P.m.r. spectra for solutions in chloroform-*d* were recorded at 80 MHz (internal Me_4Si) with a Tesla BS-487-B spectrometer. Proton-signal assignments were made by the INDOR technique. T.l.c. was performed on Silica gel G with *A*, benzene–methyl acetate (6:1); and *B*, carbon tetrachloride–acetone (10:1). Detection was effected by charring with 5% sulfuric acid in ethanol. Solutions were dried with anhydrous sodium sulfate and concentrated at 2 kPa (15 Torr) and 40°.

*Methyl 2,3-di-*O*-acetyl-1-chloro-1-deoxy-4-*O*-methyl-β-*D*-glucopyranuronate* (**2**). — Boron trifluoride etherate (0.02 ml) was added to a solution of **1** (1 g) in dichloromethyl methyl ether (3 ml), and the solution was kept at 40° for 1 h with the exclusion of moisture. T.l.c. (solvent *A*) then showed that no starting material remained. The solution was concentrated, and a solution of the residue in ether was treated with a little charcoal, filtered, and concentrated. P.m.r. spectrum of the crude product did not contain a doublet at δ 6.24 (Table I), showing that α-halide **3** was not formed. Crystallization from ether gave **2** (770 mg, 82.6%), m.p. 117–119° (sintering at 104°), $[\alpha]_D^{22}$ −42° (*c* 1.07, chloroform). One recrystallization from the same solvent gave material having m.p. 117.5–119.5°, $[\alpha]_D^{22}$ −44° (*c* 0.8, chloroform); no change in m.p. or $[\alpha]_D$ was observed on repeated recrystallization (Found: C, 44.44; H, 5.30; Cl, 11.24. $C_{12}H_{17}ClO_8$ calc.: C, 44.38; H, 5.28; Cl, 10.92%).

*Methyl 2,3-di-*O*-acetyl-1-chloro-1-deoxy-4-*O*-methyl-α-*D*-glucopyranuronate* (**3**). — (*a*) A catalytic amount of freshly fused zinc chloride was added to a solution of the β-1-acetate **1** (or an αβ-mixture[4]) (1 g) in dichloromethyl methyl ether (4 ml). The mixture was stirred with the exclusion of moisture at 65–70° (bath) until t.l.c. (solvent *A*) showed that the reaction was complete (1.5–2 h), and was then concentrated. A solution of the residue in chloroform was washed with cold, aqueous sodium hydrogen carbonate and water, dried, and concentrated. The crude product in ether was decolorized with a little charcoal, and crystallisation from isopropyl ether then gave **3** (0.8 g, 86%), m.p. 63–65°. Recrystallization of a portion from the same solvent gave the analytical sample having m.p. 64–65°, $[\alpha]_D^{22}$ +160° (*c* 0.76, chloroform) (Found: C, 44.30; H, 5.13; Cl, 11.10%).

(*b*) Anhydrous aluminium chloride (0.4 g) was added to a solution of **1** (or an $\alpha\beta$-mixture) (1 g) in dry, alcohol-free chloroform (20 ml), and the mixture was stirred under reflux with the exclusion of moisture for 20 h. The orange solution was washed with ice–water (2 × 10 ml), dried, and concentrated, and a solution of the residue in ether was treated with a little charcoal. The colourless solution was concentrated, and the residue was crystallised from isopropyl ether (with seeding) to give **3** (600 mg, 73%) which was identical with the material obtained in (*a*).

*Methyl 4-*O*-methyl-1,2,3-tri-*O*-p-nitrobenzoyl-α-*D*-glucopyranuronate* (**4**). — *p*-Nitrobenzoyl chloride (7.5 g, 40.4 mmol) was added to a solution of methyl 4-*O*-methyl-D-glucopyranuronate[7] (2 g, 9 mmol) in dry pyridine (50 ml), and the reaction mixture was kept at 30–40° for 2 h. T.l.c. then showed that the reaction was complete, and the product (R_F 0.8, solvent *A*), after isolation in the usual manner, was crystallized from methyl acetate. A second crop of the same material (total yield, 4.7 g, 78%; m.p. 196–198°) was obtained from the concentrated mother liquor. A portion was recrystallized from the same solvent to give the analytical sample of **4**, m.p. 197.5–199.5°, $[\alpha]_D^{22}$ +285° (*c* 1.06, chloroform) (Found: C, 52.08; H, 3.58; N, 6.06. $C_{29}H_{23}N_3O_{16}$ calc.: C, 52.02; H, 3.46; N, 6.26%).

*Methyl 1-chloro-1-deoxy-4-*O*-methyl-2,3-di-*O*-p-nitrobenzoyl-α-*D*-gluco-pyranuronate* (**5**). — The *p*-nitrobenzoate **4** (1 g, a foam obtained on concentration of a solution of crystalline **4** in chloroform) was dissolved in dichloromethyl methyl ether (4 ml) containing a catalytic amount of freshly fused zinc chloride, and the mixture was stirred with the exclusion of moisture at 75–80° (bath) for 4 h. More chloro-ether (2 ml) was then added to the thick syrup which still contained (t.l.c.) ~30% of the starting material (R_F 0.2, solvent *B*), together with **5** (R_F 0.3). After an additional 3 h at 80°, when only traces of **4** could be detected, the mixture was worked up as described in the preparation of **3** (*b*), and a solution of the crude product in acetone was decolorized with charcoal. Addition of ether to the filtrate gave 660 mg (82%) of chromatographically homogeneous, crystalline chloride **5**, m.p. 165–168°. Recrystallization from the same solvent mixture gave the analytical sample having m.p. 167–168°, $[\alpha]_D^{22}$ +194° (*c* 0.92, chloroform) (Found, C, 49.04; H, 3.57; N, 5.17. $C_{22}H_{19}ClN_2O_{12}$ calc.: C, 49.03; H, 3.55; N, 5.20%).

*Methyl 1-bromo-1-deoxy-4-*O*-methyl-2,3-di-*O*-p-nitrobenzoyl-α-*D*-gluco-pyranuronate* (**6**). — A suspension of **4** (1 g) in 35% hydrogen bromide in glacial acetic acid (10 ml) was stirred with the exclusion of atmospheric moisture at 45–50° (bath). The starting material slowly dissolved, and *p*-nitrobenzoic acid started to separate after 30 min. After a total period of 1.5 h, when t.l.c. (solvent *B*) showed that only traces of the starting material remained, the mixture was diluted with chloroform (20 ml), the solution was washed with ice–water, cold aqueous sodium hydrogen carbonate, and cold water, dried, and concentrated. A solution of the residue in benzene–heptane (2:1) was filtered through a layer (2 × 0.5 cm) of silica gel wetted with the same solvent mixture. The filtrate was combined with the benzene–heptane (2:1) washings and concentrated to give chromatographically homogeneous bromide **6** (0.7 g, 80%) which, when crystallized from benzene–ether (twice), had m.p. 174–175°,

$[\alpha]_D^{22}$ +198° (*c* 1, chloroform) (Found: C, 45.30; H, 3.43; N, 4.77; Br, 13.85. $C_{22}H_{19}BrN_2O_{12}$ calc.: C, 45.30; H, 3.28; N, 4.80; Br, 13.70%).

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