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GLUCURONIC ESTERS

PART V*. SYNTHESIS AND PROPERTIES OF BENZYL 2,3,4-TRI-*O*-BENZYL-1-CHLORO-1-DEOXY-β-D-GLUCOPYRANURONATE

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ABSTRACT

By the action of thionyl chloride on benzyl 2,3,4-tri-*O*-benzyl-D-glucopyranuronate at 0°, a crystalline benzyl 2,3,4-tri-*O*-benzyl-1-chloro-1-deoxy-D-glucopyranuronate was obtained. On the basis of its chemical behavior, the β-D configuration has been established for this compound. The n.m.r. spectra of the glucuronic acid halides are described and discussed.

INTRODUCTION

In Part III[1] of this series, benzyl 2,3,4-tri-*O*-benzyl-1-bromo-1-deoxy-α-D-glucopyranuronate (**1a**) and benzyl 2,3,4-tri-*O*-benzyl-1-chloro-1-deoxy-α-D-glucopyranuronate (**1b**) were described as intermediates in the synthetic pathway to the fully benzylated derivative of D-glucuronic acid having the C-1 hydroxyl group unblocked. Both halides, prepared from the corresponding 1-*O*-acetyl derivative, were obtained as oils showing positive rotation in chloroform; the α-D configuration of compound **1a** was established by its conversion into benzyl 1-*O*-acyl-2,3,4-tri-*O*-benzyl-β-D-glucopyranuronates[2]. Because of the rather low yields of compound **1b**, other methods leading to 1-chloro compounds were also investigated. In this paper, the synthesis and characteristics of crystalline benzyl 2,3,4-tri-*O*-benzyl-1-chloro-1-deoxy-β-D-glucopyranuronate (**2**) are presented.

RESULTS AND DISCUSSION

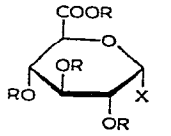
Glaudemans and Fletcher[3] obtained 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride of nearly pure α-configuration by the action of hydrogen chloride in dichloromethane on an anomeric mixture of the corresponding 1-*O*-*p*-nitrobenzoyl derivative. The same treatment applied to benzyl 2,3,4-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-α-D-glucopyranuronate[2] failed; even after a six-day reaction period neither *p*-nitrobenzoic acid nor compound **1b** could be detected, and, from the reaction mixture, 67% of the starting ester was recovered. When the same ester was treated with

*Part IV: D. Keglević, N. Pravdić, and J. Tomašić, *J. Chem. Soc.* (*C*), (1968) 511.

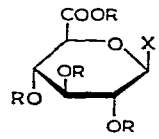
hydrogen chloride in acetic acid, a rapid formation of *p*-nitrobenzoic acid, followed by slow appearance of the chloro derivative, was observed. It was found that, in this case, the reaction proceeded through transesterification, affording benzyl 1-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranuronate[1], which was then subsequently converted into the chloro compound **1b**.

When benzyl 2,3,4-tri-*O*-benzyl-D-glucopyranuronate[1] was treated with thionyl chloride at 0°, following essentially the procedure of Baddiley and his collaborators[4], a crystalline product of high purity was obtained. It showed negative rotation in chloroform, and the elemental analysis corresponded to the fully benzylated compound, benzyl 2,3,4-tri-*O*-benzyl-1-chloro-1-deoxy-β-D-glucopyranuronate (**2**). Apparently, this is the first crystalline example of this class of compound.

The chloride **2** proved to be surprisingly stable; its physical constants have not changed after storage in a stoppered vial at room temperature for one year. Treatment of compound **2** with benzyl alcohol gave benzyl tetra-*O*-benzyl-α-D-glucopyranuronate (**3**) having $[\alpha]_D$ +35°, whereas the same reaction performed with the bromide **1a** resulted in the formation of the β-D anomer **4** showing $[\alpha]_D$ −33°.



1a X = Br
1b X = Cl
3 X = OCH_2Ph
5 X = $OCOC_6H_4$–OMe(*p*)



2 X = Cl
4 X = OCH_2Ph

R = CH_2Ph

At room temperature, a suspension of compound **2** and the silver salt of *p*-methoxybenzoic acid in benzene gave, after five days, 38% of benzyl 2,3,4-tri-*O*-benzyl-1-*O*-*p*-methoxybenzoyl-α-D-glucopyranuronate[2] (**5**); under identical conditions, the dextrorotatory chloride **1b** remained unchanged. On the other hand, at reflux temperature with silver *p*-methoxybenzoate, compound **2** yielded an almost equimolar mixture of anomeric *p*-methoxybenzoyl derivatives, whereas compound **1b** gave a mixture enriched with the β-D anomer. As expected, in the presence of silver perchlorate, the configuration of the 1-*O*-*p*-methoxybenzoyl derivative did not greatly depend on the initial configuration of the chloride; with each halide, an anomeric mixture, enriched in the α-D anomer **5**, was obtained.

Hence, in comparison with compound **1b**, the crystalline chloride **2** proved to be more reactive, thus representing a convenient intermediate in the synthesis of 1-*O*-acyl-α-D-glucopyranuronates.

The n.m.r. spectra of the benzylated halides **2**, **1a**, and **1b** could not be analyzed readily, due to the presence of benzyl groups. We then turned our attention to the acetylated halides and compared the spectra of the anomeric pair of 1-chloro derivatives [**6** (Ref. 5) and **7**]. Heyns *et al.*[6] recorded the n.m.r. spectra of methyl 2,3,4-tri-*O*-acetyl-1-bromo-1-deoxy-α-D-glucopyranuronate and its β-D anomer, and established the *C1* conformation for the α-D anomer. The spectrum of methyl 2,3,4-tri-*O*-acetyl-

1-chloro-1-deoxy-α-D-glucopyranuronate (**6**) proved to be considerably simpler than the spectra of the corresponding aldopyranosyl halides[7]; due to the lack of C-6 protons, the signal for H-5 appears as a doublet. The splitting patterns and magnitudes of the coupling constants[8,9] in the spectrum fully support the *trans*-diaxial arrangement of the ring protons and are consistent with the formulation of the α-D anomer **6** in the *C1* conformation. In the spectrum of the β-D anomer **7***, the ring protons are observed as four-proton and one-proton multiplets with narrow spacings. If this compound had been in the *C1* conformation, the H-1 signal would have been a wide doublet (1,2-diaxial coupling) and the other part of the spectrum would have been similar to that of the α-D anomer. It seems plausible that, in this case, conformational inversion has occurred, and that compound **7** in chloroform-*d* adopts the *1C* conformation. This conformation is supported by the fact that the signals for the methoxy and all acetoxy groups are observed at lower field than in the spectrum of the α-D anomer **6**, indicative[8] of axial orientation. On the other hand, steric repulsion of axial groups may cause some flattening of the ring, and the existence of this compound in a flexible form cannot be excluded. Moreover, the large coupling of the one-proton multiplet at τ 5.72–5.88, which probably arises from H-5 ($J_{4,5}$ 9.6 Hz), makes the possibility of a conformation in the flexible cycle even more probable[7].

Although the spectra of the fully benzylated halides **1a**, **1b**, and **2** are not very informative, the small coupling ($J_{1,2}$ 3.9 and 3.6 Hz) of the doublets at τ 3.81 and 3.99 in the spectrum of the α-D anomers **1a** and **1b**, respectively, denote the equatorial–axial orientation, thus providing an indication of the α-D configuration[13]. On the other hand, in the spectrum of the β-D-chloro derivative **2**, no signal has been found in the region from τ 3.0–4.4. Since, in the spectra of all of the α-D anomers described, the signal for H-1 appears as a narrow doublet in the region 3.35–3.99, the nonexistence of such a signal in the spectrum of compounds **2** and **7**, as well as in that of methyl 2,3,4-tri-*O*-acetyl-1-bromo-1-deoxy-β-D-glucopyranuronate[6], suggests the β-D configuration for compound **2**.

There is not enough evidence to assign the *1C* conformation to compound **2**, although this assumption would be consistent with the published n.m.r. data for various aldopyranosyl halides[12,14,15]. Horton *et al.*[12] have pointed out that the favored conformation of the acetylated aldopyranosyl halides in chloroform solution is that chair form in which the halogen atom is axial, *i.e.*, the *1C* conformation for the β-D anomers.

On the basis of the findings presented in this paper, the β-D configuration has been established for the chloro derivative **2**. Baddiley and his collaborators first used thionyl chloride in the synthesis of 1-chloro derivatives bearing nonparticipating groups in the molecule; from tetra-*O*-benzyl-α-D-glucose[4] or -galactose[16], they obtained the α-D anomer of the corresponding chloride. Since, for benzyl 2,3,4-tri-*O*-benzyl-D-glucopyranuronate, the β-D configuration, or at least a strong predominance

*This compound, prepared already by Heyns *et al.*[6], was obtained also by the action of thionyl chloride on methyl 2,3,4-tri-*O*-acetyl-D-glucopyranuronate[10], as well as from methyl tetra-*O*-acetyl-β-D-glucopyranuronate[11] by treatment with aluminum chloride[12].

of this configuration was proposed[1], it would follow that the reaction with thionyl chloride proceeds without isomerization at the anomeric carbon atom.

EXPERIMENTAL

Melting points are uncorrected. Specific rotations were measured in chloroform (*ca.* 1% at 20–23°). Thin-layer chromatography was conducted on Silica Gel G (Merck), components being detected by spraying with 10% sulfuric acid and heating at 100°. Column chromatography was conducted on silica gel (0.2–0.5 mm, Merck). The i.r. spectra were recorded for Nujol mulls on a Perkin–Elmer Model 137 instrument. The n.m.r. spectra were obtained for chloroform-*d* solutions with a Varian A-60A spectrometer, and tetramethylsilane as an internal standard.

*Treatment of benzyl 2,3,4-tri-*O*-benzyl-1-*O*-p-nitrobenzoyl-α-*D*-glucopyranuronate with acetic acid–dry hydrogen chloride.* — The title ester[2] (250 mg) was added to an acid solution (5 ml, 2.6 g of dry hydrogen chloride per 100 ml of acetic acid); the reaction was monitored by t.l.c. in ether–light petroleum (1:2). After storage for 6 days at room temperature, chloroform was added, and the reaction mixture was processed in the standard way. The remaining oil was chromatographed on a silica-gel column (15 g) with ether–light petroleum (1:2). The solvent displaced 25% of the chloride **1b**, showing $[\alpha]_D$ +28°, followed by benzyl 1-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranuronate[1] (35%), $[\alpha]_D$ +22°. Further elution with chloroform and ethanol gave benzyl 2,3,4-tri-*O*-benzyl-D-glucopyranuronate[1] (10%) and *p*-nitrobenzoic acid (60%).

*Benzyl 2,3,4-tri-*O*-benzyl-1-chloro-1-deoxy-β-D-glucopyranuronate* (**2**). — Benzyl 2,3,4-tri-*O*-benzyl-D-glucopyranuronate[1] (554 mg) was dissolved in freshly distilled thionyl chloride (5 ml), and the solution was kept for 48 h at 0° and then concentrated *in vacuo*. Residual traces of the reagent were removed by codistillation with toluene, and the crude oily residue, on storage in a vacuum desiccator over sodium hydroxide, started to crystallize. Recrystallization from light petroleum–ether gave compound **2** as fine needles (380 mg, 66%), m.p. 85–86°, $[\alpha]_D$ −6°.

Anal. Calc. for $C_{34}H_{33}ClO_6$: C, 71.26; H, 5.80; Cl, 6.19. Found: C, 71.04; H, 5.79; Cl, 5.98.

*Benzyl tetra-*O*-benzyl-α-D-glucopyranuronate* (**3**). — A solution of compound **2** (120 mg) in absolute benzene (5 ml) and benzyl alcohol (1 ml) was stirred with freshly prepared silver carbonate (120 mg) for 6 h at room temperature in the dark. T.l.c. (ether–light petroleum, 1:2) of the reaction mixture then showed the absence of compound **2**. The precipitate was filtered off and washed with benzene. The filtrate and washings were combined, the solvent was evaporated, and benzyl alcohol was distilled off *in vacuo*. The residual oil was chromatographed on a column of silica gel (25 g) with ether–light petroleum (1:2). The product was isolated as a colorless oil (88 mg, 66%), $[\alpha]_D$ +35°.

Anal. Calc. for $C_{41}H_{40}O_7$: C, 76.38; H, 6.25. Found: C, 76.11; H, 6.31.

*Benzyl tetra-*O*-benzyl-β-D-glucopyranuronate* (**4**). — Benzyl 2,3,4-tri-*O*-benzyl-1-bromo-1-deoxy-α-D-glucopyranuronate[1] (**1a**, 230 mg) was treated in the same way

as described for the preparation of compound **3**, except that the reaction mixture was shaken overnight. After the removal of the silver salts, the solvent and benzyl alcohol were distilled off, and the residual oil was crystallized from methanol. Recrystallization from the same solvent gave 118 mg (49%) of compound **4**, m.p. 93–94°, $[\alpha]_D$ −33°.

Anal. Calc. for $C_{41}H_{40}O_7$: C, 76.38; H. 6.25. Found: C, 76.65; H, 6.47.

T.l.c. of compound **4** in several solvent systems showed a slightly higher mobility than that for compound **3**.

Reactions of compound **2** *with silver* p-*methoxybenzoate.* — (*a*) *Without heating.* A suspension of compound **2** (100 mg) and silver *p*-methoxybenzoate (50 mg) in absolute benzene (8 ml) was stirred in the dark for 5 days at room temperature. Examination of the reaction mixture (t.l.c., benzene–ether, 15:1) revealed a trace of product after one day; after 5 days, compound **2** was still present. The insoluble salts were filtered off, and washed with benzene, and the filtrates were concentrated *in vacuo* leaving a crystalline residue. Recrystallization from ethanol gave benzyl 2,3,4-tri-*O*-benzyl-1-*O*-*p*-methoxybenzoyl-α-D-glucopyranuronate[2] (**5**) as needles (45 mg, 38%), m.p. and mixed m.p. 110–111°, $[\alpha]_D$ +29°. The i.r. spectrum was superimposable on that of the compound prepared earlier[2].

(*b*) *Under reflux.* The mixture described above was heated under reflux for 30 h. The product (58%) was obtained as the mixture of anomers, m.p. 89–93°, $[\alpha]_D$ +3°.

In a similar preparation, the α-chloro derivative **1b** was refluxed for 10 h; the resulting mixture of anomers (28%) showed m.p. 88–98°, $[\alpha]_D$ −11°.

(*c*) *With silver perchlorate.* To a solution of compound **2** (285 mg) in chloroform (10 ml), silver *p*-methoxybenzoate (140 mg) and silver perchlorate (30 mg) were added, and the mixture was refluxed for 5 h. Benzyl 2,3,4-tri-*O*-benzyl-1-*O*-*p*-methoxybenzoyl-D-glucopyranuronate (164 mg, 48%) showed m.p. 93–109°, $[\alpha]_D$ +22°.

In a similar preparation with compound **1b**, the product had m.p. 92–105°, $[\alpha]_D$ +15°.

*Methyl 2,3,4-tri-*O*-acetyl-1-chloro-1-deoxy-β-*D*-glucopyranuronate* (**7**). — (*a*) Methyl 2,3,4-tri-*O*-acetyl-D-glucopyranuronate[10] (0.8 g) was treated with freshly distilled thionyl chloride (10 ml) as described in the preparation of compound **2**. The crystalline residue, after removal of the reagent, was triturated with absolute ether. The product (520 mg, 62%) showed m.p. 142–144°, $[\alpha]_D$ −20°; Heyns *et al.*[6] gave m.p. 151–152°, $[\alpha]_D$ −15.8°.

Anal. Calc. for $C_{13}H_{17}ClO_9$: C, 44.27; H, 4.86; Cl, 10.05. Found: C, 44.01; H, 4.88; Cl, 10.32.

(*b*) A solution of methyl tetra-*O*-acetyl-β-D-glucopyranuronate[11] (2.0 g) in absolute chloroform (20 ml) was shaken with crushed aluminium chloride[12] (5 g) for 18 h at room temperature. The mixture was poured onto ice–water and worked up by the standard procedure; the colorless syrup spontaneously crystallized (1.4 g, 75%). The optical rotation, m.p., and i.r. spectrum were identical with those of compound 7 prepared as in (*a*).

N.m.r. data. (*a*) *Methyl 2,3,4-tri-*O*-acetyl-1-chloro-1-deoxy-α-*D*-glucopyranuronate* (**6**). — Signals at τ 3.70 (doublet, $J_{1,2}$ 4.0 Hz, H-1), 4.43 (triplet, $J_{2,3}=J_{3,4}$ 9.5 Hz, H-3), 4.82 (quartet, $J_{3,4}$ 9.5, $J_{4,5}$ 9.8 Hz, H-4), 5.02 (quartet, $J_{1,2}$ 4.0, $J_{2,3}$ 9.5 Hz, H-2), 5.46 (doublet, $J_{4,5}$ 9.8 Hz, H-5), 6.32 (OCH_3, 3 protons), 7.97 and 8.00 (OAc, 9 protons).

(*b*) *Methyl 2,3,4-tri-*O*-acetyl-1-chloro-1-deoxy-β-*D*-glucopyranuronate* (**7**). — Signals in the regions τ 4.48–4.94 (4-proton multiplet), 5.72–5.88 (1-proton multiplet), singlet at τ 6.22 (OCH_3, 3 protons), 7.91 and 7.96 (OAc, 9 protons).

(*c*) *Benzyl 2,3,4-tri-*O*-benzyl-1-bromo-1-deoxy-α-*D*-glucopyranuronate* (**1a**). — Signals at τ 2.81–2.96 (aromatic protons), 3.81 (doublet, $J_{1,2}$ 3.9 Hz, H-1), and 5.0–6.8 (methylene and ring protons).

(*d*) *Benzyl 2,3,4-tri-*O*-benzyl-1-chloro-1-deoxy-α-*D*-glucopyranuronate* (**1b**). — Signals at τ 2.70–2.85 (aromatic protons), 3.99 (doublet, $J_{1,2}$ 3.6 Hz, H-1), and in the region 4.9–6.3 (methylene and ring protons).

(*e*) *Benzyl 2,3,4-tri-*O*-benzyl-1-chloro-1-deoxy-β-*D*-glucopyranuronate* (**2**). — Signals in the region τ 2.7–2.9 (aromatic protons), and 4.7–6.6 (methylene and ring protons).

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