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Note

Reinvestigation of the preparation of cholesteryl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside

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Among the recent syntheses of α-D-glucosides[1–6], the method of Ferrier *et al.*[7] seemed recommended by its simplicity. An example given was the preparation of cholesteryl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (**1**). These workers[7] prepared the required intermediate, phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**2**), by a method that involved heating the mixture. After their report had been submitted for publication, another worker in their laboratory[7] discovered that heating was unnecessary, as the reaction is exothermic. His procedure, which omitted external heating, gave a product having different constants, which essentially agreed, however, with those of the product (**2**) previously reported by Pfäffli *et al.*[8]. Our product (**2**), prepared by either procedure, proved to be identical ($[\alpha]_D$, m.p. and mixed m.p.) with that of the latter workers[8]. Ferrier *et al.*[7] appear to have used exclusively in all their experiments a product having different constants, which gave impure **1** and impure cholestanyl α-D-glucopyranoside.

All attempts to prepare **1** by the method of Ferrier *et al.*[7] failed*. According to the procedure of these workers, a mixture of **2**, cholesterol, and mercuric sulfate is stirred and boiled in anhydrous oxolane for 3 h under reflux. Under these conditions, no reaction was observed by the present investigator. Addition of a small amount of sulfuric acid to the mixture boiling under reflux appeared to initiate reaction, but a substantial amount of **2** remained after 3 h. However, in the presence of a catalytic amount of anhydrous perchloric acid generated *in situ*, the reaction proceeded to completion in 3 h at room temperature. Use of anhydrous mercuric benzoate instead of mercuric sulfate halved the reaction time. The product was readily purified, but the yield of pure **1** was about half that reported by Ferrier *et al.*[7]. Perchlorate ion was ineffective as a catalyst in neutral or basic medium.

Note added in proof.* — Since this paper was submitted, R. J. Ferrier has reported, *via* personal communication, that P. C. Tyler in his laboratory has achieved success with this method only when "freshly powdered" mercuric sulfate was used, his results then being comparable to those described herein. Thus Tyler obtained **1 having m.p. 139–141°, $[\alpha]_D$ +46° (*c* 1.3, chloroform), yield 28%.

Oxolane hydroperoxide (3) in the refluxing mixture of Ferrier *et al.* appeared to promote the reaction; but, unfortunately, it led in fact to the production of 2,3,4,6-tetra-*O*-benzyl-D-glucose (**4**), as did an attempt to prepare **1** by reaction of **2**, cholesterol, and mercuric oxide (yellow) in the presence of boron trifluoride etherate in diglyme. The latter reaction, as well as the thermal degradation[9] of **3** in the former reaction, led to the production of water, with which **2** evidently underwent preferential reaction.

Catalytic hydrogenation of **1** gave the known[10] cholestanyl α-D-glucopyranoside (**5**), the α-glycosidic linkage of which was verified by n.m.r. spectroscopy.

EXPERIMENTAL

General methods. — Anhydrous oxolane was prepared by storing the stabilized, peroxide-free solvent over calcium hydride under subdued light. The mercuric sulfate[11] and anhydrous mercuric benzoate[12] were prepared. All reactions were monitored by t.l.c., with plates precoated with silica gel (0.25 mm thick)*. Benzene was the irrigating solvent. The developed plates were viewed under u.v. light. Reactions were deemed complete when t.l.c. examination showed the disappearance of **2** along with the formation of the maximum amount of (phenylthio)mercurithioxide[13]. The palladium–charcoal catalyst was prepared essentially according to the method of Mozingo[14]. All evaporations were performed *in vacuo* (water pump). Melting points are uncorrected. N.m.r. spectra were recorded at 100 MHz with a Varian HA-100 spectrometer, with tetramethylsilane as internal standard.

Phenyl 1-thio-β-D-glucopyranoside (**6**). — Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside[15] (60 g), deacetylated by the Zemplén method, gave **6**; yield 34 g (86%), m.p. 133–134°, $[\alpha]_D^{20}$ −61° (*c* 1, ethanol), −69.7° (*c* 2, water) (lit.[15] $[\alpha]_D$ −70.5° in water).

*Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside* (**2**). — To a solution of **6** (20 g) in dry *N,N*-dimethylformamide (250 mL) was added sodium hydride (7 g) with stirring. When evolution of hydrogen had mostly subsided, benzyl bromide (44 ml) was added and the mixture, which became hot from the exothermic reaction, was stirred for 1 h. The mixture was then cooled and poured over cracked ice (600 mL), and ethanol (400 mL) was added with stirring. Crystallization occurred on overnight refrigeration. After two recrystallizations from ethanol, the product (yield 20.9 g, 45%) had m.p. and mixed m.p. 94°, $[\alpha]_D^{20}$ +0.8° (*c* 5, chloroform). [lit.[8], m.p. 93.5–94.5°, $[\alpha]_D^{25}$ +0.65° (chloroform)].

*Cholesteryl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside* (**1**). — (*a*) *Mercuric sulfate method.* To a solution of **2** (0.51 g) and cholesterol (0.34 g) in anhydrous oxolane (10 mL) were added mercuric sulfate (0.15 g), anhydrous magnesium per-

*E. M. Laboratories, 500 Exec. Blvd., Elmsford, New York 10523. Mention of firm names or trade products does not imply that they are endorsed or recommended by the U.S. Department of Agriculture over other firms or similar products not mentioned.

chlorate ("Anhydrone" supplied by J. T. Baker Chemical Co., Phillipsburg, N.J.) (0.75 g), and concentrated sulfuric acid (0.01 mL). The mixture was stirred vigorously for 3 h at room temperature; t.l.c. examination then indicated complete reaction. The mixture was diluted with chloroform and filtered, and the filtrate was shaken with water and then saturated with hydrogen sulfide. The resulting mixture was shaken twice with 5% sodium hydroxide, twice with water, dried, and evaporated. The residue (semi-crystalline) was crystallized from ethanol and then from acetone–water (10:1, v/v) to give **1**; yield 0.18 g (25%), m.p. 143–144°, $[\alpha]_D^{20}$ +48° (*c* 1, chloroform). [Ferrier *et al.*[7] gave m.p. 127–128°, $[\alpha]_D$ +40° (*c* 1, chloroform) for **1**.]

Anal. Calc. for $C_{61}H_{80}O_6$: C, 80.6; H, 8.9. Found: C, 80.5; H, 9.2.

(*b*) *Mercuric benzoate method.* To a solution of **2** (0.51 g) and cholesterol (0.34 g) in anhydrous oxolane (10 mL) were added anhydrous mercuric benzoate (0.25 g), anhydrous magnesium perchlorate ("Anhydrone") (0.078 g), and concentrated sulfuric acid (0.01 mL). The mixture was stirred vigorously for 1.5 h at room temperature, whereupon reaction was complete. The mixture was then processed as before to give **1**; yield 0.14 g (19%), m.p. and mixed m.p. (with preceding preparation) 143°.

Attempt to prepare **1** *via a water-producing reaction.* — To a solution of **2** (1 g) and cholesterol (0.68 g) in anhydrous diglyme (20 mL) containing peroxide (spontaneously generated) were added mercuric oxide (yellow) (0.5 g), barium carbonate (5 g), and boron trifluoride etherate (1 mL). The mixture was stirred vigorously for 2 h at 55° (bath), whereupon t.l.c. revealed the reaction to be complete. The mixture was then diluted with chloroform and filtered. The filtrate was shaken with saturated sodium hydrogencarbonate, and evaporated to a syrup that was dissolved in heptane. The heptane solution was shaken several times with water, evaporated to dryness, and the residue was dissolved in chloroform. The chloroform solution was saturated with hydrogen sulfide, shaken twice with 5% sodium hydroxide and twice with water, and evaporated to dryness. The resulting, crystalline residue was recrystallized from methanol to give **4** (0.32 g), m.p. and mixed m.p. 152–153°, $[\alpha]_D^{20}$ +20° (*c* 2, chloroform).

Anal. Calc. for $C_{34}H_{36}O_6$: C, 75.5; H, 6.7. Found: C, 75.4; H, 6.8.

From the foregoing product was prepared[16] the known 2,3,4,6-tetra-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-α-D-glucopyranose (**6**), m.p. and mixed m.p. 127°.

Anal. Calc. for $C_{41}H_{39}NO_9$: C, 71.4; H, 5.7; N, 2.0. Found: C, 71.4; H, 5.9; N, 2.3.

Cholestanyl α-D-glucopyranoside (**5**). — To a solution of **1** (0.51 g) in anhydrous oxolane (50 mL) was added freshly prepared palladium–charcoal catalyst (9%, 3.2 g). The mixture was hydrogenated for 2 h at room temperature and at 40–60 $lb.in^{-2}$ with shaking, and filtered; the catalyst was washed with oxolane, and the filtrate was evaporated to dryness. The residue was crystallized from ethanol, and after recrystallization from the same solvent gave **5** (0.12 g), m.p. 218–219°, $[\alpha]_D^{20}$ +94.6° (*c* 1.1, pyridine) [lit.[10] $[\alpha]_D^{26.7}$ +94° (*c* 1.267, pyridine)], n.m.r. (pyridine-d_5): δ 6.41 (one-proton doublet, J 4 Hz, H-1). Ferrier *et al.*[7] gave $[\alpha]_D^{20}$ +73° (*c* 1,

methanol) and +82° (*c* 1, pyridine) for **5**. The $[\alpha]_D^{20}$ value in methanol could not be determined at 1% concentration, because **5** was not sufficiently soluble. The product (**5**) apparently crystallized with 0.5 mol of ethanol. The ethanol could not be removed by heating at 100° *in vacuo* or by recrystallization from benzene.

Anal. Calc. for $C_{33}H_{58}O_6 \cdot 0.5C_2H_5OH$: C, 71.2; H, 10.7. Found: C, 71.4; H, 10.6.

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