Carbohydrate Research, 77 (1979) 252–254

Note

Synthesis of 4-O-β-D-glucopyranosyl derivatives of phenolic acids of natural occurrence in plants*

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(Received March 8th, 1979; accepted for publication, March 16th, 1979)

Recently, there has been interest in the natural plant polyphenols as possible causes of the bitter and/or astringent character of seed- and leaf-protein meals. Syntheses of some of these naturally occurring glucosides for sensory evaluation tests were therefore required. We now describe an improved Koenigs–Knorr method that gives greatly improved yields compared to those of other methods[1–4]. Condensation[5] of hydroxyphenolic acids with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in the presence of silver salts could yield glucosyloxy acids, 1-*O*-acylglucoses, and 1-*O*-(glucosyloxyacyl)glucoses. These side reactions and the general alkalilability of the condensation product accounts for the low yields reported[4] in the synthesis of 4-*O*-β-D-glucopyranosylprotocatechuic acid.

Esterification of the phenolic carboxyl group followed by condensation with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide under conditions similar to those described by Kent and Brunet[4], but replacing pyridine by quinoline, gave the 4-*O*-(tetra-*O*-acetyl-β-D-glucopyranosyl)-vanillic and -*p*-coumaric esters in greatly improved yields (47.9 and 17.0%, respectively). Deacetylation then yielded the 4-*O*-β-D-glucopyranosyl-vanillic and -*p*-coumaric methyl esters, which were saponified to give the corresponding 4-β-D-glucopyranosides. The highly negative $[\alpha]_D$ values and susceptibility to β-D-glucosidase confirmed the β-D configuration.

EXPERIMENTAL

General methods. — The organic phase of 1-butanol–acetic acid–water was used for p.c. with detection by aniline hydrogen phthalate. Reactions were monitored by t.l.c. on Silica Gel G, with detection by charring with sulphuric acid. Melting points are corrected. Optical rotations were measured on a Perkin–Elmer 141 polarimeter. Solvents were evaporated at 35°.

4-O-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)vanillic acid methyl ester (**1**). —

*Contribution No. 403 from the Food Research Institute.

A solution of vanillic acid methyl ester (11 g, m.p. 60–62°) in dry pyridine (25 ml) was stirred with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (22 g) and dry silver oxide (20 g) at room temperature, in the dark, and under anhydrous conditions for 3 h. The insoluble silver salts were collected, and washed with pyridine, and the combined filtrate and washings were concentrated to half volume and poured into a mixture of ice and water. The dark-brown solid was collected and washed with cold water, and a solution in chloroform (1 L) was dried (Na_2SO_4) and concentrated. A solution of the residue (18.8 g) in methanol was decolorised with charcoal (Norit A) and concentrated to dryness, and the residue was crystallised from ethanol to give **1** as fine needles (14.8 g, 47.9%), m.p. 143–144°, $[\alpha]_D^{26}$ −34° (*c* 1, chloroform).

Anal. Calc. for $C_{23}H_{28}O_{13}$: C, 53.90; H, 5.51. Found: C, 53.78; H, 5.15.

4-O-β-D-Glucopyranosylvanillic acid methyl ester (**2**). — A solution of **1** (11 g) in methanol (200 ml) was treated with 0.2M sodium methoxide (4 ml). The solution was cooled to room temperature for 5–6 h and then stored at 5° overnight. Removal of methanol and addition of water yielded a solid that was crystallised from hot water to give **2** (6.84 g, 92.5%), m.p. 170–171°, $[\alpha]_D^{25}$ −71° (*c* 0.7, methanol).

Anal. Calc. for $C_{15}H_{20}O_9$: C, 52.32; H, 5.81. Found: C, 51.81; H, 5.98.

4-O-β-D-Glucopyranosylvanillic acid (**3**). — To a solution of **2** in hot water (200 ml) was added M sodium hydroxide (20 ml). The solution was stored at room temperature for 24 h with occasional shaking and then deionised with Rexyn-101(H^+) resin, and methanol (70 ml) was added to dissolve the glucoside. The mixture was filtered and concentrated, and the residue was crystallised from hot water to yield **3** as the monohydrate (5.08 g, 80.5%), m.p. 207–208°, $[\alpha]_D^{20}$ −71° (*c* 0.7, methanol).

Anal. Calc. for $C_{14}H_{18}O_9 \cdot H_2O$: C, 48.28; H, 5.74. Found: C, 48.41; H, 5.71.

4-O-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-p-coumaric acid methyl ester (**4**). — 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (23 g), *p*-coumaric acid methyl ester (10 g, m.p. 139–140°), and dry silver oxide (20 g) in dry pyridine (20 ml) were reacted as described above. Repeated extraction of the tarry product with ethanol–isopropyl ether (1 :9, 2 L), removal of the isopropyl ether, and decolorisation with charcoal gave a solid that was crystallised twice from ethanol to give **4** (4.8 g, 17%), m.p. 164–165°, $[\alpha]_D^{32}$ −19° (*c* 1.45, chloroform).

Anal. Calc. for $C_{24}H_{28}O_{12}$: C, 56.69; H, 5.51. Found: C, 56.36; H, 5.39.

4-O-β-D-Glucopyranosyl-p-coumaric acid methyl ester (**5**). — Using the method described above for **2**, **4** was converted into **5**, m.p. 165–166°, $[\alpha]_D^{20}$ −65° (*c* 0.7, methanol).

Anal. Calc. for $C_{16}H_{20}O_8$: C, 56.47; H, 5.88. Found: C, 56.38; H, 5.88.

4-O-β-D-Glucopyranosyl-p-coumaric acid (**6**). — De-esterification of **5**, as described for **3**, gave **6** (2.25 g, 75.5%), m.p. 197–199° (from water), $[\alpha]_D^{20}$ −73° (*c* 0.3, methanol).

Anal. Calc. for $C_{15}H_{18}O_8$: C, 55.21; H, 5.52. Found: C, 54.98; H, 5.54.

Hydrolyses with β-D-glucosidase. — Solutions of **2**, **3**, **5**, or **6** (2 mg) and yeast β-D-glucosidase (2 mg) in water (0.5 ml) were incubated at 37°. P.c. revealed the formation of glucose in each experiment.

ACKNOWLEDGMENTS

The authors thank Dr. A. Paquet for valuable discussion and Mr. P. Thivierge for technical assistance. Analyses were performed by Mr. G. Morris, Analytical Chemistry Research Service, Canada Department of Agriculture.

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