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Note

A practical synthesis of 6-*O*-methyl-D-glucose

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A continuing interest at this laboratory in the Maillard reaction has recently focused on the preparation of Amadori compounds from glucoses having labeled mono-*O*-methyl substitution. Such compounds could be of value in studies of the Maillard reaction or in the formation of reductones and their transformations[1]. As the pyranoid ring appears to be the favored cyclic form[1] of Amadori compounds, it was of interest to prepare Amadori compounds having an *O*-methyl group at C-6, thus limiting cyclization to the furanoid form. Such compounds, especially with a labeled methyl ether group, might afford useful insights into the Maillard reaction.

The adequate supply of 6-*O*-methyl-D-glucose (**1**) required was not available commercially nor did existing methods for its preparation provide a crystalline product in suitable amounts[2–5a,b,c]. However, a modification of the method of Bell[6] furnished adequate amounts of crystalline **1** in excellent yield.

1,2-*O*-Isopropylidene-α-D-glucofuranose (**2**), which is available commercially or by the large-scale method of Mehltretter *et al.*[7,8], reacted with *p*-nitrobenzoyl chloride (1.1 mol) in pyridine at low temperature to give the 6-*p*-nitrobenzoate **3** in ~50% yield. Its structure was established by elemental analysis and n.m.r. spectroscopy. Acetalation of **3** with benzaldehyde–zinc chloride gave the 3,5-benzylidene acetal **4**, which on saponification with barium hydroxide–methanol gives the known 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-α-D-glucofuranose[9] (**5**). Methylation of **5** with methyl iodide–silver oxide in *N,N*-dimethylformamide (DMF) gives the known 6-*O*-methyl derivative[6] (**6**), which on deacetalation with trifluoroacetic acid[10] gives **1**. The identity of **1** was confirmed by elemental analysis, n.m.r. spectroscopy, m.p., and specific rotation (equil.). It was characterized as its phenylosazone **7** and 1,2,3,4-tetra-*p*-nitrobenzoate **8**. For the practical synthesis of **1**, the readily prepared **3** is a convenient starting compound. In a typical run without isolation of intermediates, **3** (10 g) gave crystalline, analytically pure **1** (3.5 g, 66%).

As a practical method of preparing **1**, we believe our procedure has distinct advantages over the method of Bell[6]. The key intermediate for Bell's preparation ,

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which started with D-glucose, was 1,2-*O*-isopropylidene-α-D-glucofuranose 6-acetate, obtained in poor yield (25%) by a laborious procedure. In contrast, our key intermediate **3** may be easily obtained directly from readily available **2** in 50% yield. In the deacetalation step, we found that Bell's method employing sulfuric acid gave a 50% yield of **1**, whereas our procedure using trifluoroacetic acid was nearly quantitative. Finally, our practical synthesis of **1** avoids tedious isolation of intermediates, thereby making possible not only simplification of procedure but an improved overall yield of **1**. An added advantage of our procedure is that it can be readily adapted for preparing **1** containing a labeled methyl ether group, a consideration important for the preparation of labeled Amadori compounds.

EXPERIMENTAL

General methods. — Evaporations were performed under diminished pressure (water aspirator). Melting points are uncorrected. The benzaldehyde was freshly distilled, the pyridine was redistilled and anhydrous, and the silver oxide was freshly prepared. The petroleum ether had b.p. 35–60°. The zinc chloride was fused and ground under heptane immediately before use. The t.l.c. plates [5 × 20 cm, "Precoated TLC Plates, Silica Gel 60 F-254," E. Merck, Darmstadt, Germany; 2309 Highland Ave., Cincinnati, OH 45212 (U.S.A.)]* fluoresced under u.v. light of appropriate wavelength and were especially effective for locating substances that absorbed in the u.v. Other substances were located by spraying with 5% sulfuric acid and heating for 15 min at 130–140°. Sensitivity of detection was greatly enhanced by subsequent viewing under u.v. light of appropriate wavelength. The silica gel column and its preconditioning before use have been previously described[11]. ^{1}H- and ^{13}C-n.m.r. spectra were recorded with a Bruker WH-90 spectrometer with tetramethylsilane (^{1}H-n.m.r.) and 1,4-dioxane (^{13}C-n.m.r.) as internal standards.

*1,2-O-Isopropylidene-α-D-glucofuranose 6-*p*-nitrobenzoate* (**3**). — To a solution of **2** (5 g) in pyridine (50 mL) cooled to 0–5° (ice bath) was added *p*-nitrobenzoyl chloride (4.5 g, 1.1 mol). The mixture was stirred until solution was complete, refrigerated (0–5°) for 2 days, and poured into saturated sodium hydrogencarbonate (500 mL). After 2 h, the mixture was extracted with chloroform, and the extract steam-distilled (100°) to remove all chloroform and pyridine. The resulting suspension, after cooling, was reextracted with chloroform; the extract was evaporated to give a solid cake that was digested (steam bath) with hot heptane (250 mL). After 20–30 min, the hot extract was decanted, and the remaining solid crystallized from benzene (~1600 mL) to give **3** [4.28 g (2 crops), 51%]; m.p. 167°, $[\alpha]_D^{20}$ +9.5° (*c* 2, ethyl acetate); ^{1}H-n.m.r. (acetone-d_6): δ 8.34 (4 H, phenyl), 5.90 (d, 1 H, *J* 3.6 Hz, H-1), 4.1–4.7 (6 H), 1.43 (3 H, CH_3), and 1.28 (3 H, CH_3); ^{13}C-n.m.r.: δ 165.4 (aromatic C=O), 151.7 (C-4'), 136.8 (C-1'), 131.7 (C-2',6'),

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124.4 (C-3′,5′), 112.0 (Me_2CO_2), 106.1 (C-1), 86.3 (C-2), 81.3 (C-4), 75.2 (C-3), 69.0 (C-5), 67.7 (C-6), 27.2 (CH_3), and 26.6 (CH_3).

Anal. Calc. for $C_{16}H_{19}NO_9$: C, 52.0; H, 5.2; N, 3.8. Found: C, 52.2; H, 5.3; N, 3.6. Enlarging the scale of the reaction resulted in lower percentage yields of **3**.

3,5-O-Benzylidene-1,2-O-isopropylidene-α-D-glucofuranose 6-p-nitrobenzoate (**4**). — To a solution of **3** (1 g) in benzaldehyde (50 mL) was added zinc chloride (5 g). The mixture was stirred for 4 h and then poured into chloroform (250 mL). The resulting solution was shaken twice with ice-cold water (250 mL) and once with saturated sodium hydrogencarbonate (300 mL), and then steam-distilled (100°) in the presence of barium carbonate (5 g) until all chloroform and benzaldehyde had been removed. After cooling, the mixture was shaken with chloroform and filtered. The chloroform layer of the filtrate was separated and evaporated, and the residue extracted with hot heptane (250 mL). Examination of the extract by t.l.c. [5:1 (v/v) petroleum ether–acetone] revealed a preponderant zone and three minor zones. This principal product was purified by passage through the silica gel column using the aforementioned solvent. Combination of the appropriate fractions and evaporation to dryness gave a residue that was crystallized from heptane to give **4** (0.73 g); m.p. 130°, $[\alpha]_D^{20}$ +23.5° (*c* 2, ethyl acetate).

Anal. Calc. for $C_{23}H_{23}NO_9$: C, 60.4; H, 5.1; N, 3.1. Found: C, 60.6; H, 5.3; N, 2.9.

3,5-O-Benzylidene-1,2-O-isopropylidene-α-D-glucofuranose (**5**). — To a solution of **4** (0.99 g) in anhydrous methanol (200 mL) was added anhydrous methanol (50 mL) in which a small piece of sodium metal had been dissolved. After 15 min, t.l.c. [3:2 (v/v) petroleum ether–ethyl acetate] revealed deacylation of **4** to be complete. The mixture was carbonated with an excess of Dry Ice, evaporated to dryness, and shaken with 1:1 (v/v) chloroform–water. The separated chloroform layer was evaporated to dryness and the residue, dissolved in the petroleum ether–ethyl acetate solvent, was passed through the silica gel column and developed with the same solvent. Combination of the appropriate fractions and evaporation gave a residue which, crystallized from 1:5 (v/v) ethyl acetate–heptane, gave **5** (0.58 g); m.p. 151–152° [lit.: 148.5–150° (ref. 12), 149° (ref. 13), 149–150° (ref. 14)], $[\alpha]_D^{20}$ +23.9° (*c* 2.2, chloroform) (lit.[13]; +22.4°).

Anal. Calc. for $C_{16}H_{20}O_6$: C, 62.3; H, 6.5. Found: C, 62.2; H, 6.6.

3,5-O-Benzylidene-1,2-O-isopropylidene-6-O-methyl-α-D-glucofuranose (**6**). — To a mixture of DMF (10 mL) and methyl iodide (10 mL) was added **5** (0.36 g). To the vigorously stirred mixture was added silver oxide (3 g). Vigorous stirring was continued for 17 h, whereupon the mixture was diluted with chloroform and filtered. Examination of the filtrate by t.l.c. [5:1 (v/v) petroleum ether–acetone] revealed methylation to be complete. Evaporation gave a residue that was dissolved in the petroleum ether–acetone solvent and passed through the silica gel column, development being with the same solvent. Combination of the appropriate fractions, followed by evaporation to dryness and crystallization of the residue from hot water, gave **6** (0.16 g, 3 crops); m.p. 94–95°. The product had a specific rotation too small to determine. [lit.: m.p. 95–96°; $[\alpha]_D^{20}$ +3.8° (chloroform)][6].

Practical synthesis of **1**. — To a solution of **3** (10 g) in benzaldehyde (150 mL) was added zinc chloride (15 g). The mixture was stirred for 4 h and poured into chloroform (1 L). The resulting solution was washed with ice-cold water (2 × 250 mL), with saturated sodium hydrogencarbonate (250 mL), and with water (250 mL). Subsequent steam-distillation (100°) of the solution in the presence of barium carbonate (5 g) removed the chloroform and excess benzaldehyde, giving an aqueous suspension that on cooling was shaken with chloroform. The resulting mixture was filtered, and the chloroform layer of the filtrate evaporated to a syrup that was digested (steam bath) with hot heptane (4 × 250 mL, 10 min each). Each extract was decanted from undissolved residue, and the combined extracts were evaporated to a syrup.

To the syrup was added a saturated solution of barium hydroxide octahydrate in methanol (400 mL). After 3 days, the solution was saturated with carbon dioxide and evaporated to dryness. The solid residue was extracted with hot ethyl acetate and the extract filtered. Evaporation of the filtrate gave a residue that was extracted with boiling benzene (~700 mL). The extract was filtered hot and evaporated.

The solid residue was dissolved in a mixture of DMF (75 mL) and methyl iodide (20 mL). To the solution was added silver oxide (35 g), and the mixture was vigorously stirred (20 h). It was then diluted with chloroform and filtered, and the separated silver compounds were washed with more chloroform. The filtrate was shaken with water and evaporated to low volume. Water (20 mL) was added and distillation (bath $\ngtr$55°) was resumed to give a syrupy residue. After two more distillations (200 mL each) with water, a DMF-free residue resulted. Residual moisture was removed by evaporating abs. ethanol from the residue. The solid residue was dissolved in heptane (500 mL), and the solution was filtered and evaporated to a crystalline residue.

The residue was dissolved in 9:1 (v/v) trifluoroacetic acid–water (80 mL). The darkening solution was kept for 1 h at ambient temperature and then evaporated (bath, 40–50°) to a syrup. Benzaldehyde and most residual trifluoroacetic acid were removed by distilling water (2 × 200 mL) from the syrup. The final residue was dissolved in 0.1M sulfuric acid (250 mL). The solution was kept for 16–20 h at ambient temperature, made neutral with an excess of barium carbonate, and the mixture filtered. The filtrate was agitated with an excess of Dowex 50 (H^+) cation-exchange resin until barium ions were absent. It was then filtered and evaporated to dryness, residual moisture being removed by evaporating abs. ethanol from the residue. The solvent-free residue was boiled under reflux with 9:1 (v/v) ethyl acetate–abs. ethanol (700 mL) for ~40 min, whereupon all solids dissolved. The hot solution was rapidly filtered. On cooling, seeding, and standing for several h, the filtrate deposited crystalline **1**, m.p. 148–149°. From the mother liquor was obtained two additional crops that, on recrystallization from the foregoing solvent, had the same m.p. [lit.: m.p. 153–154° (ref. 15), 144–145° (ref. 12), 145° (ref. 6), 140° (ref. 3), 142–143° (ref. 4), 143–144° (ref. 5)] and $[\alpha]_D^{20}$ (equil.) + 55° (*c* 2, water) [lit.: $[\alpha]_D^{20}$ (equil.) + 59.9° (H_2O, ref. 16), +55° (H_2O, ref. 6), +58.5° (ref.

15), +61 ±3° (H_2O, ref. 3), +56° (H_2O, ref. 4), +61° (*c* 1.0, water, ref. 5)], total yield (3 crops), 3.49 g (66%); ^{1}H-n.m.r. (CD_3OD): δ 5.11 (1 H, d, *J* 3.6 Hz, H-1α), 4.48 (1 H, d, *J* 7.8 Hz, H-1β), and 3.38 (3 H, s, OCH_3); in Me_2SO-d_6: δ 4.94 (1 H, d, *J* 3.1 Hz, H-1α), 4.31 (1 H, *J* 7.1 Hz, H-1β), and 3.26 (3 H, OCH_3); ^{13}C-n.m.r. (D_2O): δ 96.8 (C-1β), 92.9 (C-1α), 76.6 (C-3β), 75.3 (C-5β), 74.9 (C-2β), 73.6 (C-3α), 72.3 (C-2α), 72.0 (C-6α,β), 70.6–70.7 (C-4α,β and C-5α), and 59.4 (6-OCH_3-α,β). Similar shifts have been reported by Usui *et al.*[17] for **1**.

Anal. Calc. for $C_7H_{14}O_6$: C, 43.3; H, 7.3. Found: C, 43.3; H, 7.3.

*6-O-Methyl-*D-arabino-*hexose phenylosazone* (**7**). — To a solution of **1** (0.25 g) in water (5 mL) was added acetic acid (0.3 mL, 4 mol) and phenylhydrazine (0.5 mL, 4 mol). The mixture was heated (steam bath) for 1.5 h, when it became completely solid. On cooling, triturating with water, filtering, and washing with water, the solid yellow product (**7**), three times crystallized from 60% ethanol, had m.p. 185°. [lit.: m.p. 183° (ref. 15), 180° (ref. 16), 184–187°, 177° (ref. 18), 190° (ref. 6), 186–187° (ref. 12)].

Anal. Calc. for $C_{19}H_{24}N_4O_4$: C, 61.3; H, 6.5; N, 15.1. Found: C, 61.7; H, 6.6; N, 15.3.

*6-O-Methyl-*D-*glucose 1,2,3,4-tetra-*p-*nitrobenzoate* (**8**). — To a solution of **1** (0.2 g) in pyridine (10 mL) was added *p*-nitrobenzoyl chloride (1.15 g). The mixture was heated for 1 h at 85–90° (bath) and then cooled and poured into saturated sodium hydrogencarbonate (300 mL). A solid precipitate immediately separated. After 2–3 h, the mixture was extracted with chloroform, and the extract was washed with water and then evaporated with water to remove chloroform and pyridine. Residual moisture was removed by distilling abs. ethanol from the residue. The resulting solid, after two crystallizations from ethyl acetate–heptane, gave **8** (0.45 g); m.p. 211°, $[\alpha]_D^{20}$ +129.6° (*c* 2, chloroform).

Anal. Calc. for $C_{35}H_{26}N_4O_{18}$: C, 53.2; H, 3.3; N, 7.1. Found: C, 52.9; H, 3.3; N, 6.8.

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