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Note

Synthesis of 3-*O*-(2-iodoethyl)-D-glucose, a stable iodo derivative of D-glucose for medical imaging

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2-Deoxy-2-fluoro-D-glucose is an almost ideal tracer for D-glucose transport and metabolic uptake, with the limitation however that the cyclotron-produced positron-emitter ^{18}F isotope has a short half-life and, consequently, the use of ^{18}F-labelled glucose derivatives for medical imaging is necessarily heavily restricted. Consequently, there has been a general search for D-glucose analogues in which iodine isotope gamma-emitters would be the detector group. Unfortunately, the corresponding iodo analogue of 2-deoxy-2-fluoro-D-glucose, namely 2-deoxy-2-iodo-D-glucose, is notably unstable[1–3]. Other simple iodo derivatives of D-glucose, of variable stability, have been prepared[2,4–7].

Our current approach to suitable iodinated D-glucose tracers aims at the compounds in which the supplementary iodine-bearing group, while being stable enough, would be as small as possible so as to minimize unfavorable interactions with the D-glucose transporter[8,9]. The known stability[10–13] of β-iodoethers prompted us to incorporate this unit into a D-glucose skeleton. This approach has already resulted in the preparation of 2-iodoethyl β-D-glucopyranoside[14], a close analogue of propyl β-D-glucopyranoside, but which does not compete with D-glucose for entry into the cell[15]. Since 3-*O*-propyl-D-glucose is known to compete with the natural substrate for its passive transport[16], the preparation of the corresponding 2-iodoether **1** became the target of choice.

For the synthesis of 3-*O*-(2-iodoethyl)-D-glucose (**1**), literature methods for the direct introduction[17–23] of a β-iodoether cannot be applied. Among other approaches tried, it is noteworthy that reaction of the silyl or sulfonyl derivatives of 2-iodoethanol gave only products resulting from an attack of the oxyanion derived

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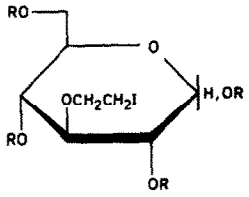
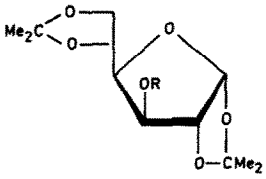


1 R = H
5 R = Ac



2 R = H
3 R = CH_2CH_2OH
4 R = CH_2CH_2I

from **2** at the silicon or sulfur atom. However, upon condensation[24] of **2** with ethyl bromoacetate, followed by reduction[25], a suitable precursor **3** was conveniently obtained. This 2-step preparation results in a higher yield of **3** (83% from **2**) than other literature preparations[26–28]. Conversion of the alcohol group to the iodide could then efficiently be accomplished with freshly prepared triiodoimidazole in the presence of triphenylphosphine[29], giving **4** in 88% yield. The incorporation of iodine was readily evidenced by the characteristic 2.6 ppm resonance of the iodine-bearing methylene group in the ^{13}C NMR spectrum. Mild-acid deprotection of both acetals then smoothly gave **1**, which was also characterized as its acetate **5**.

The stability of **1** was assayed under different conditions; it resisted both alkaline or acidic media, while being fully stable at room temperature and remained largely unchanged after having been heated overnight at 80°C in molar hydrochloric acid or in the presence of a strong base (1,8-diazabicyclo[5.4.0]undec-7-ene). Furthermore, it resisted hydrogenolysis (10% Pd–C). Most importantly, **1** was stable during the conditions generally used for the introduction of radiolabelled iodine[30].

Preliminary results obtained with ^{123}I-labelled **1** showed improved transport properties into human erythrocytes and slower wash-out when compared with other iodinated analogues; however, the incorporation by rat cardiomyocytes was negligeable. Given the stability of the 2-iodoethyl subunit, it is nevertheless anticipated that its incorporation into other carriers could result in a suitable tracer for nuclear medicine-related studies.

EXPERIMENTAL

General methods.—Toluene, CH_2Cl_2, and pyridine were dried on 4A molecular sieves and diethyl ether was distilled over Na just before use. After work-up, the volatiles were evaporated under reduced pressure without heating. Standard abreviations are used for NMR description of spectra which were recorded on Brucker apparatus using built-in software, at the field and in the solvent indicated for each compound. The residual absorption of the NMR solvent was taken as the internal reference, except for ^{13}C NMR spectra in water. Standard abreviations are used with m for multiplet and M for unresolved multiplet. IR spectra were recorded on a Perkin–Elmer 397 spectrophotometer and a Perkin–Elmer 241 polarimeter was used for the determination of optical rotations. Microanalyses were performed by the Service Central d'Analyse du CNRS, Vernaison (France).

3-O-(2-Hydroxyethyl)-1,2 : 5,6-di-O-isopropylidene-α-D-glucofuranose (**3**).—Prepared by modification of ref 25. As no physical data are given in the literature, this information is supplied here. To a stirred solution of $LiAlH_4$ (1.44 g, 38.0 mmol, 2.6 equiv) in dry diethyl ether (50 mL) under Ar at 4°C was added with a syringe over 15 min a solution of 3-*O*-carboxymethyl-1,2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranose methyl ester[24] (5.0 g, 15.06 mmol) in dry diethyl ether (75 mL). After 30 min at 4°C, then 60 min at room temperature, the excess hydride was reacted first with EtOAc, then cautiously with water (addition of water being stopped before formation of an aqueous layer). Filtration of the solid residue on Celite 521 and evaporation of the volatiles afforded pure **3** (4.0 g, 87%) as a colorless oil; $[\alpha]_D^{25}$ −42.5° (*c* 1.12, CH_2Cl_2). IR (film): 3500 cm^{-1} (OH). ^1H NMR (200 MHz, $CDCl_3$): 5.95 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.5 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-2), 4.35–4.2 (m, 1 H, H-5), 4.15–3.45 (2M, 9 H, H-3, H-4, H-6, H-6′, OCH_2CH_2OH), 1.35, 1.30, 1.20, 1.15 [4 s, 12 H, $C(CH_3)_2$]. The exchangeable proton is not seen in the spectrum. ^{13}C NMR (50 MHz, $CDCl_3$): 111.9 and 109.3 [$C(CH_3)_2$], 105.6 (C-1), 82.6, 82.2, and 81.2 (C-2, C-3, and C-4), 72.8 (C-5), 71.5 (C-1′), 60.9 (C-2′), 67.7 (C-6), 26.8, 26.7, 26.1, and 25.0 [$C(CH_3)_2$].

3-O-(2-Iodoethyl)-1,2 : 5,6-di-O-isopropylidene-α-D-glucofuranose (**4**).—To a stirred solution of **3** (900 mg, 2.96 mmol) in dry toluene (80 mL) under Ar were successively added PPh_3 (1.18 g, 4.5 mmol) and freshly prepared[29] triiodoimidazole (0.66 g, 2.24 mmol). The mixture was stirred under reflux for 3 h at which stage further PPh_3 (0.78 g, 3 mmol) and triiodoimidazole (0.66 g, 1.5 mmol) were added. After stirring at reflux temperature for 90 min, the mixture was cooled and hydrolysed with freshly prepared satd aq $NaHSO_4$ (80 mL). After 5 min stirring, iodine was added till a brown colour persisted in the organic layer. The excess iodine was then eliminated by addition of satd aq NaS_2O_3. The organic layer was separated, diluted with toluene, washed three times with water, and dried. The solvent was evaporated and the crude mixture was purified by column chromatography on silica gel. Elution with 49:1 CH_2Cl_2–MeOH gave **4** (1.08 g, 88%) as a colorless oil which crystallized on standing; mp 31–3°C; $[\alpha]_D^{25}$ −14.4° (*c* 1.12,

CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$): 5.85 (d, 1 H, $J_{1,2}$ 4.5 Hz, H-1), 4.55 (d, 1 H, $J_{1,2}$ 4.5 Hz, H-2), 4.4–4.2 (M, 1 H, H-5), 4.15–3.75 (M, 6 H, H-3 to H-6′, and $-OCH_2CH_2I$), 3.3–3.1 (m, 2 H, $-OCH_2CH_2I$), 1.4, 1.3, 1.2, and 1.15 [4 s, 12 H, $C(CH_3)_2$] ^{13}C NMR (50 MHz, $CDCl_3$): 111.9 and 109.0 [$C(CH_3)_2$], 105.2 (C-1), 82.7, 82.3, and 81.1 (C-2, C-3, and C-4), 72.3 (C-5), 71.2 (C-1′), 67.3 (C-6), 26.8 (2 peaks) 26.2, 25.4 [$C(CH_3)_2$], 2.6 (C-2′). Anal. Calcd for $C_{14}H_{23}IO_6$: C, 40.59; H, 5.60; I, 30.63. Found: C, 40.75; H, 5.48; I, 30.57.

3-O-(2-Iodoethyl)-D-glucose (**1**).—To a solution of **4** (600 mg, 1.45 mmol) in 1:1 THF–water (10 mL) was added Dowex 50W X8 (50–100 mesh, prewashed and dried, 11.6 g, 67.6 mequiv) and this suspension was stirred at 60°C for 8 h. After filtration of the resin and abundant washing with water and THF, the solution was concentrated to half of its volume and neutralized with dilute (0.05 M) aq NaOH to neutral pH. This aqueous layer was then extracted three times with CH_2Cl_2 and evaporated under reduced pressure without heating. It was then purified by chromatography on silica gel (prewashed with MeOH, then dried overnight at 60°C). Elution with 3:1 CH_2Cl_2–MeOH afforded **1** (0.420 g, 87%) which crystallized after standing for two months in the cold; mp 111–3°C. $[\alpha]_D^{25}$ +27.2° (60 min) and +32.6° (4 h) (*c* 0.5, H_2O). ^1H NMR (200 MHz, D_2O): 5.25 (large s, 1 H, H-1α), 4.70 (d, 1 H, $J_{1,2}$ 7.4 Hz, H-1β, α,β ratio ~1:1), 4.1 (t, 2 H, J_{CH_2,CH_2} 6.3 Hz, OCH_2CH_2I), 4.0–3.25 (M, 20 H, all other protons except for exchangeable ones). ^{13}C NMR (50 MHz, D_2O: 95.8: (C-1β), 92.0 (C-1α) 84.5, 81.9, 75.75, 73.65, 73.4, 73.3, 71.4, 71.05, 69.1 (C-2, C-3, C-4, C-5 (α and β), and C-1′), 60.6 and 60.4 (C-6α and β), 3.6 (C-2′). Anal. Calcd for $C_8H_{15}IO_6$: C, 28.76; H, 4.53; I, 37.98. Found: C, 29.10; H, 4.60; I, 38.52.

3-O-(2-Iodoethyl)-1,2,4,6-tetra-O-acetyl-α- and -β-D-glucopyranose (**5**).—To a stirred solution of **1** (63 mg, 0.19 mmol) in CH_2Cl_2 (6 mL) and pyridine (1 mL) under Ar at 4°C were added successively a crystal of 4-dimethylamino-pyridine and freshly distilled Ac_2O (250 μL). After 3 days the mixture was hydrolyzed with water (2 mL) and extracted three times with CH_2Cl_2 (2 mL). After washing the organic extracts with water, drying, and evaporation of the volatiles, the crude acetates were purified by silica gel column chromatography to give, after elution with 99:1 CH_2Cl_2–MeOH, a mixture of α and β acetates of **5** as an off-white solid (70 mg, 74%). The specified NMR assignments were secured with the help of various 2D-TOCSY and DQF-COSY experiments. ^1H NMR (300 MHz, $CDCl_3$): β anomer: 5.5 (d, 1 H, $J_{1,2}$ 8, Hz, H-1), 5.1–5.0 (M, 2 H, H-4 and H-2), 4.2–4.0, (M, 2 H, H-6 and H-6′), 3.9–3.75 (M, 2 H, OCH_2CH_2I), 3.75–3.65 (M, 1 H, H-5), 3.6 (t, 1 H, $J_{2,3} = J_{3,4}$ 10 Hz, H-3); α anomer: 6.2 (d, $J_{1,2}$ 4 Hz, H-1), 5.1–5.0 (m, 1 H, H-4), 5.0–4.9 (m, 1 H, H-2); 4.2–4.0 (M, 2 H, H-6 and H-6′), 4.0–3.9 (M, 3 H, H-5 and $-OCH_2CH_2I$). The resonance at 3.2 (seemingly quartet, 2 H, J app.$_{CH_2CH_2}$ 7.3 Hz, $-OCH_2CH_2I$) and the 8 singlets (3 H each) at 2.11, 2.07, 2.06, 2.05 (2 peaks), 2.03, 2.025, and 2.02 ($COCH_3$) have not been specifically assigned to each anomer. ^{13}C NMR (50 MHz, D_2O): β anomer: 91.8 (C-1), 80.25 (C-3), 72.8 (C-5), 71.1 (C-2), 61.55 (C-6); α anomer: 89.2 (C-1), 77.1 (C-3), 71.1 (C-2), 70.05 (C-5), 61.55 (C-6).

The following resonances have not been specifically assigned to an isomer: 170.6, 169.4, 169.1, 168.9, 168.6 (C=O), 73.0 and 72.3 ($-OCH_2CH_2I$), 68.7 and 68.6 (C-4), 2.3 and 2.05 ($-OCH_2CH_2I$). Anal. Calcd for $C_{16}H_{23}IO_6$: C, 38.26; H, 4.62. Found C, 38.49; H, 4.91.

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