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Note

Synthesis of 2-*O*-(2-iodoethyl)-D-glucose, a stable iodinated analogue of 2-deoxy-2-fluoro-D-glucose

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2-Deoxy-2-[^{18}F]fluoro-D-glucose, **1** (FDG) is used in nuclear medicine for brain and ischemic myocardiac tissue imaging [1–3]. The required fluorine isotope, a positron emitter, has however a short half-life ($t_{1/2}$ 110 min) which severely limits its usefulness, and production of FDG and its medical use require the proximity of the ^{18}F producing cyclotron. Therefore, efforts are being made in order to replace the fluorine atom with iodinated units so as to be able to use the γ-emitter ^{123}I ($t_{1/2}$ 13.2 h) for the widespread Single Photon Emmitting Computer Tomography (SPECT) imaging [4].

Unfortunately, direct replacement of the fluorine atom by iodine as in 2-deoxy-2-iodo-D-glucose [5,6] **2** leads to an unstable derivative. Hence, several analogues in which iodine is linked to a vinyl [7] or an aromatic group [8–13] have been prepared. Having recently disclosed that the β-iodoethoxy moiety behaves as a stable and less bulky iodinated unit [14], we now report the preparation of the corresponding β-iodoethoxy analogue of FDG, namely **3**.

For the synthesis of **3**, a D-glucose acetate derivative having a free hydroxyl group at C-2 was selected as the starting material. However, as literature methods for the introduction of the β-iodoethoxyl group [14–21] were not compatible with the presence of acetates, another procedure for the introduction of the β-iodoethoxyl group was needed. The silver salt of **4**, readily available from D-glucose [22], was reacted with allyl bromide to afford **5** [23]. Surprisingly however, **5** turned out to be inert to prolonged ozonolysis which thus required modification of the protection at the anomeric position. Conversion [23] of **5** to **6** gave a ~ 1:1 mixture of α/β anomers which then could be reacted with ozone. The intermediate aldehyde was immediately reduced to **7**, the ratio

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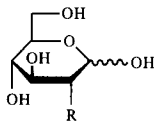
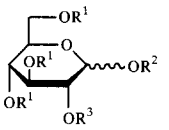
of anomers becoming ~ 1: 3, a fact which is most likely due to a difference in the reactivity of each anomer. Conversion of the anomeric mixture of alcohols **7** to iodides **8** was then accomplished conventionally using freshly prepared [24] triiodoimidazole. While removal of the acetates by using a stoichiometric amount of sodium methoxide unexpectedly led to the known [25–27] bicyclic **9**, the desired conversion to **3** could be achieved in 80% yield with a catalytic amount of sodium methoxide (−30° C, 13 days).

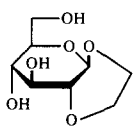
Compound **3** is a simple and stable iodinated analogue of FDG and, since its radiolabelling can be performed efficiently by isotopic exchange, it is currently being evaluated as a metabolic tracer of D-glucose.



1 R = F
2 R = I



3 $R^1 = R^2 = H$, $R^3 = CH_2CH_2I$
4 R^1 = Ac, R^2 = (α)-N-piperidinyl, R^3 = H
5 R^1 = Ac, R^2 = (α)-N-piperidinyl, $R^3 = Ch_2$-CH=CH_2
6 $R^1 = R^2$ = Ac, $R^3 = CH_2$-CH=CH_2
7 $R^1 = R^2$ = Ac, $R^3 = CH_2CH_2OH$
8 $R^1 = R^2$ = Ac, $R^3 = CH_2CH_2I$



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1. Experimental

General methods.—Toluene and CH_2Cl_2 were dried over 4 Å molecular sieves and MeOH was distilled over magnesium. 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 Bruker and Varian 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.

1,3,4,6-tetra-O-*acetyl*-2-O-*(2-hydroxyethyl)-α- and -β*-D-*glucopyranose* (**7**).—A stirred solution of **6** [23] (280 mg, 0.72 mmol) in dry CH_2Cl_2 (40 mL) and dry MeOH (12 mL) at −78° C was ozonized till persistence of a blue color (1 h). Ozone was removed by a slow stream of oxygen followed by argon. Excess dimethyl sulfide was then slowly added at −78° C to the now colorless solution, and the cooling bath was removed. Evaporation of volatiles left the crude aldehyde [^1H NMR (300 MHz, $CDCl_3$): 9.6 (m, 1 H, –CHO), 6.4 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1α), 5.6 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1β), 5.4–4.95 (M, 4 H), 4.6–4.4 (M, 1 H), 4.3–3.2 (M, 11 H), 2.14–1.98 (4 s, 12 H, –COCH_3)]. To a solution of the freshly prepared preceeding aldehyde in MeOH (20

mL) at 4° C, was added portionwise $NaBH_4$ (136 mg, 3.6 mmol). After stirring for 30 min, excess hydride was quenched with Me_2CO (3 mL). The solution was neutralized with dilute (0.5 M) aq HCl and MeOH evaporated under reduced pressure. The aqueous layer was then extracted with CH_2Cl_2 (4 × 20 mL) and the organic layers were dried. After evaporation of the volatiles, the mixture was purified by column chromatography on silica gel. Elution with 49:1 CH_2Cl_2–MeOH gave **7** as a ~1:3 α/β mixture of anomers (colorless oil, 161 mg, 57%). IR (film): 3500 cm^{-1} (OH), 1750 cm^{-1} (CO). The specified NMR assignments were confirmed with the help of TOCSY 1D experiments. ^1H NMR (500 MHz, $CDCl_3$); α anomer: 6.30 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 5.28 (t, 1 H, J 9.7 Hz, H-3), 5.01 (t, 1 H, J 9.80 Hz, H-4), 4.25–4.00 (M, 3 H, H-5, H-6 and H-6′), 3.8–3.5 (M, 5 H, H-2, $-OCH_2CH_2OH$); β anomer: 5.55 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1), 5.13 (t, 1 H, J 9.4 Hz, H-3), 4.98 (t, 1 H, J 9.8 Hz, H-4), 4.25–4.00 (M, 2 H, H-6 and H-6′), 3.80–3.70 (M, 1 H, H-5), 3.8–3.5 (M, 4 H, $-OCH_2CH_2OH$), 3.44 (t, 1 H, J 8.2 Hz, H-2). The 8 singlets (3 H each) at 2.12, 2.10, 2.02, 2.01 (2 ×), 2.00, 1.98 and 1.96 ($-COCH_3$) have not been specifically assigned to each anomer and the exchangeable proton is not seen in the spectrum. ^{13}C NMR (50 MHz, $CDCl_3$): 170.5, 170.3, 170.2, 169.5, 169.3, 168.8 (CO), 93.3 (C-1 β anomer), 89.6 (C-1 α), 78.9, 77.4, 74.0, 72.4, 71.7, 69.7, 67.7 (C-2, C-3, C-4 and C-5), 74.4 and 73.6 ($-OCH_2CH_2OH$) 61.6, 61.4 (C-6), 20.9, 20.8, 20.6, 20.5 ($-COCH_3$). CIMS (NH_3–isobutane): 410 (100%, $[M + NH_4]^+$), 350 (10%, $[M - AcOH]^+$), 333 (5%, $[392 - OAc]^+$), 273 (3%, $[333 - AcOH]^+$), 255 (2%, $[273 - H_2O]^+$), 213 (55%, $[273 - AcOH]^+$), 153 (31%, $[213 - C_2H_4O_2]^+$). HMRS: Calcd for $C_{16}H_{24}O_{11}$ + Na: 415.1216. Found: 415.1219.

1,3,4,6-Tetra-O-*acetyl-2*-O-*(2-iodoethyl)-α- and -β-*D-*glucopyranose* (**8**).—To a stirred solution of alcohol **7** (62 mg, 0.16 mmol) in dry toluene (10 mL) under Ar, were successively added Ph_3P (62 mg, 0.24 mmol) and freshly prepared triiodoimidazole [24] (53 mg, 0.12 mmol). The mixture was stirred under reflux for 3 h at which stage further Ph_3P (45 mg, 0.17 mmol) and triiodoimidazole (40 mg, 0.09 mmol) were added. After stirring at reflux temperature for 14 h, the mixture was cooled and hydrolyzed with freshly prepared satured aq $NaHSO_4$ (10 mL). After 5 min stirring, iodine was added till a brown color persisted in the organic layer. The excess of iodine was then removed by addition of saturated aq NaS_2O_3 (30 mL). The organic layer was separated, diluted with toluene and Me_2CO (3 mL), washed with water (3 × 20 mL), and dried. The solvent was evaporated and the crude mixture was purified by column chromatography on silica gel. Elution with 99.5:0.5 CH_2Cl_2–MeOH gave **8** as an unseparable mixture of anomers (colorless oil, 63 mg, 79%); IR (film): 1750 cm^{-1} (CO). The specified NMR assignments were confirmed by TOCSY 1D and COSY DQF experiments. ^1H NMR (500 MHz, $CDCl_3$); α anomer: 6.38 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 5.38 (t, 1 H, J 9.7 Hz, H-3), 5.04 (t, 1 H, J 9.8 Hz, H-4), 4.32–4.27 (m, 1 H, H-6 or H-6′), 4.10–4.05 (M, 2 H, H-5 and H-6 or H-6′), 3.94–3.60 (M, 2 H, $-OCH_2CH_2I$), 3.65 (dd, 1 H, J 9.9 Hz, H-2), 3.18–3.14 (M, 2 H, $-OCH_2CH_2I$), 2.19, 2.10, 2.08, 2.04 (s, 12 H, $-COCH_3$); β anomer: 5.61 (d, 1 H, $J_{1,2}$ 8.1 Hz, H-1), 5.20 (t, 1 H, J 9.4 Hz, H-3), 5.02 (t, 1 H, J 9.7 Hz, H-4), 4.32–4.27 (m, 1 H, H-6 or H-6′), 4.10–4.05 (m, 1 H, H-6 or H-6′), 3.90–3.67 (M, 3 H, H-5 and $-OCH_2CH_2I$), 3.51 (dd, 1 H, J 8.5, H-2), 3.18–3.14 (M, 2 H, $-OCH_2CH_2I$), 2.18, 2.09, 2.07, 2.03 (s, 12 H, $-COCH_3$). ^{13}C NMR (50 MHz, $CDCl_3$): 170.5, 170.1, 169.6, 169.0, 168.6 (CO), 93.9 (C-1 β), 89.2 (C-1 α), 78.5, 76.9, 73.8,

72.4, 71.2, 69.7, 68.0, 67.9,(C-2, C-3, C-4 and C-5), 73.2 and 71.9 ($-OCH_2CH_2I$), 61.5 (C-6), 21.1, 21.0, 20.7, 20.6 ($-COCH_3$), 2.1 ($-OCH_2CH_2I$). CIMS (NH_3–isobutane): 520 (1%, $[M + NH_4]^+$), 443 (18%, $[502 - OCOCH_3]^+$), 442 (6%, $[502 - AcOH]^+$), 383 (1%, $[443 - AcOH]^+$), 323 (82%, $[383 - AcOH]^+$), 197 (32%, $[383 - C_8H_{10}O_5]^+$), 186 (6%, $[383 - C_4H_7IO]^+$), 168 (13%, $[323 - CH_2CH_2I]^+$), 155 (100%, $[CH_2CH_2I]^+$), 127 (13%, $[155 - CH_2=CH_2, I]^+$), 108 (17%, $[168 - AcOH]^+$). HMRS: Calcd for $C_{16}H_{23}IO_{10}$+Na: 525.0233. Found: 525.0247.

2-O-(2-Iodoethyl)-D-glucose (**3**).—To a stirred solution at −30° C of **8** (44 mg, 0.088 mmol) in dry MeOH (3 mL) was added NaOMe (10.8 μL of a 1 M solution in dry MeOH). The mixture was stirred for 14 days at −30° C, diluted with water (10 mL) and MeOH was evaporated under reduced pressure. The pH was brought to 7.0 with dilute H_2SO_4 (0.012 M); after extraction with CH_2Cl_2 (3 × 10 mL), the aq layer was evaporated without heating and the crude product was purified by column chromatography on silica gel. Elution with 45:5 EtOAc–isopropanol gave **3** as a white solid (23.4 mg, 80%); mp 139–143° C; $[\alpha]_D^{20}$ + 22.1° (5 min) → +21.2° (3 h) (*c* 1.25, MeOH). The specified NMR assignments were secured with the help of various TOCSY 1D and GHMQC experiments. ^{1}H NMR (500 MHz, D_2O); β anomer: 4.7 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1), 3.87 (A part of an ABM system, 1 H, J_{ab} 12.3 Hz, H-6 or H-6′), 3.69 (B part of an ABM system, 1 H, J_{ab} 12.3 Hz, H-6 or H-6′), 3.53 (t_{app}, 1 H, *J* 9.0 Hz, H-3), 3.45–3.37 (M, 2 H, H-5 and H-4), 3.34 (M, 2 H, $-OCH_2CH_2I$), 3.12 (dd, 1 H, *J* 9.3 Hz and *J* 7.9 Hz, H-2); α anomer: 5.4 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 3.82–3.60 (M, 4 H, H-3, H-5, H-6 and H-6′), 3.40–3.37 (M, 2 H, H-2 and H-4), 3.34 (M, 2 H, $-OCH_2CH_2I$). The signals at 4.12–4.0 (M) and 3.94–3.92 (t) for $-OCH_2CH_2I$ have not been specifically assigned to each anomer. ^{13}C NMR (125 MHz, D_2O); β anomer: 95.7 (C-1), 82.6 (C-2), 75.8 (C-5), 75.2 (C-3), 73.1 or 71.4 (OCH_2CH_2I), 69.6 or 69.5 (C-4), 60.7 (C-6), 3.3 ($-OCH_2CH_2I$); α anomer: 90.2 (C-1), 79.55 (C-2), 73.1 or 71.4 (OCH_2CH_2I), 72.0 and 71.2 (C-3 and C-5), 69.6 or 69.5 (C-4), 3.3 (OCH_2CH_2I. CIMS (NH_3–isobutane): 352 (0.5%, $[M + NH_4]^+$), 334 (2%, $[M]^+$), 317 (3%, $[334 - OH]^+$), 299 (6%, $[334 - 2H_2O]^+$), 281 (1%, $[334 - 3H_2O]^+$), 239 (3%, $[299 - HOCH_2 - CHO]^+$), 155 (100%, $[-CH_2CH_2I]^+$), 154 (61%, $[281 - I]^+$), 146 (8%, $[317 - OCH_2CH_2I]^+$), 144 (10%, $[299 - CH_2CH_2I]^+$), 127(5%, $[I]^+$), 126 (3%, $[144 - H_2O]^+$).

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References

[1] B.M. Gallagher, A. Ansari, H. Atkins, V. Casella, D.R. Christman, J.S. Fowler, T.Ido, R.R. MacGregor, P. Som, C.N. Wan, A.P. Wolf, D.E. Kuhl, and M. Reivich, *J. Nucl. Med.*, 18 (1977) 990–996.

[2] M.E. Phelps, S.C. Huang, E.J. Hoffman, C. Selin, L. Sokoloff, and D.E. Kuhl, *Ann. Neurol.*, 6 (1979) 371–388.
[3] M.E. Phelps, M.E. Hoffmann, C.Selin, S-C. Huang, G.Robinson, N. MacDonald, H.Schelbert, and D.E. Kuhl, *J. Nucl. Med.*, 19 (1978) 1311–1319.
[4] A.Syrota and P. Jehenson, *Eur. J. Nucl. Med.*, 18 (1991) 897–923.
[5] J.S. Fowler, R.E. Lade, R.R. MacGregor, C. Shiue, C.-N. Wan, and A.P. Wolf, *J. Labelled Compd. Radiopharm.*, 16 (1979) 7–9.
[6] G. Kloster, P. Laufer, W. Wutz, and G. Stöcklin, *Eur. J. Nucl. Med.*, 8 (1983) 237–241.
[7] M.M. Goodman, A.P. Callahan, and F.F. Knapp, Jr, *J. Labelled Compd. Radiopharm.*, 23 (1987) 1269–1270.
[8] H. Saji, Y. Magata, Y. Arano, K. Horiuchi, K. Torizuka, and A. Yokoyama, *J. Nucl. Med.*, 28 (1987) 571.
[9] Y. Magata, H. Saji, Y. Arano, K. Horiuchi, K. Torizuka, and A. Yokoyama, *Nucl. Med. Biol.*, 14 (1987) 7–13.
[10] T. Lutz, H. Dougan, T. Rihela, M. Hudon, P. Cohen, W.R.E. Jamieson, and D.M. Lyster, *J. Labelled Compd. Radiopharm.*, 29 (1991) 535–545.
[11] Y. Magata, H. Saji, Y. Ohmomo, C. Tanaka, J. Kanishi, and A. Yokoyama, *J. Labelled Compd. Radiopharm.*, 30 (1991) 300–301.
[12] Y. Magata, H. Saji, Y. Ohmomo, C. Tanaka, J. Kanishi, and A. Yokoyama, *J. Labelled Compd. Radiopharm.*, 31 (1992) 317–328.
[13] T. Lutz, H. Dougan, T. Rihela, C.V. Vo, and D.M. Lyster, *J. Labelled Compd. Radiopharm.*, 33 (1993) 327–344.
[14] S.Hamant, J.-P. Mathieu, C.Morin, I.Trimcev, and M.Vidal, *Bioorg Med. Chem. Lett.* 4 (1994) 1687–1690.
[15] F. Baumstark, *Ber. Dtsch. Chem. Ges.*, 7 (1874) 1172–1175.
[16] C.W. Tasker and C.B. Purves, *J. Am. Chem. Soc.*, 71 (1949) 1017–1023.
[17] C. Walling and R.T. Clark, *J. Org. Chem.*, 39 (1974) 1962.
[18] R.C. Cambie, R.C. Haywar, J.L. Roberts, and P.S. Rutledge, *J. Chem. Soc., Perkin Trans. 1*, (1974) 1858–1864.
[19] C. Georgoulis and J.M. Valery, *Synthesis*, (1978) 402–403.
[20] G. Bignan, J.-P. Mathieu, L. Mauclaire, C. Morin, and M. Vidal, *J. Labelled Compd. Radiopharm.*, 32 (1993) 584–585.
[21] G. Bignan, C. Morin, and M. Vidal, *Carbohydr. Res.*, 248 (1993) 371–375.
[22] J.E. Hodge and C.E. Rist, *J. Am. Chem. Soc.*, 74 (1952) 1498–1500.
[23] M.K. Gurjar and S.M. Pawar, *Carbohydr. Res.*, 159 (1987) 325–327.
[24] P.J. Garegg and B. Samuelsson, *J. Chem. Soc., Perkin Trans. 1*, (1980) 2866–2869.
[25] J.E. Hook and B.Lindberg, *Acta. Chem. Scand.*, 22 (1968) 2157–2160.
[26] B.H. Thewlis, *Stärke*, 278 (1975) 336–338.
[27] J. Reuben, *Carbohydr. Res.*, 197 (1990) 257–261.

Note added in proof: the synthesis of 2-iodo-FDG has just been described; see J.D. McCarter, M.J. Adam, S.G. Withers, *Carbohydr. Res.* 266 (1995) 273–277.