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Note

Synthesis of ^{18}F-labelled 2-deoxy-2-fluoro-D-galactopyranose using the acetyl hypofluorite procedure

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There has been much reported[1-6] on the synthesis of fluorinated sugars, and hexopyranoses labelled with ^{18}F ($t_{1/2}$ 110 min) have found important application in positron emission tomography[7].

2-Deoxy-2-([^{18}F]fluoro)-D-galactopyranose (**1**), which has been prepared[8,9] by the reaction of 3,4,6-tri-*O*-acetyl-D-galactal (**2**) with [^{18}F]fluorine gas followed by acid hydrolysis, is not only an excellent diagnostic liver-imaging agent but also has promise for studies of metabolism in healthy or diseased liver in humans. Adam[5] reported the preparation of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-α-D-galactopyranose (**3**) by the reaction of **2** with acetyl hypofluorite, but *O*-deacetylation was not described. We now report on the preparation of 2-deoxy-2-fluoro-D-galactopyranose (**4**) and its ^{18}F-labelled compound (**1**), using the acetyl hypofluorite procedure.

Acetyl hypofluorite[10], prepared by reaction of fluorine gas (1.8%, diluted with nitrogen) with sodium or potassium acetate in trichlorofluoromethane–acetic acid at −78°, when reacted with **2**, gave 90% of **3**. Hydrolysis[8,9] of **3** with dilute hydrochloric acid afforded 77% of **4**. The overall yield of **4** from **2** was 69% (*cf.* 16% for the reaction with fluorine gas[8]) and the reaction of acetyl hypofluorite with **2** to give **3** was very fast.

Acetyl hypofluorite can be transferred with the aid of a stream of inert gas[7], and a modified method was used for the preparation of radioactive acetyl hypofluorite because the [^{18}F]fluorine gas produced by deuteron bombardment of

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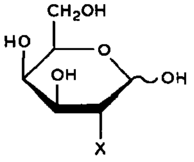
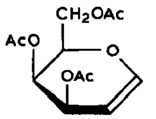
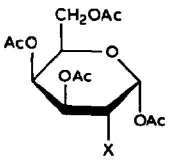


1 X = ^{18}F

4 X = F



2



3 X = F

5 X = ^{18}F

a mixture of neon and fluorine by the ^{20}Ne (d, α) ^{18}F nuclear reaction is highly diluted and in small amount. Hence, the diluted fluorine gas was passed through a column of granular potassium acetate and the acetyl hypofluorite generated was reacted directly with **2** to give **5**. Hydrolysis of **5**, as described above, then gave **1** with a radiochemical yield, purity, and specific activity of 13.2%, >98%, and 7.3 mCi/μmol, respectively.

The medical uses of **1** and **4** are being investigated.

EXPERIMENTAL

Melting points were determined using a hot-stage apparatus and are uncorrected. N.m.r. spectra (300 MHz) were recorded with a Bruker model CXP 300 spectrometer and optical rotations with a JASCO model DIP-181 instrument. The homogeneity of compounds was checked by t.l.c. and h.p.l.c.

1,3,4,6-Tetra-O-acetyl-2-deoxy-2-fluoro-α-D-galactopyranose (**3**). — (*a*) Fluorine gas (1.8%) diluted with nitrogen was passed into a stirred suspension of anhydrous sodium acetate (4 g) in acetic acid (16 mL) and trichlorofluoromethane (184 mL) at −78°, to give acetyl hypofluorite (4.6 mmol). The total acetyl hypofluorite content was determined by titration of the iodine liberated from potassium iodide. A solution of **2** (1.36 g, 5 mmol) in trichlorofluoromethane (25 mL) was then added to the resulting mixture. After 5 min, the mixture was poured into ethyl acetate, washed with aqueous sodium thiosulfate and water, dried ($MgSO_4$), and concentrated to give **3** (1.78 g, 90% based on acetyl hypofluorite). Recrystallisation from isopropyl ether afforded **3** as colorless needles, m.p. 125–126°, $[\alpha]_D^{20}$ +155° (*c* 1, chloroform); lit.[3] m.p. 102°, $[\alpha]_D^{25}$ +150° (*c* 1, chloroform). N.m.r. data ($CDCl_3$, internal Me_4Si): δ 2.04, 2.06, 2.15, and 2.19 (4 s, each 3 H, 4 Ac), 4.09 (o, 2 H, H-6), 4.34 (t, 1 H, $J_{5,6}$ 6.6 Hz, H-5), 4.91 (o, 1 H, $J_{2,F}$ 49.1, $J_{2,3}$ 10.3 Hz, H-2), 5.39 (sextet, 1 H, $J_{3,F}$ 10.7, $J_{3,4}$ 3.3 Hz, H-3), 5.52 (t, 1 H, $J_{4,F}$ ~3 Hz, H-4), and 6.46 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1).

When a suspension of anhydrous potassium acetate (480 mg) in acetic acid (1.6 mL) and trichlorofluoromethane (18.4 mL) was treated with the diluted fluorine gas as described above, an analogous result was obtained.

(*b*) The diluted fluorine gas was passed slowly through a column (1 × 10 cm) of granular potassium acetate to give acetyl hypofluorite (0.4 mmol), which was then treated with a cooled solution of **2** (135 mg, 0.5 mmol) in trichlorofluoromethane (30 mL). The mixture was worked-up as in (*a*) to give **3** (70% based on acetyl hypofluorite).

*2-Deoxy-2-fluoro-*D*-galactopyranose*[8,11] (**4**). — A mixture of **3** (1 g) and aqueous 14% hydrochloric acid (20 mL) was boiled under reflux for 1.5 h and then concentrated to dryness under reduced pressure. The residue was dissolved in water (1 mL) and purified by using a column (1.5 × 10 cm) of AG 11-A8, to afford **4** (400 mg, 77%), m.p. 128–133°, $[\alpha]_D^{20}$ +90° (*c* 2.3, water); lit.[11] m.p. 131–135°, $[\alpha]_D$ +92° (*c* 2.3, water).

*2-Deoxy-2-([^{18}F]fluoro)-*D*-galactopyranose* (**1**). — [^{18}F]Fluorine gas was produced by the deuteron bombardment (2 h, 10 μA) of a mixture of neon and fluorine (99.5:0.05) at 25 atm. in a nickel target chamber by the ^{20}Ne (d, α) ^{18}F nuclear reaction, using the Tohoku University Cyclotron. The resulting gas was released from the chamber at a controlled rate and passed through a column (0.6 × 5 cm) of granular potassium acetate. The column was swept with a stream of neon gas until all radioactive gas had been displaced. The radioactive reagent was passed with the aid of a stream of neon gas through a solution of **2** (25 mg) in trichlorofluoromethane (15 mL) to give **5**. After removal of the solvent, a suspension of the residue in aqueous 7% hydrochloric acid was boiled under reflux for 15 min, and then chromatographed over a series of columns (0.9 × 10 cm, 0.9 × 1 cm, and 0.9 × 5 cm) packed with AG 11-A8 resin, activated charcoal, and neutral alumina, respectively. From the eluate, **1** was obtained[8]; the radiochemical yield, purity, and specific activity were 13.2%, >98%, and 7.3 mCi/μmol, respectively. The total time of preparation of **1** was ~1.5 h.

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