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A Rapid Synthesis of [^{82}Br]-2-Deoxy-2-bromo-D-mannose and [^{82}Br]-2-Deoxy-2-bromo-D-glucose using D-Glucal as Precursor*

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[^{18}F]-2-Deoxy-2-fluoro-D-glucose (2-^{18}FDG), [^{18}F]-3-deoxy-3-fluoro-D-glucose and 1-[^{11}C]-2-deoxy-D-glucose are used clinically to measure regional cerebral glucose metabolism by positron emission tomography (PET). In particular, 2-^{18}FDG has been proposed as a tracer useful for *in vivo* PET measurement of glucose metabolism, and the advantages have been detailed in the literature.

Since Fischer, Bergmann, and Schotte reported the halogenation of 3,4,6-tri-O-acetyl-D-glucal (TAG), most of the methods used for the synthesis of the halogenated hexose, including those for 2-^{18}FDG, are based on the reaction of halogenation agents with TAG. The limitation of this radiopharmaceutical is that the reported production methods for the compound give relatively low chemical and radiochemical yields.

In previous reports, the present authors described the usefulness of D-glucal, which is a kind of the simplest unsaturated sugar derivatives, as a precursor for synthesis of glucose analogs and reported that the dihalogen addition products of D-glucal have reasonably greater brain uptakes than 2-deoxy-D-glucose and D-glucose. From the standpoint of blood-to-brain transport, these dihalogeno compounds are very interesting ; however, the halogen at carbon atom 1 was found to be relatively unstable *in vivo*. Therefore, we have searched for methods which will improve the yield of glucose analogs, or analogs which will behave like 2-^{18}FDG.

In this paper we report a rapid synthetic procedure for [^{82}Br]-2-deoxy-2-bromo-D-mannose (2-^{82}BrDM) and [^{82}Br]-2-deoxy-2-bromo-D-glucose (2-^{82}BrDG) which are obtained on direct addition of $^{82}Br_2$ to D-glucal.

3,4,6-Tri-O-acetyl-D-glucal (**1**) (5.86 g) was dissolved in dry methanol (100 ml), and sodium (15 mg) was added. The solution was allowed to remain at room temperature for 24 hr, treated with carbon dioxide and evaporated under diminished pressure. The residue was extracted with hot ethyl acetate. The combined extracts were concentrated to afford D-glucal (**2**) m.p. 57—59°C, $[\alpha]_{19}^{D}$-8.0 (c 1.88 in water).

Bromination of D-glucal was performed quite readily by the direct addition of bromine to the unsaturated linkage of **2** as follows. A stirred solution 0.03 g of **2** in 100 ml of $CHCl_3$ was cooled in an ice bath and protected from light. Bromine ($^{82}Br_2$) was added dropwise

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until the color caused by excess bromine was present. Then, nitrogen gas was bubbled into the solution to remove the excess bromine, and the solvent was evaporated *in vacuo* at 40—43°C to give a mixture of [^{82}Br]-2-deoxy-2-bromo-D-mannopyranosyl bromide (**3**) and [^{82}Br]-2-deoxy-2-bromo-D-glucopyranosyl bromide (**4**). The specific activity of bromine ($^{82}Br_2$) was 67.3 μCi/mmol. It is noteworthy that the bromination process was completed within a few minutes in a 98% yield. The mixture was refluxed with 1 N hydrochloric acid (2.5 ml) for 5 min at 110°C. Then the solution was cooled, neutralized with silver carbonate, filtered, and evaporated. Further purification was performed on a column consisting of charcoal, an ion-retardation resin and alumina. The reaction mixture was analysed on TLC.

Examination of the hydrolysate by TLC [$CHCl_3$–CH_3OH (6 : 4)] indicates two major components with Rf values of 0.86 and 0.77, whose configurations have been assigned to be 2-deoxy-2-bromo-D-mannose (**5**) and 2-deoxy-2-bromo-D-glucose (**6**), respectively, by the following reaction sequence. Thin layer radiochromatography (silica gel 20 cm glass plates, mobile phase chloroform-methanol 6 : 4, radiochromatogram scanner, Packard model 7201) also showed single spots with Rf 0.86 and 0.77, respectively.

The Rf values were identical to those of authentic 2-deoxy-2-bromo-D-mannose and 2-deoxy-2-bromo-D-glucose, which were obtained by hydrolyzing 3,4,6-tri-O-acetyl-2-deoxy-2-bromo-D-mannopyranosyl bromide and 3,4,6-tri-O-acetyl-2-deoxy-2-bromo-D-glucopyranosyl bromide respectively, according to the method of Fischer et al. and Lemieux et al.

The yield, which was determined by collecting and counting the peaks for **5** and **6** comparing the results with an equivalent sample of the reaction solution, was 61.1% for **5** and 27.7% for **6**, respectively.

Under standard conditions (reaction time 5 min at room temperature, hydrolysis of the products with 1 N HCl at 110°C for 5 min, followed by silica gel column purification) 4.2 μCi of **5** and 2.0 μCi of **6** were obtained with synthetic time of 20—25 min. The specific activity of the 2-^{82}BrDM and 2-^{82}BrDG was 33.6 μCi/mmol.

Advantages of this method are as follows :

(1) The reported synthetic procedures of 2-FDG and 3-FDG require 1.5—2 h, whereas direct addition to D-glucal is completed within a few minutes and the overall sample preparation for clinical studies is about 35 min. Note that this method is especially advantageous for production of glucose analogs labelled with short half-lived radionuclides such as ^{75}Br.

(2) The precursor of the proposed method, D-glucal, is synthesized from TAG by way of several nonradioactive steps and can readily be available for years without any detectable chemical alteration provided the compound is kept in a refrigerator.

(3) This method can readily be adapted for the synthesis of ^{75}Br, ^{77}Br labelled D-glucose derivatives, usefulness of which as potential radiopharmaceutical for tracing D-glucose utilization in brain and heart had been described.