NOTE

AN EFFICIENT SYNTHESIS OF 2-[*carbonyl*-^{11}C]ACETAMIDO-2-DEOXY-D-GLUCOPYRANOSE (*N*-[*carbonyl*-^{11}C]ACETYL-D-GLUCOSAMINE)

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SUMMARY

A rapid chemical synthesis of 2-[*carbonyl*-^{11}C]acetamido-2-deoxy-D-glucopyranose (*N*-[*carbonyl*-^{11}C]acetyl-D-glucosamine) starting from [^{11}C]carbon dioxide is described. The total time required for the synthesis, the radiochemical yield, and purity of the titled sugar are *ca.* 60 min, 49.5% (based on [*carbonyl*-^{11}C]acetic acid), and >98%, respectively.

Key Words: 2-[*carbonyl*-^{11}C]Acetamido-2-deoxy-D-glucopyranose, *N*-[*carbonyl*-^{11}C]acetyl-D-glucosamine, [^{11}C]carbon dioxide, [*carbonyl*-^{11}C]acetic acid, chemical synthesis.

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INTRODUCTION

In previous papers (1,2), we reported an efficient, one-pot synthesis of 2-deoxy-2-[^{18}F]fluoroacetamido-D-glucopyranose, -D-mannopyranose, and -D-galactopyranose as potential diagnostic imaging agents. In more recent work (3), it was found that 2-deoxy-2-[^{18}F]fluoroacetamido-D-glucopyranose had a good potential as a clinical tumor seeking agent.

2-Acetamido-2-deoxy-D-glucopyranose (1) is a structural analog of 2-deoxy-2-fluoroacetamido-D-glucopyranose. Fluorine atom mimics hydrogen atom with respect to steric requirements at enzyme receptor sites (4). The sugar (1) is the most aboundant aminosugar widely occurring in polysaccharides, glycoproteins and proteoglycans (5). The incorporation of the sugar (1) into hyaluronic acid, one of mucopolysaccharide, by mammalian cells has been reported (6). The sugar (1) also passes the blood brain barrier and is equally distributed in different brain areas (7). Recently, Mannens *et al.* (8) reported an enzymatic synthesis of 2-[*carbonyl*-^{11}C]acetamido-2-deoxy-D-glucopyranose (2) using a specific enzyme catalyzed reaction.

As part of the synthetic study of hexopyranoses labelled with positron emitting radionuclides, the chemical synthesis of the sugar (2) from [^{11}C]carbon dioxide using Grignard reaction and condensation is reported here in detail.

RESULTS AND DISCUSSION

Nonradioactive sugar (1) has been synthesized from the hydrochloride of 2-amino-2-deoxy-D-glucopyranose (3) in high yield by a facile procedure (9) but it is not suitable for the synthesis of (2) labelled with carbon-11 because of the half-life time constraint (β^+decay, $t_{\frac{1}{2}}$=20.4 min). We reported that (3) with fluoroacetic acid at 82°C for 20 min in the presence of dicyclohexylcarbodiimide (DCC) gave the desired sugar in *ca.* 50% yield

(1). We have adapted this method to prepare the titled sugar (2) from [*carbonyl*-^{11}C]acetic acid with some modifications. [*carbonyl*-^{11}C]Acetic acid was prepared from [^{11}C]carbon dioxide with a Grignard reagent by the ordinary procedure.

[^{11}C]Carbon dioxide was produced from the proton bombardment of nitrogen gas by the ^{14}N (p, α) ^{11}C nuclear reaction at the Tohoku University Cyclotron (10), and was bubbled into a solution of methylmagnesium bromide in tetrahydrofuran. Diluted aqueous alkali was then added to destroy an excess of the Grignard reagent. To the resulting solution was added a mixture of (3) and DCC, and the mixture was then heated for 10 min at 80°C. After removal of an excess of DCC, the desired sugar (2) was purified by high performance liquid chromatography (HPLC). The total synthesis time, the radiochemical yield, and purity of (2) were *ca.* 60 min, 49.5% (based on [*carbonyl*-^{11}C]acetic acid), and >98%, respectively.

Additionally, this easy method for the preparation of the sugar (2) could be adapted for automated synthesis. The medical use of (2) is being investigated and the result will be reported elsewhere.

EXPERIMENTAL

Methylmagnesium bromide (1*M* solution in tetrahydrofuran) was purchased from Kanto Chemical Co. Inc. Jpn. and the other reagents were from Wako Chemical Ltd. Jpn. These reagents were used without further purification. The purity of each compound was always checked by thin-layer chromatography. HPLC analyses were carried out either with a Waters Assoc. model 6000 equipped with a refractive index detector or with a Waters Assoc. model 4500 equipped with a radioactivity monitor. The packed columns [YMC-Pack PA-03 (4.6 x 250 mm) and YMC-Pack PA-23 (10.0 x 250 mm), Yamamura Chem. Lab. Co. Jpn.] were used in HPLC. The mobile

phase used was acetonitrile/water (75/25, v/v). Flow rates in the former column and in the latter were 1.5 ml/min and 5.0 ml/min, respectively.

2-[*carbonyl*-^{11}C]Acetamido-2-deoxy-D-glucopyranose (2). [^{11}C]Carbon dioxide was produced by irradiation of nitrogen gas with 18 MeV protons at 10 μA for 15 min. The irradiated target gas was released to a hot cell where [^{11}C]carbon dioxide is frozen out into a copper coil immersed in liquid argon (flow rate, 1 l/min). The coil with the trapped [^{11}C]carbon dioxide was then heated with a hot air blower. The [^{11}C]carbon dioxide was swept out by a dry argon flow (30 ml/min) and into a reaction vessel containing 1*M* solution of methylmagnesium bromide in tetrahydrofuran (0.5 mmol, 0.5 ml). After the trapping of [^{11}C]carbon dioxide, 0.05N potassium hydroxide aq. solution (0.3 ml) was added to destroy an excess of the Grignard reagent.

To the resulting solution, a mixture of hydrochloride of aminosugar (3) (0.2 mmol, 43.2 mg) and a solution of DCC (0.4 mmol, 82 mg) in pyridine (0.4 ml) was added, heated at 80°C for

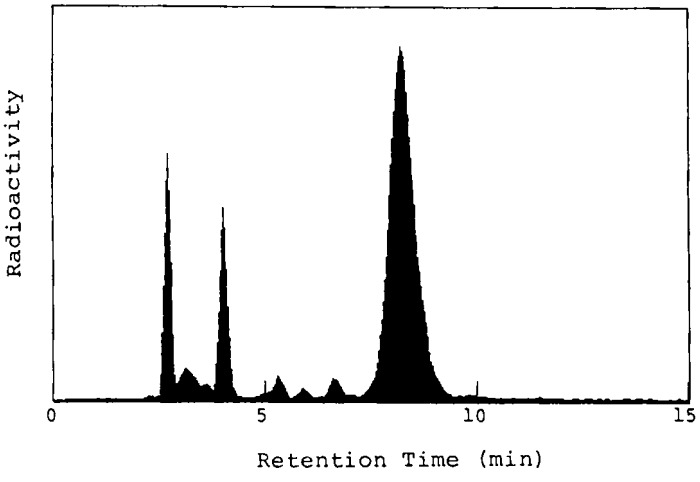

Fig. 1. Preparative HPLC chromatogram of reaction mixture. The main peak corresponds to the sugar (2).

10 min with stirring, diluted with water (2 ml) to decompose an excess of DCC, and then filtered. The filtrate was evaporated to dryness under a reduced pressure. The residue was dissolved in water (0.5 ml) and the solution was chromatographed over an ion retardation resin (AG 11-A8, 2 ml) column using water as elution solvent. The eluate was then mixed with an approximately equal portion of acetonitrile, passed through a Sep-Pak NH_2 cartridge (Waters Assoc. USA), and eluted with aqueous acetonitrile (1:1, v/v). The effluent was concentrated to 1/10 of its original volume and then subjected to preparative HPLC. The radio-chromatogram is shown in Fig 1. A radioactivity peak corresponding to (2) was then collected and the identity of the peak was confirmed by analytical HPLC. Retention times of (2) in HPLC using the YMC-Pack PA-03 and PA-23 columnswere 5.4 min and 8.3 min, respectively.

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