THE SYNTHESIS OF 6-DEOXY-6-^{18}F-α-D-GALACTOPYRANOSE (XXII)*

David R. Christman†, Zlata Orhanovic†‡, Walton W. Shreeve§,
and Alfred P. Wolf†
Chemistry Department, Brookhaven National Laboratory,
Upton, New York 11973 and
Veterans Administration Hospital, Northport, New York 11768
Received August 30, 1976
Revised October 4, 1976

SUMMARY

The synthesis of 6-deoxy-6-^{18}F-α-D-galactopyranose from the 6-tosyl-1,2:3,4-di-O-isopropylidene derivative, using tetraethylammonium fluoride-^{18}F is described. The synthesis requires 4-4½ hours for completion. The radiochemical yield (activity in compound/starting activity, corrected for decay) is about 15%. Thus 3-4% of the starting ^{18}F$^-$ activity is present at the time of delivery, in approximately 0.2 mg of product.

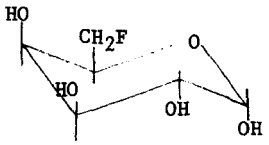
Key Words: Fluorine-18; 6-deoxy-6-^{18}F-α-D-galactopyranose

INTRODUCTION

Recently there has been increasing interest in carbohydrates labeled with nuclides suitable for external visualization. Some work has been done with ^{11}C-labeled carbohydrates (1-4), but for many studies a nuclide of longer half-life would be preferable if not essential. For this reason ^{18}F is particularly attractive if it can be introduced into a position which is not biologically active in a system under study. In many cases it has been found that substitution of fluorine for hydroxyl group in a carbohydrate has relatively little effect on the membrane transport properties of the compound (5-7). Such com-

*Research performed under the auspices of the U. S. Energy Research and Development Administration and with the support of Veterans Administration General Research funds.
†Brookhaven National Laboratory
‡Present address: Zavod 2A Org. Kemiju, Tehnoloski Fakultet, Marulićev Trg 20, 41000 Zagreb, Yugoslavia.
§Veterans Administration Hospital.

pounds thus represent potentially interesting materials for metabolic studies, if the metabolism is not appreciably altered, or for scanning agents if they are substantially organ specific and their metabolism is clocked in the organ of interest. Galactose is known to accumulate in the liver and to show altered metabolic patterns in some disease states of the liver (8,9). Since the 6-position of galactose might not be involved in at least some of the metabolic pathways, the synthesis of 6-deoxy-6-^{18}F-α-D-galactopyranose (I) was undertaken.



I

While a number of fluoro analogs of such carbohydrates were known previously (10-13), the preparation of the 6-fluoro galactose compound had been found to be particularly difficult, apparently due to steric effects in the displacement of the usual leaving groups from this position (14). The formation of the 6-fluoro glucose analog by a similar process is, by contrast, particularly rapid. In view of the difficulties with galactose, a number of different conditions for the displacement were investigated.

Compound I had been prepared previously by displacement of the mesyl group with anhydrous KF in several solvents (9). However, numerous attempts at a small scale synthesis using this method, as required here, produced only low yields of impure material under a variety of conditions and reaction times. This was also the case when the tosyl group was used in place of mesyl. Attempts were then made to produce the material using KF with 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6) in acetonitrile at temperatures ranging from 85-160°C (in small pressure bottles), with both tosyl and iodo as leaving groups. In all cases there was either no reaction or a very poor yield, even with reaction times as long as 22 hours. However, the use of tetraethylammonium fluoride in acetonitrile (15), using the tosyl leaving group, was found to give reasonable results in an acceptable length of time, and this system is the one reported on here. Results and parameters of eight runs using this process are listed in Table I.

EXPERIMENTAL

Inactive Et_4NF was obtained from K and K Laboratories; 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (II) was obtained from Pfanstiehl Laboratories. The $^{18}F^-$ was produced on the Brookhaven 60" cyclotron by irradiation of water with 54 MeV $^3He^{++}$ particles (16), with the yield being 10 mCi/μA-hr in a volume of 8 cc. This layer chromatography was performed in silicic acid media obtained from the Gelman Instrument Co. (SA ITLC), using ethyl acetate:ethanol (6:1 V/V) as solvent. The tosyl derivative was prepared from II in pyridine by standard methods (17).

Four cc of the irradiated water solution was placed in a small round bottom flask with one drop of a 10% tetramethylammonium hydroxide solution, and this was taken to dryness under reduced pressure on a rotary evaporator using water at 50-60°C as a heating medium. The remaining target water was then added, along with the desired amount of carrier Et_4NF, and it was again evaporated to dryness. The residue was then taken up in 0.5 cc of acetonitrile and transferred to a 2 ml pressure bottle (Microflex tubes, Kontes Glass Co.), where it was blown to dryness with a stream of nitrogen gas. This was repeated three times, after which the bottle was kept for 10 minutes in a vacuum desiccator over P_2O_5 to insure complete dryness. The dry tosylate was then added, along with the amount of acetonitrile indicated (Table I). The bottle was closed with a screw cap and Teflon-coated septum and inserted to about half its depth in an oil bath, then heated as indicated. The bottle was then removed and cooled with cold water, after which the contents were taken up in 2 ml of ether. The ether was washed three times with 0.7 ml of water, using a pipette, and then the material was evaporated to dryness. Methanol (0.4 ml) and 0.1 ml of 0.2 N H_2SO_4 were added. The mixture was refluxed with magnetic stirring for 35 minutes. The solution was neutralized with 0.2 N $Ba(OH)_2$ and filtered using a glass fritted funnel. The solution was extracted twice with a small amount of ether. The aqueous layer evaporates under reduced pressure to about 0.2 mg of oil. The compound can be crystallized from absolute methanol-ether. However it is normally dissolved in an appropriate solvent for direct use or for chromatographic analysis.

Table I. Reaction conditions and results*†

Run	Tosylate (mg)	Molar Ratio (tos./Et_4NF)	Solvent (ml)	Temp (°C)	Reaction Time (hr)	Radiochem. Yield (%)	Total Time (min)	Radiochem. Purity (%)
1	4.2	1:2.88	0.1	160	2.5	13.0	321	91
2	4.2	1:2.88	0.1	160	2.5	8	340	85
3	3.7	1:2.63	0.08	160	2.5	11	305	81
4	4.0	1:2.78	0.06	160	2.5	15	360	92
5	3.6	1:2.5	0.06	160	2.5	13	290	96
6	2.6	1:2.57	0.04	160	2.5	14	280	60
7‡	2.2	1:2.65	0.04	170	2.0	17	260	98
8	2.0	1:2.9	0.04	160	2.5	15	285	97

*Starting activity was 5 mCi in all cases.

†In all cases after run 3, the bulk of the activity not in I was at the origin on the TLC plate (unhydrolyzed I). In earlier runs it was mainly at the solvent front ($^{18}F^-$).

‡Run 7 represents the optimum conditions.

The total synthesis takes 4-4½ hours from end of bombardment, including 1 hour for preparation of dry Et_4NF, 2 hours for the displacement, 1 hour for hydrolysis, neutralization and filtration, and 15 minutes for evaporation and final solution. The decay-corrected radiochemical yield averages 15%, so that 3-4% of the starting activity is actually present in about 0.2 mg of the final product.

REFERENCES

1. Ruben S., Hassid W.Z. and Kamen M.D. - J. Amer. Chem. Soc. 61: 661 (1939)
2. Lifton J.F. and Welch M.J. - Radiat. Res. 45: 35 (1971)
3. Straatman M.G. and Welch M.J. - Int. J. Appl. Radiat. Isotop. 24: 234 (1973)
4. Palmer A.J. and Goulding R.W. - J. Label. Compounds 10: 627 (1974)
5. Barnett J.E.G., Jarvis W.T.S. and Munday K.A. - Biochem. J. 109: 61 (1968)
6. Kent P.W. and Wright J.R. - Carbohyd. Res. 22: 193 (1972)
7. Barnett J.E.G., Holman G.D. and Munday K.A. - Biochem. J. 131: 211 (1973)
8. Shreeve W.W. - Physiological Chemistry of Carbohydrates in Mammals, Saunders, Philadelphia, 1974, p 304
9. Shreeve W.W., Shoop J.D., Ott D.G. and McInteer B.B. - J. Nucl. Med. 15: 532 (1974)
10. Taylor N.F. and Kent P.W. - J. Chem. Soc.: 872 (1958)
11. Barnett J.E.G. - Advan. Carbohyd. Chem. 22: 177 (1967) and references therein
12. Foster A.B. and Westwood J.H. - Pure and Applied Chemistry 35: 147 (1973)
13. Szarek W.A. - Advan. Carbohyd. Chem. : 225 (197) and references therein
14. Richardson A.C. - Carbohyd. Res. 10: 395 (1969)
15. Foster A.B., Hems R. and Webber J.M. - Carbohyd. Res. 5: 292 (1967)
16. Tilbury R.S., Dahl R., Mamacos J.P. and Laughlin J.S. - Int. J. Appl. Rad. Isotopes 21: 277 (1970)
17. Helferich B., Dressler H. and Griebel R. - J. prakt. Chem. 152: 285 (1939)