Carbohydrate Research, 27 (1973) 141–147

THE SYNTHESIS OF 2-ACETAMIDO-2,6-DIDEOXY-6-FLUORO-α-D-GLUCOPYRANOSE AND OF ITS PER-*O*-BENZYL AND PER-*O*-METHYL DERIVATIVES

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(Received August 30th 1972; accepted for publication, November 1st, 1972)

ABSTRACT

Benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside was mesylated selectively at position 6. Benzylation of the resulting 6-*O*-mesyl derivative gave benzyl 2-acetamido-3,4-di-*O*-benzyl-2-deoxy-6-*O*-mesyl-α-D-glucopyranoside which was treated with cesium fluoride in boiling 1,2-ethanediol to afford benzyl 2-acetamido-3,4-di-*O*-benzyl-2,6-dideoxy-6-fluoro-α-D-glucopyranoside (**8**). The benzyl groups of **8** were removed by hydrogenolysis to give 2-acetamido-2,6-dideoxy-6-fluoro-α-D-glucopyranose (**10**) with a total yield of *ca.* 15% based on the starting material 2-acetamido-2-deoxy-D-glucopyranose. The use of methyl protecting groups instead of benzyl ones appeared to be detrimental because the demethylation of methyl 2-acetamido-2,6-dideoxy-6-fluoro-3,4-di-*O*-methyl-α-D-glucopyranoside with boron trichloride gave only traces of **10**.

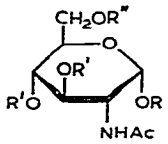
INTRODUCTION

The fluorinated carbohydrates are of interest both for the study of the mechanism of carbohydrate metabolism enzymes and as potential antitumor agents. The syntheses of fluoro derivatives of various neutral monosaccharides having significant biological activity have been reported recently (see Refs. 1, 2 and literature cited therein). The present paper reports the synthesis of the fluoro derivative of an amino sugar, 2-acetamido-2,6-dideoxy-6-fluoro-α-D-glucopyranose (**10**).

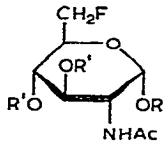
RESULTS AND DISCUSSION

2-Acetamido-2,6-dideoxy-6-fluoro-α-D-glucopyranose (**10**) was prepared by a five-stage synthesis (**1**→**2**→**3**→**4**→**8**→**10**). A mesyl group was used as a leaving group in nucleophilic substitution, whereas the benzyl groups served as protective ones in the course of the synthesis.

Benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside (**2**) was obtained from 2-acetamido-2-deoxy-D-glucose (**1**) according to a modified procedure of Gross and



1 R = R′ = R″ = H
2 R = CH_2Ph, R′ = R″ = H
3 R = CH_2Ph, R′ = H, R″ = Ms
4 R = R′ = CH_2Ph, R″ = Ms
5 R = Me, R′ = R″ = H
6 R = Me, R′ = H, R″ = Ms
7 R = R′ = Me, R″ = Ms



8 R = R′ = CH_2Ph
9 R = R′ = Me
10 R = R′ = H

Jeanloz[3]; it was found that compound **2** could be completely separated from the β anomer by a single recrystallization from 2-propanol.

Benzyl 2-acetamido-2-deoxy-6-*O*-mesyl-α-D-glucopyranoside (**3**) was the major product of the reaction[4] of a pyridine solution of **2** with a small excess of methanesulfonyl chloride at −35°.

Treatment of **3** with a 50%-molar excess of benzyl bromide in *N,N*-dimethylformamide in the presence of barium oxide and barium hydroxide afforded benzyl 2-acetamido-3,4-di-*O*-benzyl-2-deoxy-6-*O*-mesyl-α-D-glucopyranoside (**4**). Use of a greater excess of benzyl bromide led to a reduction in the yield of **4**.

Replacement of the mesyl group by a fluorine atom was achieved in high yield by a short treatment of **4** with cesium fluoride in boiling 1,2-ethanediol[5] to give benzyl 2-acetamido-3,4-di-*O*-benzyl-2,6-dideoxy-6-fluoro-α-D-glucopyranoside (**8**). Hydrogenolysis of **8** over palladium-on-charcoal in acetic acid removed smoothly the benzyl protecting groups to give 2-acetamido-2,6-dideoxy-6-fluoro-α-D-glucopyranose (**10**). The total yield of **10** based on the starting compound **1** was *ca.* 15%.

In an analogous synthesis (**5**→**6**→**7**→**9**) benzyl groups were replaced by methyl groups to afford methyl 2-acetamido-2,6-dideoxy-6-fluoro-3,4-di-*O*-methyl-α-D-glucopyranoside (**9**). However, treatment[6] of **9** with boron trichloride in dichloromethane at −70° gave a mixture of products among which only a small amount of **10** was detected by t.l.c. and paper chromatography.

The structure of the fluorinated compounds **8**, **9**, and **10** was confirmed by n.m.r. and mass-spectral data. The ^{19}F n.m.r. spectrum of **8** contained a sextet at 154.3 p.p.m. (upfield relative to the external standard trifluoroacetic acid) having coupling constants $J_{F,6} = J_{F,6'} = 47.5$ Hz and $J_{F,5}$ 29 Hz, which values are close to those reported for 6-deoxy-6-fluoro-D-glucopyranose derivatives[7].

The ^1H n.m.r. spectrum of **8** contained the signal for H-1 as a doublet (δ 5.27, $J_{1,2}$ 3.6 Hz) and the signals for protons of the CH_2F-grouping as two doublets (δ 5.02 and 4.55, $J_{5,6}$ 2.5 Hz and $J_{6,F}$ 47.5 Hz).

The ^{19}F n.m.r. spectrum of **9** was similar to that of **8** (centre of sextet at 154.9 p.p.m., coupling constants $J_{F,6} = J_{F,6'} = 48$ Hz and $J_{F,5}$ 27.5 Hz). The ^1H n.m.r. spectrum of **9** showed a three-line pattern, composed of two overlapped

doublets, δ 4.92 (due to H-1) and δ 4.95 (due to CH_2F-grouping). The position of the second doublet of the CH_2F-grouping was δ 4.47. The spectrum contained the following constants: $J_{1,2}$ 3.4 Hz, $J_{5,6}$ 2.4 Hz, and $J_{6,F}$ 48 Hz.

The ^1H n.m.r. spectrum (pyridine) of **10** showed the H-1 proton as a doublet (δ 5.86, $J_{1,2}$ 3.2 Hz) and protons of the CH_2F-grouping as two doublets (δ 5.26 and 4.78, $J_{5,6}$ 2.7 Hz and $J_{6,F}$ 48.7 Hz). A singlet for the *N*-acetyl protons was observed at δ 2.12; in the course of the mutarotation the signal at δ 2.07 caused by the formation of the β anomer of **10** appeared and increased (cf. Ref. 8). The ^1H n.m.r. spectrum as well as the changes of optical rotation during mutarotation were evidence that compound **10** is the pure α anomer.

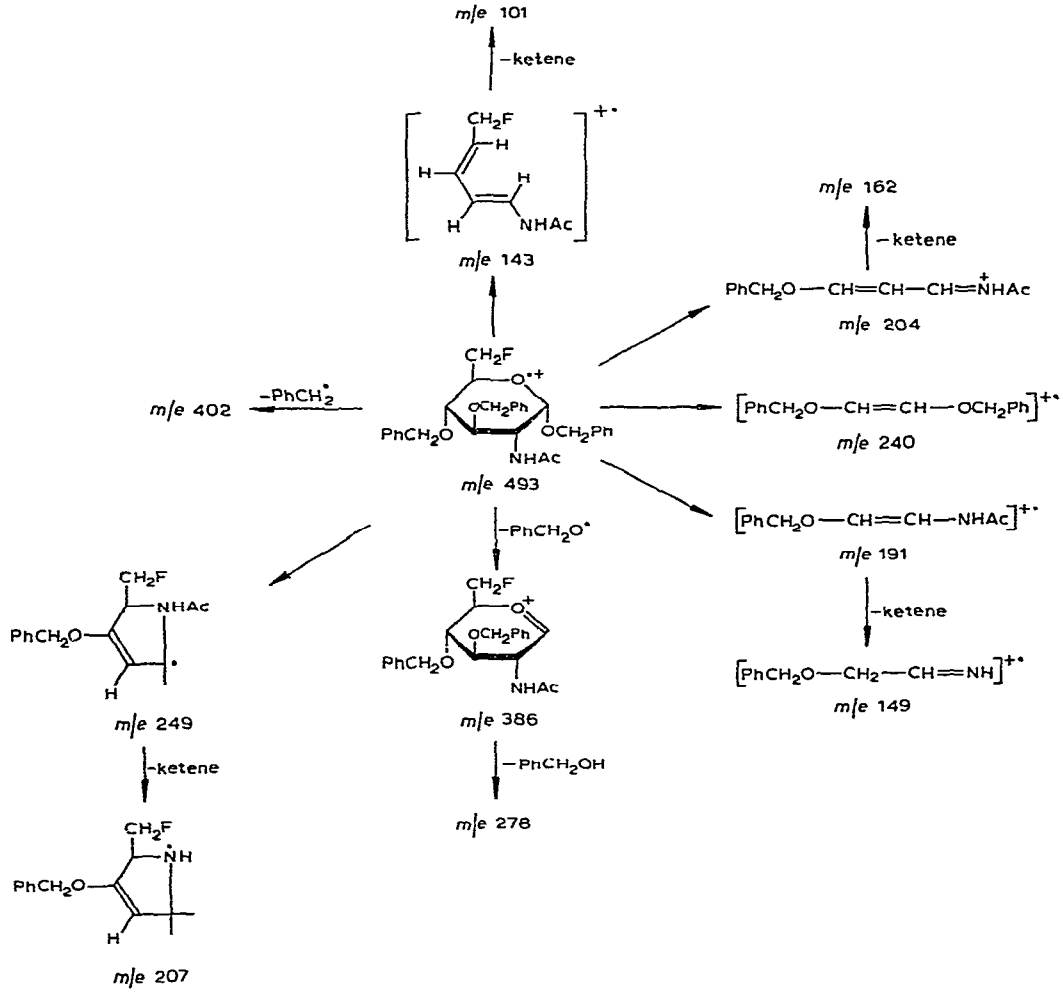


Fig. 1. Mass-spectral fragmentation pattern of benzyl 2-acetamido-3,4-di-*O*-benzyl-2,6-dideoxy-6-fluoro-α-D-glucopyranoside (**8**).

The fragmentation of **9** under electron-impact is quite similar to that of the methylated monosaccharides[9]. The mass spectrum of **9** shows peaks corresponding to the following series: A (*m/e* 234, 202, 170, and 128), B (*m/e* 203 and 172), C (*m/e* 173, 131, and 98), F and G (*m/e* 128 and 86), H (*m/e* 115 and 73), and *J* (*m/e* 75). It should be noted that the ions of the E series which arise from the cleavage of the C-5–C-6 bond are absent. This phenomenon, caused by the presence of a fluorine atom at C-6, is in accordance with previous work[10].

The characteristic feature of the fragmentation of compound **8** is the scission of a benzyl radical from a molecular ion M^+ (*m/e* 493) with the formation of a corresponding fragment (*m/e* 402). The fragmentation of M^+ seems to be similar to that of **9** since a scission of the benzyloxy radical, benzyl alcohol, and ketene, and also cleavage of the monosaccharide ring takes place (Fig. 1).

EXPERIMENTAL

General methods. — T.l.c. was performed on Silica Gel KSK (<300 mesh) containing 5% of gypsum with chloroform–methanol, 99.1 (A), 97:3 (B), 9:1 (C) and 4:1 (D); the spots were revealed by conc. sulfuric acid at 100–120°. Column chromatography was performed on Silica Gel KSK (75–100 mesh); the ratio of weight of substance to weight of adsorbent was 1:100 and the ratio of diameter to length of columns was 1:25. Paper chromatography was performed on Whatman No. 1 paper with 4:1:1 butyl alcohol–acetic acid–water (E), and detection with acid aniline phthalate. Solutions were evaporated *in vacuo* at a bath temperature below 45°. Melting points were determined with a Boëtius apparatus with a velocity of heating of 4°/min and are corrected. Optical rotations were determined with a Perkin–Elmer Model 141 polarimeter. I.r. spectra were recorded, for potassium bromide discs, with a Perkin–Elmer Model 257 spectrophotometer. P.m.r. spectra were recorded at 100 MHz with a JEOL JNM-4H-100 spectrometer, for solutions in pyridine-d_5 with tetramethylsilane as internal standard. ^{19}F N.m.r. spectra were recorded at 56.46 MHz with a Hitachi–Perkin–Elmer Model R-20 spectrometer, for solutions in chloroform-*d* with trifluoroacetic acid as external standard. Mass spectra were recorded with a LKB Model 9000 spectrometer at 70 eV and a source temperature of 120°.

Benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside (**2**). — A suspension of 2-acetamido-2-deoxy-D-glucose (**1**, 20 g) in a solution of hydrogen chloride (4 g) in benzyl alcohol (200 ml) was stirred for 4 h at 75°. The solution was cooled and poured into ether (1.5 l) with stirring. The mixture was kept overnight at 5° and filtered. The precipitate was washed with ether, dissolved in hot 2-propanol (200 ml), and the hot solution filtered and kept for 16 h at room temperature. The crystalline precipitate was filtered off, washed with a small amount of 2-propanol and ether, and dried to give **2** (18.2 g, 64%), m.p. 185–186°, $[\alpha]_D^{20}$ +168° (*c* 0.2, water) (*cf.* Ref. 3).

Benzyl 2-acetamido-2-deoxy-6-O-mesyl-α-D-glucopyranoside (**3**). — A solution of mesyl chloride (2.52 g, 22 mmoles) in dry pyridine (15 ml) was added dropwise to a

stirred solution of **2** (6.22 g, 20 mmoles) in dry pyridine (50 ml) for 1 h at −35°. The solution was stirred for 4 h at −35°, kept overnight at −10°, filtered, and evaporated to give a residue which was chromatographed on silica gel with Solvent C. Crystallisation of the eluted syrup from methanol–ether gave 5.56 g (71%) of **3**, m.p. 157–158° (dec.), $[\alpha]_D^{20}$ +156° (*c* 1.0, methanol); i.r. data: ν_{max}^{KBr} 1185, 1355 (SO_2), 1560 (amide II), 1625, 1650 (amide I, splitting caused by hydrogen bond), 3340 in broad band 3200–3600 cm^{-1} (OH and NH); t.l.c.: R_F 0.4 (Solvent C).

Anal. Calc. for $C_{16}H_{23}NO_8S$: C, 49.35; H, 5.95; S, 8.2%. Found: C, 49.3; H, 5.9; S, 8.0.

*Benzyl 2-acetamido-3,4-di-*O*-benzyl-2-deoxy-6-*O*-mesyl-α-*D*-glucopyranoside* (**4**). — Barium oxide (8 g) and barium hydroxide octahydrate (2 g) were added to a solution of **3** (3.89 g, 10 mmoles) and benzyl bromide (5.13 g, 30 mmoles) in *N*,*N*-dimethylformamide (35 ml) at 0°. The suspension was stirred for 1 h at 0°, and then for 24 h at 20°, diluted with chloroform (600 ml), filtered, washed with water (3 × 100 ml), and evaporated. The residue was chromatographed on silica gel with an increasing concentration of ether in light petroleum (1.5 l), and then with Solvent A (1 l). The syrup was crystallized from chloroform–ether to give **4** (3.08 g, 54%), m.p. 177–179°, $[\alpha]_D^{20}$ +109° (*c* 1.0, chloroform); i.r. data: ν_{max}^{KBr} 1180, 1350 (SO_2), 1560 (amide II), 1660 (amide I), 3310 cm^{-1} (NH); t.l.c.: R_F 0.3 (Solvent A)

Anal. Calc. for $C_{30}H_{35}NO_8S$: C, 63.25; H, 6.2; S, 5.6%. Found: C, 63.3; H, 6.2; S, 5.8.

*Benzyl 2-acetamido-3,4-di-*O*-benzyl-2,6-dideoxy-6-fluoro-α-*D*-glucopyranoside* (**8**). — The mesyl derivative **4** (2.85 g) was dissolved in a boiling solution of cesium fluoride (14 g) in dry 1,2-ethanediol (50 ml), and the resulting solution was boiled under reflux for 2 min, cooled, poured into water (150 ml), and extracted with chloroform (3 × 100 ml). The solution was evaporated and the residue chromatographed on silica gel with 1:1 chloroform–light petroleum (500 ml) and chloroform (1 l). A fraction was obtained that crystallized from chloroform–ether to give 1.8 g (73%) of **8**, m.p. 204–205°, $[\alpha]_D^{20}$ +108° (*c* 1.0, chloroform); i.r. data: ν_{max}^{KBr} 1560 (amide II), 1660 (amide I), 3305 cm^{-1} (NH); t.l.c.: R_F 0.47 (Solvent A); the n.m.r. data are reported in the Discussion; m.s. (% intensity based on *m/e* 143): *m/e* 28 (22), 43 (25), 65 (17), 91 (>100), 92 (42), 101 (28), 120 (8), 126 (4), 129 (11), 130 (14), 138 (4), 143 (100), 144 (12), 145 (8), 146 (9), 148 (4), 149 (4), 150 (4), 158 (8), 162 (13), 163 (6), 171 (11), 172 (50), 173 (14), 174 (4), 179 (5), 181 (16), 188 (14), 190 (4), 191 (7), 192 (3), 204 (24), 205 (5), 206 (4), 207 (2), 222 (3), 240 (16), 241 (3), 248 (3), 249 (4), 250 (2), 278 (5), 279 (39), 280 (29), 281 (10), 282 (11), 294 (8), 296 (24), 297 (5), 310 (2), 360 (2), 374 (5), 386 (2), 387 (5), 402 (26), 403 (8), 404 (1), 430 (0.4), 450 (0.3), 476 (0.2), 493 (0.3), 494 (1.2), 495 (0.4).

Anal. Calc. for $C_{29}H_{32}FNO_5$: C, 70.6; H, 6.5; F, 3.85; N, 2.8% Found: C, 70.2; H, 6.5; F, 3.9; N, 2.9.

*2-Acetamido-2,6-dideoxy-6-fluoro-α-*D*-glucopyranose* (**10**). — Compound **8** (493 mg) was hydrogenolyzed in acetic acid (30 ml) in the presence of 20% palladium-on-charcoal (1 g) for 16 h. The reaction mixture was filtered and evaporated, and

toluene was repeatedly added to and distilled from the residue to remove traces of acetic acid. The residue (220 mg, 98%) showed one spot on t.l.c. in Solvent D, and was crystallized from methanol–ether, m.p. 209–210° (dec.), $[\alpha]_D^{20}$ +64° (after 2 min)→ +33° (equilibrium after 16 h; *c* 1.0, water); i.r. data: ν_{max}^{KBr} 1560 (amide II), 1640 (amide I), 3330 in broad band 3200–3600 cm^{-1} (OH and NH); t.l.c.: R_F 0.3 (Solvent D); p.c.: R_1 1.74 (Solvent E); the n.m.r. data are reported in the Discussion.

The chloro and bromo analogs of **10** show R_1 2.04 and 2.14, respectively, in the same solvent system[8].

Anal. Calc. for $C_8H_{14}FNO_5$: C, 43.0; H, 6.3; F, 8.5; N, 6.3%. Found: C, 42.9; H, 6.3; F, 8.1; N, 6.2.

*Methyl 2-acetamido-2-deoxy-6-*O*-mesyl-α-*D*-glucopyranoside* (**6**). — Methyl 2-acetamido-2-deoxy-α-D-glucopyranoside[11] was mesylated, as described for **2**, to give compound **6** in a yield of 68%, m.p. 153–153.5° (dec.) after recrystallization from methanol–ether, $[\alpha]_D^{20}$ +120° (*c* 0.5, methanol); i.r. data: ν_{max}^{KBr} 1180, 1330 (SO_2), 1560 (amide II), 1660 (amide I), 3320 in broad band 3200–3600 cm^{-1} (OH and NH); t.l.c.: R_F 0.25 (Solvent C).

Anal. Calc. for $C_{10}H_{19}NO_8S$: C, 38.3; H, 6.1; S, 10.2%. Found: C, 38.0; H, 6.3; S, 10.2.

*Methyl 2-acetamido-2-deoxy-6-*O*-mesyl-3,4-di-*O*-methyl-α-*D*-glucopyranoside* (**7**). — Barium oxide (6 g) and barium hydroxide octahydrate (2 g) were added to a solution of **6** (3.13 g) and methyl iodide (12 ml) in *N*,*N*-dimethylformamide (50 ml), and stirred for 20 h. The suspension was treated with chloroform (700 ml) and sodium thiosulfate solution (*ca.* 50 ml), and filtered. The organic layer was separated, washed with water (3 × 100 ml), and evaporated. The residue was chromatographed on silica gel with Solvent B and crystallized from chloroform–ether to yield **7** (2.12 g, 62%), m.p. 180–181°, $[\alpha]_D^{20}$ +117° (*c* 0.5, chloroform); i.r. data: ν_{max}^{KBr} 1185, 1350 (SO_2), 1560 (amide II), 1650 (amide I), 2845 (C-H in OMe), 3315 cm^{-1} (NH); t.l.c.: R_F 0.35 (Solvent B).

Anal. Calc. for $C_{12}H_{23}NO_8S$: C, 42.2; H, 6.8; N, 4.1; S, 9.4%. Found: C, 42.3; H, 7.0; N, 3.8; S, 9.3.

*Methyl 2-acetamido-2,6-dideoxy-6-fluoro-3,4-di-*O*-methyl-α-*D*-glucopyranoside* (**9**). — Mesyl derivative **7** was treated with cesium fluoride in boiling 1,2-ethanediol, as described for **4**, to give **9** in a yield of 70%; it was recrystallized from methanol–ether, m.p. (in sealed capillary, sublimation) 203–204°, $[\alpha]_D^{20}$ +127° (*c* 0.5, chloroform) i.r. data: ν_{max}^{KBr} 1570 (amide II), 1650 (amide I), 2845 (C-H in OMe), 3305 cm^{-1} (NH); t.l.c.: R_F 0.43 (Solvent B); the n.m.r. data are reported in the Discussion; m.s. (% intensity based on *m/e* 73): *m/e* 15 (4), 28 (9), 29 (5), 41 (5), 43 (23), 45 (10), 58 (12), 71 (5), 73 (100), 75 (27), 84 (4), 86 (19), 88 (17), 89 (6), 90 (12), 98 (5), 101 (7), 115 (71), 116 (7), 117 (11), 128 (75), 129 (7), 130 (3), 131 (3), 143 (7), 160 (7), 170 (2), 172 (2), 173 (9), 201 (2), 202 (11), 203 (5), 206 (2), 234 (2), 250 (0.1), 265 (0.2), 266 (0.2).

Anal. Calc. for $C_{11}H_{20}FNO_5$: C, 49.8; H, 7.6; F, 7.2; N, 5.3%. Found: C, 50.2; H, 8.0; F, 6.9; N, 5.2.

ACKNOWLEDGEMENTS

The authors are indebted to Dr. L. S. Golovkina, Dr. S. L. Portnova and Dr. L. B. Senyavina for their help and for useful discussions.

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