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Note

A facile synthesis of 2-acetamido-2-deoxy-5-thio-D-glucopyranose*

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In our continuing work on the synthesis and the biological activity of 2-acetamido-2-deoxyhexopyranoses having sulfur replacing the ring-oxygen atom, we had need for a substantial quantity of 2-acetamido-2-deoxy-5-thio-D-glucopyranose. In earlier work[2,3], this sugar was synthesized from methyl 2-acetamido-2-deoxy-5,6-*O*-isopropylidene-β-D-glucopyranoside[4] or ethyl 2-acetamido-2-deoxy-1-thio-α-D-glucofuranoside[5] by a rather long and low-yielding route. The present report describes a facile synthesis of it that uses 2-acetamido-2-deoxy-3,4-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal[6] (**1**), which is readily prepared in high yield from 2-acetamido-2-deoxy-D-glucose.

Selective benzoylation of the primary hydroxyl group on C-6 in **1** with benzoyl chloride in pyridine at −20° afforded the 6-benzoate (**2**) in 88% yield, and **2** was mesylated with methanesulfonyl chloride, to give the 5-*O*-mesyl derivative (**3**) in 96% yield. Compound **3** in dry chloroform was treated with methanolic sodium methoxide to afford 2-acetamido-5,6-anhydro-2-deoxy-3,4-*O*-isopropylidene-*aldehydo*-L-idose dimethyl acetal (**4**) in 90% yield, and **4** was treated with thiourea for 1.5 h at 60° to give crystalline 2-acetamido-2,5,6-trideoxy-5,6-epithio-3,4-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (**5**) in 96% yield. Nucleophilic ring-opening of compound **5** with potassium acetate in acetic acid–acetic anhydride by refluxing for 15 h yielded 2-acetamido-6-*O*-acetyl-5-*S*-acetyl-2-deoxy-3,4-*O*-isopropylidene-5-thio-*aldehydo*-D-glucose dimethyl acetal (**6**) in 85% yield, whose i.r. and n.m.r. spectra showed the characteristic, *S*-acyl absorptions at ν 1700 cm^{-1} and at δ 2.37, respectively. Hydrolysis of **6** in 10:1 acetic acid–2M hydrochloric acid for 6 h at 40°, and subsequent acetylation, yielded crystalline 2-acetamido-1,3,4,6-tetra-*O*-acetyl-5-*S*-acetyl-2-deoxy-5-thio-α-D-glucopyranose (**7**) in 75% yield; this was converted into the title compound **8** (92%) by Zemplén *O*-deacetylation.

*Studies on Hetero Sugars, Part VII. For Part VI, see ref. 1
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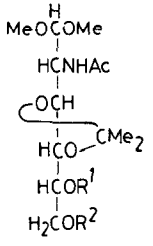
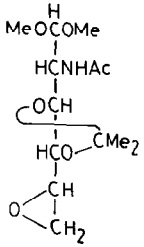


1 $R^1 = R^2 = H$
2 $R^1 = H$, $R^2 = Bz$
3 $R^1 = Ms$, $R^2 = Bz$

Ac = MeCO
Bz = PhCO
Ms = $MeSO_2$



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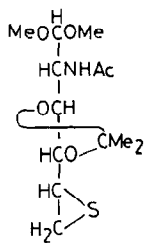

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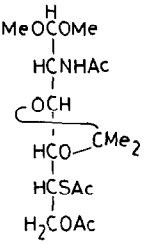

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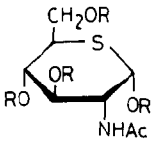

7 R = Ac
8 R = H

EXPERIMENTAL

General methods. — Melting points were determined with a Yanagimoto micro melting-point apparatus and are uncorrected. Specific rotations were determined at 25° with a Union PM-201 polarimeter, and i.r. spectra were recorded with a Jasco IRA-1 spectrophotometer. Preparative chromatography was performed on silica gel (Waco Co.; 200 mesh) with the solvent systems specified. Evaporations were conducted *in vacuo*. ^{1}H-N.m.r. spectra were recorded at 90 MHz with a Hitachi R-22 spectrometer, and were confirmed by use of decoupling techniques. The ^{13}C-N.m.r. spectrum was recorded with a Jeol FX-100 spectrometer operated at 25.05 MHz.

2-Acetamido-6-O-benzoyl-2-deoxy-3,4-O-isopropylidene-aldehydo-D-*glucose dimethyl acetal* (**2**). — To a stirred solution of 2-acetamido-2-deoxy-3,4-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal[6] (**1**; 3.0 g) in dry pyridine (12 mL) was added benzoyl chloride (1.36 mL) at −20°. The mixture was stirred for 6 h at −10 to −5°, and then extracted with chloroform. The extract was successively washed with 2M hydrochloric acid, M sodium carbonate, and water, dried (sodium sulfate), and evaporated. The product was purified by chromatography on a column of silica gel (60 g) with chloroform and then 70:1 chloroform–methanol. The latter eluate gave **2** (3.52 g, 88%) as needles; m.p. 125°, $[\alpha]_D$ +45° (*c* 0.2, methanol); ν_{max}^{Nujol} 3350–3250 (OH, NH), 1710 and 1285 (ester), 1620 and 1555 (amide), 890 (Me_2C), and 720 cm^{-1} (phenyl); ^{1}H-n.m.r. data (in chloroform-*d*): δ 1.34 (s, 6 H, Me_2C), 2.03 (s, 3 H, AcN), 3.26, 3.36 (2 s, 6 H, 2 MeO), 6.64 (d, 1 H, $J_{2,NH}$ 8.0 Hz, NH), and 7.28–8.20 (m, 5 H, Ph).

Anal. Calc. for $C_{20}H_{29}NO_8$: C, 58.38, H, 7.10; N, 3.40. Found: C, 58.29; H, 7.12; N, 3.36.

*2-Acetamido-6-O-benzoyl-2-deoxy-3,4-O-isopropylidene-5-O-mesyl-*aldehydo-D-*glucose dimethyl acetal* (**3**). — To an ice-cooled solution of **2** (14 g) in dry pyridine (30 mL) was added methanesulfonyl chloride (5.4 g), and the mixture was kept for 12 h at 0°, evaporated, the residue extracted with chloroform, and the extract successively washed with 2M hydrochloric acid, M sodium carbonate, and water, dried (sodium sulfate), and evaporated to a syrup. The product was purified by chromatography on a column of silica gel (250 g) with chloroform and then 80:1 chloroform–methanol. The latter eluate afforded **4** as a syrup (16 g, 96%); $[\alpha]_D$ +31° (*c* 1.0, methanol); ν_{max}^{film} 3360 (NH), 1720 and 1270 (ester), 1650 and 1520 (amide), 1180 (SO_2), 870 (Me_2C), and 750 and 710 cm^{-1} (phenyl); ^{1}H-n.m.r. data (in chloroform-*d*): δ 1.42 (s, 6 H, Me_2C), 2.04 (s, 3 H, AcN), 3.15 (s, 3 H, MeS), 3.29, 3.40 (2 s, 6 H, 2 MeO), 4.01 (dd, 1 H, $J_{3,4}$ 8.0, $J_{4,5}$ 5.5 Hz, H-4), 5.11 (m, 1 H, H-5), 6.33 (d, 1 H, $J_{2,NH}$ 9.0 Hz, NH), and 7.31–8.20 (m, 5 H, Ph).

Anal. Calc. for $C_{21}H_{31}NO_{10}S$: C, 51.52; H, 6.38; N, 2.86. Found: C, 51.28; H, 6.49; N, 2.58.

*2-Acetamido-5,6-anhydro-2-deoxy-3,4-*O-*isopropylidene-*aldehydo-L-*idose dimethyl acetal* (**4**). — To a cooled solution of **3** (1.22 g) in chloroform (12 mL) at −20° was added, with stirring, sodium methoxide in methanol (100 mg of sodium in 4 mL of methanol). The mixture was stirred for 5 h below 0°. Methanol (20 mL) was added to the mixture, which was then treated with Amberlite IR-120 (H^+) and Amberlite IR-45 (OH^-) ion-exchange resins; the resins were filtered off, and washed with methanol. The filtrate and washings were combined, and evaporated. The residue was chromatographed on a column of silica gel (20 g) with chloroform and then 80:1 chloroform–methanol. The latter eluate gave **4** (650 mg, 90%). Recrystallization from ether-hexane gave prisms; m.p. 95°, $[\alpha]_D$ +15.5° (*c* 1.0, methanol); ν_{max}^{Nujol} 3240 (NH), 1630 and 1540 (amide), and 870 cm^{-1} (Me_2C); ^{1}H-n.m.r. data (in chloroform-*d*): δ 1.39 (s, 6 H, Me_2C), 2.01 (s, 3 H, AcN), 2.68–3.15 (m, 3 H, H-5,6,6'), 3.30, 3.42 (2 s, 6 H, 2 MeO), and 6.20 (d, 1 H, $J_{2,NH}$ 9.0 Hz, NH).

Anal. Calc. for $C_{13}H_{23}NO_6$: C, 53.96; H, 8.01; N, 4.84. Found: C, 53.83; H, 8.01; N, 4.85.

*2-Acetamido-2,5,6-trideoxy-5,6-epithio-3,4-*O-*isopropylidene-*aldehydo-D-*glucose dimethyl acetal* (**5**). — To a solution of **4** (1.4 g) in methanol (30 mL) was added thiourea (1.1 g), and the mixture was heated, with stirring, for 1.5 h at 60°, cooled and evaporated. The residue was chromatographed on a column of silica gel (20 g) with chloroform and then 80:1 chloroform–methanol. From the latter eluate was obtained compound **5** (1.42 g, 96%) as needles; m.p. 97°, $[\alpha]_D$ +12.5° (*c* 1.0, methanol); ν_{max}^{Nujol} 3220 (NH), 1630 and 1540 (amide), and 870 cm^{-1} (Me_2C); ^{1}H-n.m.r. data (in chloroform-*d*): δ 1.43, 1.47 (2 s, 6 H, Me_2C), 2.02 (s, 3 H, AcN), 2.29, 2.56 (2 dd, 2 H, $J_{5,6} = J_{5,6'} = 5.0$, $J_{6,6'}$ 2.0 Hz, H-6,6'), 2.91 (m, 1 H, H-5), 3.40, 3.45 (2 s, 6 H, 2 MeO), and 5.87 (broad s, 1 H, NH).

Anal. Calc. for $C_{13}H_{23}NO_5S$: C, 51.12; H, 7.59; N, 4.59. Found: C, 51.06; H, 7.59; N, 4.53.

2-Acetamido-6-O-acetyl-5-S-acetyl-2-deoxy-3,4-O-isopropylidene-5-thio-aldehydo-D-*glucose dimethyl acetal* (**6**). — A mixture of **5** (200 mg), potassium acetate (300 mg), acetic acid (1 mL), and acetic anhydride (10 mL) was boiled under reflux, with stirring, for 15 h, cooled, and evaporated. The residue was extracted with chloroform, and the extract successively washed with 2M hydrochloric acid, M sodium carbonate, and water, dried (sodium sulfate), and evaporated to a syrup. The product was purified by chromatography on a column of silica gel (10 g) with chloroform and then 70:1 chloroform–methanol. The latter eluate yielded **6** (230 mg, 85%) as crystals. Recrystallization from ether–hexane gave needles, m.p. 111°, $[\alpha]_D$ +9.5° (*c* 0.47, methanol); ν_{max}^{Nujol} 3220 (NH), 1740 and 1225 (ester), 1700 (AcS), and 1630 and 1560 cm^{-1} (amide); ^{1}H-n.m.r. data (in chloroform-*d*): δ 1.34 (s, 6 H, Me_2C), 2.02 (s, 3 H, AcN), 2.05 (s, 3 H, AcO), 2.37 (s, 3 H, AcS), 3.32, 3.39 (2 s, 6 H, 2 MeO), and 5.82 (broad s, 1 H, NH).

Anal. Calc. for $C_{17}H_{29}NO_8S$: C, 50.11; H, 7.17; N, 3.44. Found: C, 50.21; H, 7.26; N, 3.40.

*2-Acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-5-thio-α-*D*-glucopyranose* (**7**). — A solution of **6** (1.0 g) in 10:1 acetic acid–2M hydrochloric acid (30 mL) was heated for 6 h at 40°, cooled, and treated with Amberlite IR-45 (OH^-) resin; the resin was filtered off, and washed with methanol. The filtrate and washings were combined, and evaporated. The residue was acetylated with acetic anhydride (5 mL)–pyridine (10 mL) overnight at 0°. The product was purified by passage through a column of silica gel (20 g) with chloroform and then 150:1 chloroform–methanol. The latter eluate afforded **7** (750 mg, 75%) as needles; m.p. 166–167°, $[\alpha]_D$ +179° (*c* 0.5, chloroform) (lit.[7] m.p. 166–167°, $[\alpha]_D^{25}$ +178.5°).

*2-Acetamido-2-deoxy-5-thio-α-*D*-glucopyranose* (**8**). — To an ice-cooled solution of **7** (500 mg) in methanol (20 mL) was added sodium methoxide (10 mg), and the mixture was kept for 30 min at 0°, and then treated with Amberlite IRC-50 (H^+) resin to remove the base; the resin was filtered off, and washed with methanol. The filtrate and washings were combined, and evaporated, whereupon the residue crystallized. Recrystallization from ethanol gave **8** (270 mg, 92%) as needles; m.p. 152–163°, $[\alpha]_D$ +140.9 (initial)→141.0° (20 h; *c* 0.2, methanol) (lit.[3] m.p. 115–117°, $[\alpha]_D^{23}$ +88°); ^{13}C-n.m.r. data (in D_2O; Me_4Si): δ 22.8 (Me), 44.0 (C-5), 59.1 (C-2), 61.1 (C-6), 72.4, 72.6 (C-3,4), and 74.9 (C-1).

Anal. Calc. for $C_8H_{15}NO_5S$: C, 40.49; H, 6.37; N, 5.90. Found: C, 40.68; H, 6.34; N, 5.91.

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