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STEREOSELECTIVE HYDROGENATION OF METHYL DIDEOXY- AND TRIDEOXY-β-D-HEX-5-ENOPYRANOSIDES

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ABSTRACT

Hydrogenation, severally, of methyl 3-azido-2,3,6-trideoxy-β-D-*erythro*-hex-5-enopyranoside, its 3-benzamido analogue, and methyl 2,6-dideoxy-β-D-*threo*-hex-5-enopyranoside in the presence of palladium-on-barium sulphate gave the corresponding 6-deoxy-β-D-hexopyranoside derivatives. Stereoselective addition of hydrogen was observed in each case. Methyl 2,6-dideoxy-β-D-*arabino*-hexopyranoside was also prepared by reductive dehalogenation of methyl 3,4-di-*O*-benzoyl-6-bromo-2,6-dideoxy-β-D-*arabino*-hexopyranoside.

INTRODUCTION

In connection with the synthesis of rare 2,6-dideoxy and 3-amino-2,3,6-trideoxy sugars[1], carbohydrate constituents of various antibiotics, the hydrogenation of methyl 2,6-dideoxy- and 3-azido-(amino or acetamido)-2,3,6-trideoxy-D-hex-5-enopyranoside derivatives has been reported.

Of the foregoing methyl α-hex-5-enopyranosides, those with D-*erythro*[2–5] or D-*threo*[6,7] configuration were transformed selectively, or mainly, into the corresponding methyl 6-deoxy-β-L-*lyxo* or -β-L-*xylo* analogues, respectively. Similarly, L sugars were obtained from several methyl 6-deoxy-α-D-*xylo*-hex-5-enopyranosides*[8,9], whereas the hydrogenation of the β anomers of the latter compounds[9,10] or of 1-*O*-acetyl-6-deoxy-β-D-*xylo*-hex-5-enopyranoses[11,12] gave mainly** products of the D series. Presumably the direction of the hydrogen addition to the C-5 *exo*-methylene group is determined by the configuration of the glycosidic centre[4,8].

*Apparently the only exception was reported by Brockhaus *et al.*[10] who obtained 82% of methyl 4-acetamido-2,3-di-*O*-acetyl-4,6-dideoxy-α-D-glucopyranoside by hydrogenation of methyl 4-acetamido-2,3-di-*O*-acetyl-4,6-dideoxy-α-D-*xylo*-hex-5-enopyranoside.

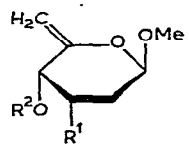
**Descotes *et al.*[9] reported that addition of hydrogen to methyl 2,3,4-tri-*O*-acetyl-β-L-*arabino*-hex-5-enopyranoside gave a 1:1 mixture of the corresponding 6-deoxy-β-L-altro- and -α-D-galacto-pyranoside derivatives.

Analogous reduction of methyl 2,6-dideoxy-3-*O*-methyl-β-D-*erythro*-hex-5-enopyranoside, the only representative[4] of the 2,6-dideoxy-β-series, gave[4] a 3:1 mixture of methyl 2,6-dideoxy-3-*O*-methyl-β-D-*ribo*- and -α-L-*lyxo*-hexopyranoside.

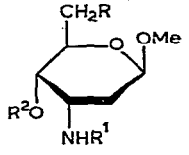
We now report on the hydrogenation of three new methyl di- and tri-deoxy-β-D-hex-5-enopyranoside derivatives (**2**, **7**, and **11**) prepared from the intermediates used for the synthesis[13,14] of D-ristosamine (3-amino-2,3,6-trideoxy-D-*ribo*-hexopyranose).

RESULTS AND DISCUSSION

Hydrogenation of methyl 3-azido-2,3,6-trideoxy-β-D-*erythro*-hex-5-enopyranoside (**2**), obtained from the corresponding 4-benzoate[14] (**1**), in the presence of palladium-on-barium sulphate gave a chromatographically homogeneous product. Mild, acid hydrolysis of this product gave[14] D-ristosamine contaminated with <5% of the C-5 epimeric L-*lyxo* compound (L-daunosamine[15]).



1 R^1 = N_3, R^2 = Bz
2 R^1 = N_3, R^2 = H
6 R^1 = NHBz, R^2 = Bz
7 R^1 = NHBz, R^2 = H



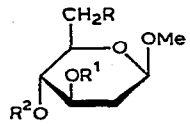
3 R = H, R^1 = R^2 = Bz
4 R = Br, R^1 = Bz, R^2 = H
5 R = Br, R^1 = R^2 = Bz
8 R = H, R^1 = Bz, R^2 = H

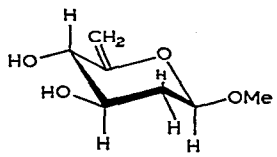
In a parallel experiment, the product of the hydrogenation was benzoylated to give 92% of crystalline methyl 3-benzamido-4-*O*-benzoyl-2,3,6-trideoxy-β-D-*ribo*-hexopyranoside (**3**), the physical constants and spectral data of which were identical with those of methyl *N*,*O*-dibenzoyl-β-D-ristosaminide[13,14].

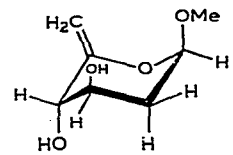
Conversion of methyl 3-benzamido-6-bromo-2,3,6-trideoxy-β-D-*ribo*-hexopyranoside[14,16] (**4**) into the 4-benzoate, followed by treatment with silver fluoride in dry pyridine[2], furnished methyl 3-benzamido-4-*O*-benzoyl-2,3,6-trideoxy-β-D-*erythro*-hex-5-enopyranoside (**6**). Saponification of **6** and hydrogenation of the product **7** in the presence of palladium-on-barium sulphate gave a nearly quantitative yield of methyl 3-benzamido-2,3,6-trideoxy-β-D-*ribo*-hexopyranoside (**8**). The physical data and ^{1}H-n.m.r. spectrum of **8** were identical with those of methyl *N*-benzoyl-β-D-ristosaminide[13,14].

Methyl 2,6-dideoxy-β-D-*threo*-hex-5-enopyranoside (**11**) was synthesised as follows. Methyl 4,6-*O*-benzylidene-2-deoxy-β-D-*arabino*-hexopyranoside, prepared[13,14] from 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol, was converted into the 3-benzoate (**9**) which, with *N*-bromosuccinimide[17], gave methyl 3,4-di-*O*-benzoyl-6-bromo-2,6-dideoxy-β-D-*arabino*-hexopyranoside (**10**). Treatment of **10** with silver fluoride in pyridine, followed by Zemplén debenzoylation, gave methyl 2,6-dideoxy-β-D-*threo*-hex-5-enopyranoside (**11**) in good yield. Hydrogenation of **11**

in the presence of palladium-on-barium sulphate afforded optically pure methyl 2,6-dideoxy-β-D-*arabino*-hexopyranoside (**12**, methyl β-D-chromoside C^{18}) in nearly quantitative yield.







10 R = Br, $R^1 = R^2$ = Bz

12 R = $R^1 = R^2$ = H

11

The above examples demonstrate that addition of hydrogen to the exocyclic double-bond of **2**, **7**, and **11** occurred stereoselectively to give the corresponding 6-deoxy analogues of the D series. These results agree with the findings for several hex-5-enopyranosides of the β-D-*xylo* series[9,11,12].

Compound **12** was prepared also from **10** by hydrogenation in the presence of Raney nickel and subsequent debenzoylation. The physical data of **12** obtained from **10** or **11** were in good agreement with those given[19] for the enantiomer.

Methyl 2,6-dideoxy-α-D-*arabino*-hexopyranoside (methyl α-D-chromoside C^{18}) has been synthesised[20] from the α anomer of **10** by reductive dehalogenation.

The observed $J_{2e,4e}$ couplings (0.5–1.0 Hz) in the ^{1}H-n.m.r. spectra of **1**, **2**, **6**, and **7** (Table I) indicate that the $^1C_4$(D) conformation is favoured. The values of $J_{1,2a}$, $J_{2a,3}$, and $J_{3,4}$ (6.8, 8.8, and 7.8 Hz, respectively) for **11** indicate a $^4C_1$(D) ⇌ $^1C_4$(D) equilibrium.

TABLE I

^{1}H-N.M.R. DATA FOR COMPOUNDS **1**, **2**, **6**, **7**, **10**, AND **11**

Compound	*Solvent*	*Chemical shifts (δ)*								
		H-1	*H-2e*	*H-2a*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	*Others*
1	$CDCl_3$	5.03	2.09	2.42	3.88	5.77	—	4.83	4.79	OCH_3 3.42
2	$CDCl_3$	4.95	1.95	2.34	3.87	4.31	—	4.68	4.62	OCH_3 3.41, O*H* 2.65
6	$CDCl_3$	~5	2.12	2.40	~5	5.81	—	4.82		OCH_3 3.44, N*H* 6.61
7	$(CD_3)_2CO$	4.91	1.82	2.32	4.60	4.30	—	4.50	4.48	OCH_3 3.37, O*H* 2.98
10	$CDCl_3$	4.66	2.59	1.92		← 5.26–5.51 →				OCH_3 3.57
11	CD_3OD	4.63	2.28	1.70	3.60	3.91	—	4.69	4.65	OCH_3 3.47

Compound	*J values (Hz)*							
	$J_{1,2e}$	$J_{1,2a}$	$J_{2e,3}$	$J_{2a,3}$	$J_{2e,2a}$	$J_{2e,4e}$	$J_{3,4}$	*Others*
1	3.4	2.0	4.8	11.8	13.2	1.0	3.5	
2	2.5	3.4	4.6	11.2	13.1	1.0	3.2	
6	~2	3.3	4.8	12.5	13.1	0.5	~3	
7	~2	3.5	4.4	12.2	12.5	~1	~3	
10	1.8	9.5	4.7	11.3	13.0	—	—	
11	3.0	6.8	4.9	8.8	13.5	—	7.8	$J_{4,6} \approx J_{4',6'} \sim 1.5$

EXPERIMENTAL

General methods. — Melting points were determined on a Kofler hot-stage and are uncorrected. Optical rotations were measured with Schmidt–Haensch and Perkin–Elmer 241 polarimeters. ^{1}H-N.m.r. spectra (100 MHz) were recorded with a JEOL MH-100 instrument (internal Me_4Si). Mass spectra were recorded with an AEI MS-902 spectrometer. T.l.c. and column chromatography were performed on Kieselgel G (Merck) with *A*, benzene–methanol (85:15); and *B*, benzene–ethanol (99:1). Concentrations were carried out under diminished pressure at 40°.

*Methyl 3-azido-2,3,6-trideoxy-β-*D-erythro-*hex-5-enopyranoside* (**2**). — To a solution of **1**[14] (190 mg) in methanol (5 ml) was added 0.1M methanolic sodium methoxide (0.2 ml). After standing at room temperature for 24 h, the solution was neutralised with AG 50W-X12(H^+) resin and concentrated. The syrupy residue was extracted with light petroleum (4 × 3 ml) and then dried to constant weight, to give syrupy **2** (101 mg, 83%), $[\alpha]_D^{25}$ −54.5° (*c* 0.66, chloroform), R_F 0.52 (solvent *A*). Mass spectrum: *m/e* 186 (1.5%, M + 1), 185.080 (2, M^+; calc. 185.180), 154 (10), 153 (20), 142 (3), 126 (2), 110 (4), 100 (10), 96 (80), 84 (50), 75 (15), 69 (25), 58 (100), and 43 (90).

Hydrogenation of **2**. — A mixture of **2** (95 mg) and 10% palladium-on-barium sulphate (0.15 g) in methanol (8 ml) was hydrogenated at atmospheric pressure for 10 h. T.l.c. (solvent *A*) then indicated that **2** had disappeared, and a single spot of R_F 0.85 could be detected. The catalyst was removed, the filtrate was concentrated, and the colourless, syrupy residue (80 mg) was treated conventionally with benzoyl chloride (0.146 g) in pyridine (3 ml) at room temperature for 24 h to give methyl 3-benzamido-4-*O*-benzoyl-2,3,6-trideoxy-*β*-D-*ribo*-hexopyranoside (**3**; 175 mg, 92%), m.p. 124–126° (from aqueous ethanol), $[\alpha]_D^{25}$ −75° (*c* 0.62, methanol); lit.[13,14] m.p. 124–126°, $[\alpha]_D^{25}$ −75.1° (*c* 0.73, methanol). The R_F value of **3** and its ^{1}H-n.m.r. spectrum were identical with those of methyl *N,O*-di-benzoyl-*β*-D-ristosaminide[13,14].

*Methyl 3-benzamido-4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-β-*D-ribo-*hexopyranoside* (**5**). — Conventional treatment of **4**[14,16] (493 mg, 1.44 mmol) with benzoyl chloride (0.22 g, 1.57 mmol) in pyridine (10 ml) for 24 h gave **5** (590 mg, 92%), m.p. 131.5–132.5° (from ethanol–water), $[\alpha]_D^{25}$ −110° (*c* 0.5, chloroform), R_F 0.45 (solvent *A*).

Anal. Calc. for $C_{21}H_{22}BrNO_5$: C, 56.25; H, 4.95; Br, 17.82. Found: C, 56.13; H, 4.92; Br, 17.91.

*Methyl 3-benzamido-4-*O*-benzoyl-2,3,6-trideoxy-β-*D-erythro-*hex-5-enopyranoside* (**6**). — To a solution of **5** (390 mg, 0.87 mmol) in pyridine (6 ml), dry silver fluoride (350 mg, 2.72 mmol) was added. The mixture was stirred in the dark for 48 h, and then poured into ether (20 ml), filtered, washed with water, dried ($MgSO_4$), decolorised with Celite, and concentrated. The residue was recrystallised from methanol to give **6** (230 mg, 72%), m.p. 162–164°, $[\alpha]_D^{25}$ −179° (*c* 0.84, methanol), R_F 0.85 (solvent *A*). Mass spectrum: *m/e*: 367 (8%, M^+), 336 (2), 262 (8), 246 (6),

230 (1), 215 (5), 214 (4), 204 (2), 202 (3), 190 (30), 174 (12), 145 (2), 122 (2), 105 (100), and 77 (30).

Anal. Calc. for $C_{21}H_{20}NO_5$: C, 68.83; H, 5.50; N, 3.82. Found: C, 68.93; H, 5.51; N, 3.88.

*Methyl 3-benzamido-2,3,6-trideoxy-β-*D-erythro-*hex-5-enopyranoside* (**7**). — A solution of **6** (0.2 g) in 0.1M methanolic sodium methoxide (10 ml) was stored at room temperature for 24 h, and then neutralised with AG 50W-X12(H^+) resin and concentrated. The crystalline residue was washed with light petroleum to yield **7** (128 mg, 95.5%), m.p. 138.5–139.5°, $[\alpha]_D^{25}$ −67° (*c* 0.54, methanol), R_F 0.4 (solvent *A*). Mass spectrum: *m/e* 263 (15%, M^+), 246 (5), 231 (8), 220 (2), 214 (1), 206 (2), 205 (2), 202 (1), 190 (13), 188 (5), 176 (3), 174 (3), 163 (5), 146 (3), 142 (10), 122 (12), 105 (100), and 77 (30).

Anal. Calc. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.70; H, 6.50; N, 5.38.

Hydrogenation of **7**. — Hydrogenation of **7** (80 mg), as described above for **2**, gave syrupy methyl 3-benzamido-2,3,6-trideoxy-*β*-D-*ribo*-hexopyranoside (**8**; 78 mg, 96.7%), $[\alpha]_D^{25}$ −39° (*c* 0.6, chloroform), R_F 0.64 (solvent *A*), which was identical with methyl *N*-benzoyl-*β*-D-ristosaminide[13,14], $[\alpha]_D^{25}$ −38° (*c* 0.5, chloroform).

The mass and ^{1}H-n.m.r. spectra of **8** were identical with those of methyl *N*-benzoyl-*β*-D-ristosaminide[13,14].

*Methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-2-deoxy-β-*D-arabino-*hexopyranoside* (**9**). — Conventional treatment of methyl 4,6-*O*-benzylidene-2-deoxy-*β*-D-*arabino*-hexopyranoside[14] (2.9 g, 0.108 mol) with benzoyl chloride (1.43 g, 0.113 mol) in pyridine (11 ml) gave **9** (3.6 g, 89%), m.p. 125–126° (from ethanol), $[\alpha]_D^{25}$ −133° (*c* 0.76, chloroform), R_F 0.4 (solvent *B*).

Anal. Calc. for $C_{21}H_{22}O_6$: C, 68.09; H, 5.98. Found: C, 68.40; H, 5.94.

*Methyl 3,4-di-*O*-benzoyl-6-bromo-2,6-dideoxy-β-*D-arabino-*hexopyranoside* (**10**). — A mixture of **9** (3.5 g, 9.4 mmol), *N*-bromosuccinimide (2 g, 11.2 mmol), and barium carbonate (3.3 g) in dry carbon tetrachloride (80 ml) was boiled under reflux for 5 h, filtered, and concentrated to dryness. A solution of the syrupy residue in ether (35 ml) was washed with water, dried ($MgSO_4$), and concentrated, and the residue was crystallised from cold methanol to give **10**, m.p. 75–76°, $[\alpha]_D^{25}$ −90.5° (*c* 0.74, chloroform), R_F 0.6 (solvent *B*).

Anal. Calc. for $C_{21}H_{21}BrO_6$: C, 56.13; H, 4.71; Br, 17.78. Found: C, 56.32; H, 4.69; Br, 17.74.

*Methyl 2,6-dideoxy-β-*D-threo-*hex-5-enopyranoside* (**11**). — Treatment of **10** (1 g, 2.22 mmol) with pyridine–silver fluoride, as described above for **5**, gave a syrupy product which was purified by column chromatography (solvent *B*). The fractions containing the component of R_F 0.69 were combined and concentrated. The syrupy residue was then subjected to Zemplén debenzoylation (see above) to yield **11** (250 mg, 71.4%), m.p. 81–81.5°, $[\alpha]_D^{25}$ −136° (*c* 0.74, methanol), R_F 0.3 (solvent *A*). Mass spectrum: *m/e*: 143 (1%, M + 1 − 18), 129 (8), 117 (10), 103 (60), 99 (10), 86 (30), 85 (50), 75 (50), 74 (70), 57 (60), 45 (50), and 43 (100).

Anal. Calc. for $C_7H_{12}O_4$: C, 52.48; H, 7.49. Found: C, 52.32; H, 7.47.

*Methyl 2,6-dideoxy-β-*D-arabino-*hexopyranoside* (**12**). — (*a*) A solution of **11** (91.5 mg) in methanol (8 ml) was hydrogenated in the presence of 10% palladium-on-barium sulphate (0.2 g) for 8 h; during this time, **11** disappeared (t.l.c., solvent *A*) and **12** (R_F 0.4) appeared. The mixture was filtered and concentrated to give **12** (92.4 mg, 99.7%), m.p. 78.5–79.5°, $[\alpha]_D^{25}$ −65.5° (*c* 0.9, acetone); lit.[19] for the L enantiomer, m.p. 76–81°, $[\alpha]_D^{25}$ +65.6 ±2° (*c* 0.8, acetone).

Anal. Calc. for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.90; H, 8.71.

(*b*) A solution of **10** (0.3 g, 0.67 mmol) in methanol (12 ml) containing triethylamine (73 mg, 0.72 mmol) was hydrogenated in the presence of Raney nickel (1 g) for 12 h. The mixture was filtered and concentrated, and the residue was partitioned between chloroform and water. The organic layer was washed with water, dried ($MgSO_4$), and concentrated to dryness. The residue was debenzoylated with 0.1M methanolic sodium methoxide in methanol to give **12**, m.p. 79–79.5°, $[\alpha]_D^{25}$ −65° (*c* 0.7, acetone).

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