Carbohydrate Research, 142 (1985) 141–145
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

Formation of amino sugars by catalytic reduction of the *O*-methyloximes of methyl 4,6-*O*-ethylidene-α- and -β-D-*arabino*-hexopyranosidulose

ROLF ANDERSSON, IBRAHIM GOUDA*, OLLE LARM, MARIA ELENA RIQUELME, AND ELISABETH SCHOLANDER

Department of Chemistry and Molecular Biology, Swedish University of Agricultural Sciences, S-750 07 Uppsala (Sweden)

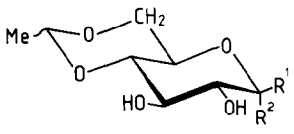
(Received January 29th, 1985; accepted for publication, March 11th, 1985)

On oxidation[1] of glycopyranosides with bromine water at neutral pH, the secondary alcohol groups react preferentially. Bulky substituents in *syn*-diaxial relation to an axial hydrogen in a CHOH group will hinder oxidation at that position. Hence, the reaction can be highly regioselective.

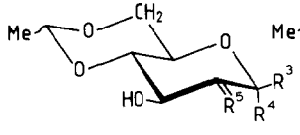
We now report on the formation of 2-amino-2-deoxy sugars by catalytic reduction of the *O*-methyloxime derivatives of partially protected hexopyranosid-2-uloses.

The 4,6-*O*-ethylidene derivatives (**1** and **2**, respectively)[2] of methyl α- and β-D-glucopyranoside were treated with bromine in water at pH 7 and room temperature. As expected[1], **1** was oxidised only at C-2 (C-4 is protected by the *O*-ethylidene group and C-3 by the *O*-methyl group at C-1), yielding the *arabino*-hexopyranosidulose derivative **3**. The β anomer **2** was oxidised at C-2 or C-3, yielding the *arabino*-hexopyranosidulose **4** and *ribo*-hexopyranosid-3-ulose **5**.

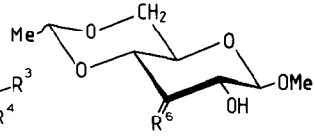
The uloses were not isolated but converted into their more stable *O*-methyloximes[1] which were isolated by chromatography on silica gel. The *O*-methyloxime (**7**) of methyl 4,6-*O*-ethylidene-β-D-*arabino*-hexopyranosidulose did



1 R^1 = H, R^2 = OMe
2 R^1 = OMe, R^2 = H



3 R^3 = H, R^4 = OMe, R^5 = O
4 R^3 = OMe, R^4 = H, R^5 = O
6 R^3 = H, R^4 = OMe, R^5 = N~OMe
7 R^3 = OMe, R^4 = H, R^5 = N~OMe



5 R^6 = O
8 R^6 = N~OMe

*Present address: MEDICARB, Björnnäsvägen 21, S-113 47 Stockholm, Sweden.

0008-6215/85/$ 03.30

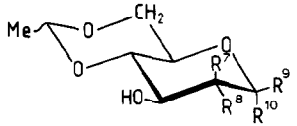
not crystallise and was isolated exclusively in the (*E*) form as established by comparing its ^{1}H-n.m.r. spectrum with those of the corresponding (*E*) and (*Z*) forms[3] of silylated *O*-methyloximes of methyl β-D-*arabino*-hexopyranosidulose[1]. In the (*Z*) form of this compound, the chemical shifts of the signals of H-1 and H-3 are 5.38 and 3.85–4.05 p.p.m., respectively, whereas in the (*E*) form[1] they are 4.77 and 4.50 p.p.m. The chemical shift difference between the signals of H-1 and H-3 in the latter compound agrees well with that for H-1 (4.97 p.p.m.) and H-3 (4.70 p.p.m.) in **7**.

The *O*-methyloxime (**6**) of methyl 4,6-*O*-ethylidene-α-D-*arabino*-hexopyranosidulose and the silylated *O*-methyloxime of methyl α-D-*arabino*-hexopyranosidulose cannot be compared so readily, as the latter substance exists in one form only. The chemical shift difference between the signals for H-1 and H-3 is 1.3 p.p.m. in the silylated compound[1], whereas in **6** it is 1.1 p.p.m., which is close to the corresponding chemical shift difference of the (*Z*) form of the silylated *O*-methyloxime of methyl β-D-*arabino*-hexopyranosidulose (see above). However, as H-1*e* (usually the α anomer) always resonates at lower field, additional evidence was necessary. The chemical shifts of the signals for H-1 of the (*E*) and (*Z*) forms of the oxime derivative of methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosidulose were 5.30 and 5.78 p.p.m., respectively[4], and that for H-1 of **6** was 5.69 p.p.m. By comparing the chemical shifts of the signals for H-1 and H-3 of isopropyl 3,4,6-tri-*O*-acetyl-α-D-*arabino*-hexopyranosidulose with the corresponding shifts of the oxime derivatives, Lemieux and co-workers established that the oxime adopted the (*Z*) configuration[5]. The chemical shifts of the signals for H-1 and H-3 of the 3-acetate of **6** (5.72 and 5.67 p.p.m., respectively) were in close agreement with those of the oxime derivative described above. This confirms that **6** exists in the (*Z*) conformation.

By similar reasoning, the *O*-methyloxime (**8**) of methyl 4,6-*O*-ethylidene-β-D-*ribo*-hexopyranosid-3-ulose was found to adopt the (*E*) configuration. Another fraction, possibly containing the (*Z*) isomer, was also found but not further investigated.

2-Amino-2-deoxy sugars have been prepared from sugar oximes by catalytic reduction[6–11]. In general, axial amino groups are obtained, as an equatorial approach by the catalyst to the oximino group is expected to give the more stable transition-state. When the aglycon group is axial, an axial approach by the catalyst would be assumed to be favoured.

In agreement with this, hydrogenation[9] over Pd/C of the oxime **6** in methanol containing one equivalent of hydrogen chloride yielded methyl 2-amino-2-deoxy-4,6-*O*-ethylidene-α-D-glucopyranoside (**9**) and minor amounts of the mannopyranoside **10**. The small amount of **10** obtained by column chromatography did not give a satisfactory elemental analysis, but no signals other than those attributed to **10** were observed in the ^{1}H- and ^{13}C-n.m.r. spectra. Hydrogenation of **7** yielded methyl 2-amino-2-deoxy-4,6-*O*-ethylidene-β-D-mannopyranoside (**11**) exclusively. Reaction times exceeding 24 h were necessary to achieve quantitative reduction of



9 R^9=H, R^{10}=OMe, R^7=H, R^8=NH_2
10 R^9=H, R^{10}=OMe, R^7=NH_2, R^8=H
11 R^9=OMe, R^{10}=H, R^7=NH_2, R^8=H

methoximino sugars to amino sugars. The overall yield of the mannosamine derivative **11** from **2** was 37%.

The method could be of value for the preparation of other mannosamine derivatives.

EXPERIMENTAL

General methods. — Melting points are uncorrected. Concentrations were carried out under reduced pressure >40° (bath). N.m.r. spectra [external Me_4Si (^{13}C) and internal 1,1,2,2,3,3-hexadeuterio-4,4-dimethyl-4-silapentane-1-sulfonate (^1H)] were recorded for solutions in D_2O or $CDCl_3$ at 30°, using a JEOL FX 90 Q instrument. Differential ^{13}C-n.m.r. spectra were measured by using a coaxial, dual cell (Wilmad Glass Co.). T.l.c. and column chromatography were performed on Silica Gel F_{254} (Merck) and Silica Gel 60 (Merck), respectively. Optical rotations were determined with a Perkin–Elmer 141 polarimeter. For g.l.c., a Packard 427 instrument and glass capillary columns (25 m × 0.3 mm) coated with OV-225 were used.

O-*Methyloximes* (**6** *and* **7**) *of methyl 4,6-O-ethylidene-α- and -β-*D-arabino-*hexopyranosidulose.* — (*a*) A solution of methyl 4,6-*O*-ethylidene-α-D-glucopyranoside[2] (**1**, 460 mg) in 0.1M bromine water (40 mL) was kept at room temperature, and the pH was maintained at 7.0 by titration with M sodium hydroxide. When the oxidant had been consumed (after 8 h), the pH was adjusted to 5.0, the mixture was concentrated to ~5 mL, and methoxylamine hydrochloride (500 mg) was added. The mixture was kept at 50°, and the pH was maintained at 4.0 by titration with M sodium hydroxide if necessary. After 4 h, the pH was raised to 7.0, the solution was concentrated to dryness and extracted with chloroform (4 × 25 mL), and the combined extracts were dried and concentrated. The residue was eluted from a column (50 × 1.5 cm) of silica gel with light petroleum (b.p. 60–80°)–ethyl acetate (2:1), and the fractionation was monitored by t.l.c. to give **6** (215 mg), m.p. 101°, $[\alpha]_{578}^{25}$ +115° (*c* 0.4, water). N.m.r. data ($CDCl_3$): ^1H, δ 5.69 (s, H-1), 4.58 (dd, $J_{3,4}$ 9.6, $J_{3,OH}$ 3.2 Hz, H-3), 3.42 (m, H-4), 3.86 (m, $J_{5,6}$ 9.4, $J_{5,6'}$ 4.3 Hz, H-5), 3.52 (t, H-6), 4.15 (dd, $J_{6,6'}$ 9.3 Hz, H-6'), 4.78 (q, *J* 5.0 Hz, C*H*Me), 1.40 (d, CH*Me*), 3.93 (s, N–OMe), 3.43 (s, OMe), 3.26 (d, OH); ^{13}C, δ 92.12 (C-1), 151.61 (C-2), 62.73 (C-3), 83.18 (C-4), 68.67 (C-5), 68.21 (C-6), 99.65 (*C*H–CH_3), 20.34 (CH–*C*H_3), 62.33 (N–OCH_3), 55.31 (OCH_3).

Anal. Calc. for $C_{10}H_{17}NO_6$: C, 48.6; H, 6.9; N, 5.7. Found: C, 48.0; H, 7.2; N, 5.5.

(*b*) The *O*-methyloxime **7** was prepared from methyl 4,6-*O*-ethylidene-β-D-glucopyranoside (500 mg) essentially as described above. Column chromatography yielded **7** (210 mg) as a syrup, $[\alpha]_{578}^{25}$ +3° (*c* 0.4, water). N.m.r. data ($CDCl_3$): ^1H, δ 4.97 (d, $J_{1,3}$ 0.5 Hz, H-1), 4.70 (m, $J_{3,4}$ 9.1, $J_{3,OH}$ 4.3 Hz, H-3), 4.23 (t, $J_{4,5}$ 9.1 Hz, H-4), 3.40–3.64 (m, H-5,6), 4.06–4.34 (m, H-6′), 4.78 (q, *J* 5.0 Hz, C*H*Me), 1.38 (d, CH*Me*), 3.99 (s, N–OMe), 3.42 (s, OMe), 3.07 (d, OH); ^{13}C, δ 98.68 (C-1), 153.04 (C-2), 66.23 (C-3), 77.71 (C-4), 65.82 (C-5), 69.48 (C-6), 99.46 (*C*H–CH_3), 20.32 (CH–*C*H_3), 62.87 (N–OCH_3), 54.85 (OCH_3).

Anal. Found: C, 47.8; H, 6.9; N, 5.7.

Another fraction contained the *O*-methyloxime (**8**) of methyl 4,6-*O*-ethylidene-β-D-*ribo*-hexopyranosid-3-ulose, isolated as a syrup (18 mg), $[\alpha]_{578}^{25}$ −97° (*c* 0.4, water). N.m.r. data ($CDCl_3$): ^1H, δ 4.69 (s, H-1,2), 4.53 (d, $J_{4,5}$ 10.1 Hz, H-4), 3.92 (m, $J_{5,6}$ 9.7, $J_{5,6'}$ 4.4 Hz, H-5), 3.50 (t, $J_{6,6'}$ 9.7 Hz, H-6), 4.23 (dd, H-6′), 4.81 (q, *J* 5.2 Hz, C*H*Me), 1.43 (d, CH*Me*), 3.99 (s, N–OMe), 3.44 (s, OMe); ^{13}C, δ 100.01 (C-1), 67.28 (C-2), 152.74 (C-3), 74.71 (C-4), 66.42 (C-5), 69.70 (C-6), 101.52 (*C*H–CH_3), 20.34 (CH–*C*H_3), 62.57 (N–OCH_3), 55.56 (OCH_3).

Anal. Found: C, 47.9; H, 6.5; N, 5.4.

Reduction of **6** *and* **7**. — A solution of **6** (150 mg) in methanol (35 mL) containing 1.1 equiv. of hydrogen chloride was hydrogenated at atmospheric pressure and room temperature for 24–48 h over 10% Pd/C (150 mg). The mixture was filtered, water (20 mL) was added, and Cl^- was removed by using Amberlite IR-45 (HO^-) resin. T.l.c. revealed two products. Elution of the mixture from a column (50 × 1.5 cm) of silica gel with acetonitrile–ethanol–water (12:1:1) yielded, first, methyl 2-amino-2-deoxy-4,6-*O*-ethylidene-α-D-mannopyranoside (**10**). N.m.r. data (D_2O, base): ^1H δ 4.77 (d, $J_{1,2}$ 1.3 Hz, H-1), 3.33 (dd, $J_{2,3}$ 5.2 Hz, H-2), 4.00 (m, H-3), 3.67–3.82 (m, H-4,6,6′), 4.17 (m, H-5), 4.94 (q, *J* 5.0 Hz, C*H*Me), 1.36 (d, CH*Me*), 3.41 (s, OMe); ^{13}C, δ 103.61 (C-1), 55.53 (C-2), 68.31 (C-3), 78.55 (C-4), 68.94 (C-5), 64.63 (C-6), 101.74 (*C*H–CH_3), 20.75 (CH–*C*H_3), 56.29 (OCH_3).

Eluted second was methyl 2-amino-2-deoxy-4,6-*O*-ethylidene-α-D-glucopyranoside (**9**, 54 mg), m.p. 135–137°, $[\alpha]_{578}^{25}$ +96° (*c* 0.8, water). N.m.r. data (D_2O, base): ^1H, δ 4.80 (d, $J_{1,2}$ 3.5 Hz, H-1), 2.86 (b, H-2), 3.43–3.79 (m, H-3,4,6,6′), 4.18 (m, H-5), 4.91 (q, *J* 5.1 Hz, C*H*Me), 1.36 (d, CH*Me*), 3.43 (s, OMe); ^{13}C, δ 102.15 (C-1), 56.91 (C-2), 72.21 (C-3), 81.86 (C-4), 69.10 (C-5), 64.01 (C-6), 101.39 (*C*H–CH_3), 20.69 (CH–*C*H_3), 56.91 (OCH_3).

Anal. Calc. for $C_9H_{17}NO_5$: C, 49.4; H, 7.8; N, 6.4. Found: C, 48.8; H, 7.9; N, 6.0.

Compound **7** (100 mg) was hydrogenated and treated as described above, yielding methyl 2-amino-2-deoxy-4,6-*O*-ethylidene-β-D-mannopyranoside (**11**, 87 mg), m.p. 130–133°, $[\alpha]_{578}^{25}$ −131° (*c* 1.2, water). N.m.r. data (D_2O, base): ^1H, δ 4.69 (d, $J_{1,2}$ 1.7 Hz, H-1), 3.39 (dd, $J_{2,3}$ 4.2 Hz, H-2), 3.46–3.99 (m, H-3,4,5,6), 4.22 (dd, $J_{5,6'}$ 4.6, $J_{6,6'}$ 10.2 Hz, H-6′), 4.92 (q, *J* 5.1 Hz, C*H*Me), 1.36 (d, CH*Me*), 3.53

(s, OMe); ^{13}C, δ 103.36 (C-1), 55.70 (C-2), 70.64 (C-3), 78.55 (C-4), 68.80 (C-5), 67.99 (C-6), 101.69 (CH–CH_3), 20.69 (CH–CH_3), 58.56 (OCH_3).

Anal. Found: C, 49.4; H, 8.0; N, 6.1.

ACKNOWLEDGMENTS

We thank Professor Olof Theander for his interest, and the National Swedish Board for Technical Development and the Swedish Natural Science Research Council for financial support.

REFERENCES

1 O. LARM, E. SCHOLANDER, AND O. THEANDER, *Carbohydr. Res.*, 49 (1976) 69–77.
2 T. G. BONNER, *Methods Carbohydr. Chem.*, 2 (1963) 309–311.
3 G. J. KARABATSOS AND N. HSI, *Tetrahedron*, 23 (1967) 1079–1095.
4 B. B. BISSEMBER AND R. H. WIGHTMAN, *Carbohydr. Res.*, 81 (1980) 187–191.
5 R. U. LEMIEUX, R. A. EARL, K. JAMES, AND T. L. NAGABHUSHAN, *Can. J. Chem.*, 51 (1973) 19–26.
6 L. ANDERSON AND H. A. LARDY, *J. Am. Chem. Soc.*, 72 (1950) 3141–3147.
7 B. LINDBERG AND O. THEANDER, *Acta Chem. Scand.*, 13 (1959) 1226–1230.
8 P. M. COLLINS AND W. G. OVEREND, *J. Chem. Soc.*, (1965) 3448–3456.
9 R. U. LEMIEUX AND S. W. GUNNER, *Can. J. Chem.*, 46 (1968) 397–400.
10 R. U. LEMIEUX AND T. L. NAGABHUSHAN, *Can. J. Chem.*, 46 (1968) 401–403.
11 R. U. LEMIEUX, K. JAMES, T. L. NAGABHUSHAN, AND Y. ITO, *Can. J. Chem.*, 51 (1973) 33–41.