O-Benzyl Oximes of Carbohydrates

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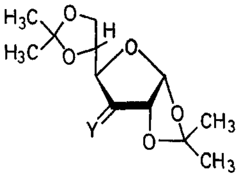
It is well known that monosaccharides display typical carbonyl reactivity towards hydroxylamine, namely, the formation of oximes[3]. The unsubstituted oximes of reducing sugars are very probably in tautomeric equilibrium with chain and ring forms, the latter arising by intramolecular addition of a hydroxy group to the C=N function; thus, they exhibit mutarotation in aqueous solution, and, on acetylation, they give a mixture of ring-chain acetylated isomers. In this communication we describe the facile preparation of *O*-benzyl oximes of sugars by treatment of the aldose or ketose with benzyloxyamine[4] in aqueous ethanol at reflux temperature; the oximes are readily crystallized and are obtained in high yield. The method should be of value for the characterization of sugars. Physical data and yields for some representative examples are given in the Table. A salient feature is the observation in each case of an absorption band for a C=N bond in the Raman spectrum, indicating the presence of an acyclic structure in the solid state, although the I.R. spectra (KBr) showed negligible C=N absorption (compare Ref. 5). The optical rotations of aqueous solutions of the *O*-benzyl oximes were found to be immeasurably low. It was also found that, whereas the *O*-benzyl oximes of L-arabinose, D-glucose and D-fructose were readily soluble in water or ethanol, that of D-galactose was only slightly soluble in these solvents; the low solubility and good crystallizing properties of *O*-benzyl-D-galactose oxime should make it particularly useful in the identification or isolation of the sugar.

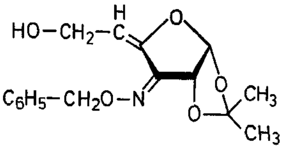
Treatment of the *O*-benzyl oximes of D-glucose and D-galactose with acetic anhydride/pyridine, initially at 0° and then at room temperature, afforded in high yield and in crystalline form *O*-benzyl 2,3,4,5,6-penta-*O*-acetyl-*aldehydo*-D-glucose oxime and *O*-benzyl 2,3,4,5,6-penta-*O*-acetyl-*aldehydo*-D-galactose oxime, respectively. The acyclic structures of these products were confirmed by the observation of C=N absorption in their Raman spectra.

The formation of *O*-benzyl oximes has been extended also to keto sugars. Thus, for example, treatment of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose[6] (**1**) with benzyloxyamine in benzene at room temperature gave the crystalline *O*-benzyl oxime **2** in good yield. The reduction of oximes derived from keto sugars is a well-established route to amino sugars[7]. In the present work, treatment of **2** with sodium borohydride in isopropyl alcohol at reflux temperature afforded in 30% yield a crystalline product which was assigned the structure of the conjugated oximinoolefin **3** on the basis of its elemental analysis and Raman, I.R. and ^{1}H-N.M.R. spectra.



1 Y = O

2 Y = N-OCH$_2$-C$_6$H$_5$



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A detailed analysis of the Raman and ^{1}H-N.M.R. spectra of some *O*-benzyl oximes of carbohydrates will be published later.

Preparation of *O*-Benzyl Oximes of Sugars; General Procedure: Equimolar quantities of the aldose or ketose and benzyloxyamine (prepared by the method of Fujii et al.[4]) are dissolved in 85% aqueous ethanol, and the solution is heated at reflux temperature for 4 hr. The solvent is evaporated, and the residue is crystallized from ethanol or ethanol/benzene (9:1).

***O*-Benzyl 2,3,4,5,6-Penta-*O*-acetyl-*aldehydo*-D-galactose Oxime:** To a mixture of acetic anhydride (30 ml) and dry pyridine (40 ml) at 0° was added, in small portions, *O*-benzyl D-galactose oxime (5 g). The mixture was stirred at 0° for 1.5 hr, and then kept at room temperature overnight. The solution was poured into 500 ml of ice and water, and the precipitated acetate was collected by filtration; yield: 8.5 g (92%); m.p. 135–136° (from ethanol); $[\alpha]_D + 37°$ (c 1.0, CHCl$_3$).

$C_{23}H_{29}NO_{11}$	calc.	C 55.75	H 5.90	N 2.83
(495.5)	found	55.99	6.02	2.93

I.R. (KBr): $\nu_{max} = 1747$ (OAc), 1639 cm^{-1} (very weak, C=N).

Raman (solid): $\Delta\nu = 1642$ cm^{-1} (medium, C=N).

^{1}H-N.M.R. (C$_6$D$_6$, TMS): $\delta = 7.10$ ppm (d, $J = 6$ Hz, —N=C$\underline{H}$—).

***O*-Benzyl 2,3,4,5,6-Penta-*O*-acetyl-*aldehydo*-D-glucose Oxime:** This compound was prepared from *O*-benzyl D-glucose oxime by the procedure described in the preceding experiment; yield: 79%; m.p. 50–52° [from petroleum ether (b.p. 60–80°)] $[\alpha]_D + 58°$ (c 1.0, CHCl$_3$).

$C_{23}H_{29}NO_{11}$	calc.	C 55.75	H 5.90	N 2.83
(495.5)	found	55.71	5.59	3.05

I.R. (KBr): $\nu_{max} = 1754$ cm^{-1} (OAc).

Table. *O*-Benzyl Oximes of Sugars

Sugar	Yield (%)	m.p.	Raman[a] $\Delta\nu_{C=N}$ (cm^{-1})[b]	N.M.R.[c] Data for —N=CH— δ(ppm)	J(Hz)	Elemental Analyses				
L-Arabinose	97	106–107°	1627 mw	7.41	6.0	$C_{12}H_{17}NO_5$	calc.	C 56.47	H 6.66	N 5.49
							found	56.45	6.55	5.46
D-Glucose	89	118–119.5°	1642 mw	7.35	6.2	$C_{13}H_{19}NO_6$	calc.	C 54.73	H 6.66	N 4.91
							found	54.77	6.83	4.73
D-Galactose	91	158–159°	1626 w	7.41[d]	6.1[d]	$C_{13}H_{19}NO_6$	calc.	C 54.73	H 6.66	N 4.91
							found	54.86	6.85	5.11
D-Fructose	85	104–105.5°	1640 mw	–	–	$C_{13}H_{19}NO_6$	calc.	C 54.73	H 6.66	N 4.91
							found	54.50	6.92	5.23

[a] Recorded on a Ramalab spectrometer (Spex Industries) with laser excitation of approximately 0.2 W at 5682 Å (Coherent Radiation Model 52 krypton-ion laser); the spectral slit width was 5.7 cm^{-1}. The accuracy of the frequency data was ±1 cm^{-1}. The samples were examined as solids at ambient temperature.

[b] mw = medium-to-weak, w = weak.

[c] ^{1}H-N.M.R. spectra were measured at 60 MHz in deuterium oxide (unless otherwise stated) with 3-(trimethylsilyl)-1-propanesulfonic acid as the internal standard.

[d] Methyl sulfoxide-d_6.

Raman (solid): $\Delta\nu = 1634\ cm^{-1}$ (weak, C=N).
^{1}H-N.M.R. ($_6D_6$, TMS): $\delta = 7.15$ ppm (d, $J = 6$ Hz, —N=CH̲—).

O-Benzyl 1,2:5,6-Di-O-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose Oxime (2):
A solution of 1,2:5,6-di-O-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose[6] (**1**; 16.4 g, 0.067 mol) and benzyloxyamine (8.24 g, 0.067 mol) in dry benzene (150 ml) was kept at room temperature overnight. The solvent was evaporated, and the residue was crystallized from ethanol to afford the O-benzyl oxime **2**; yield: 15.9 g (69%); m.p. 130–131°; $[\alpha]_D + 264°$ (c 1.0, $CHCl_3$).

$C_{19}H_{25}NO_6$	calc.	C 62.79	H 6.93	N 3.85
(363.4)	found	63.24	6.93	3.93

Raman (solid): $\Delta\nu = 1676\ cm^{-1}$ (medium-to-weak, C=N).

^{1}H-N.M.R. (acetone-d_6, TMS): $\delta = 7.20$ (s, 5H, C_6H_5), 5.84 (d, 1H, $J_{1,2} = 4$ Hz, H-1), 5.1 (dd, 1H, $J_{2,4} = 1.5$ Hz, H-2), 5.04 (s, 2H, O—CH̲$_2$—C_6H_5), 4.74 (dd, 1H, $J_{4,2} = 1.5$ Hz, $J_{4,5} = 2$ Hz, H-4), 4.43–3.56 (3H, H-5, H-6, and H-6′), 1.34, 1.28, 1.16 ppm (3s, 3H, 3H, 6H, 2 $C(CH_3)_2$).

Reaction of O-Benzyl 1,2:5,6-Di-O-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose Oxime (2) with Sodium Borohydride:
A mixture of compound **2** (3.51 g, 0.01 mol) and sodium borohydride (0.8 g, 0.022 mol) in isopropyl alcohol (55 ml) was heated at reflux temperature for 10 hr. The hot mixture was filtered, and the residue was washed with chloroform. The filtrate and washings were combined and concentrated; T.L.C. [silica gel, petroleum ether (b.p. 60–80°)/acetone (4:1)] revealed the presence of the oximinoolefin **3**, benzyl alcohol, a small amount of starting material **2**, and a component which migrated slightly slower than **2**. Compound **3** was isolated by column chromatography on silica gel, with the same solvent as used for T.L.C. as eluent; yield: 0.91 g (30%); m.p. 90–91° [benzene/pentane (1:4)]; $[\alpha]_D - 30°$ (c 1.0, $CHCl_3$).

$C_{16}H_{19}NO_5$	calc.	C 62.94	H 6.27	N 4.59
(305.3)	found	63.07	6.51	4.67

I.R. (KBr): $\nu_{max} = 3400$ (OH), 1654 and 1638 cm^{-1} (medium-to-strong, C=C—C=N).

Raman (solid): $\Delta\nu = 1656$ and 1639 cm^{-1} (very strong, C=C—C=N).

^{1}H-N.M.R. (acetone-d_6, TMS): $\delta = 7.27$ (s, 5H, C_6H_5), 6.03 (d, 1H, $J_{1,2} = 4$ Hz, H-1), 6.03 (t, 1H, $J_{5,6} = J_{5,6'} = 6$ Hz, H-5), 5.20 (s, 2H, O—CH̲$_2$—C_6H_5), 5.01 (d, 1H, $J_{2,1} = 4$ Hz, H-2), 4.36 to 4.04 (2H, H-6 and H-6′), 3.80–3.46 (1H, disappeared on deuteration, OH), 1.19 ppm (s, 6H, $C(CH_3)_2$).

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