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Note

N-Substituted methyl 3,6-di-*O*-benzoyl-2-deoxy-2-hydroxyamino-α-D-hexopyranosid-4-uloses: a configurational reassignment

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In a preliminary communication[1], we described the conjugate addition of *N*-methyl- and *N*-phenyl-hydroxylamines to methyl 3,6-di-*O*-benzoyl-2-deoxy-α-D-*glycero*-hex-2-enopyranosid-4-ulose[2] (**1**). This series has been extended and **2**–**5** have been obtained in excellent yields (Table I). The 3-deuterio analog of **2** was also prepared. The reactions were stereospecific. The large observed $^1J_{2,3}$ value led to the assignment of a $^4C_1$ chair form to **2** and **3** and to the erroneous[1] α-D-*xylo* configuration. However, discrepancies between this alleged configuration and n.m.r. data of derivatives of **2** required revision of the structure assigned, and an X-ray diffraction study was undertaken which showed **2** to exist in an almost pure $^{3,O}B$ form (Fig. 1). This same conformation was found to preponderate in solution and, contrary to observations in related series[3], was not affected by changes in solvent ($J_{1,2}$ and $J_{2,3}$ values of **3** were identical for solutions in $CDCl_3$, $(CD_3)_2SO$, and benzene-d_6). Owing to the interaction of their non-bonding orbitals (α-effect)[4] and their ability to establish hydrogen bonds, hydroxylamines constitute a special class of nucleophiles. Nevertheless, in contrast to their *O*-substituted analogs[5], they followed the classical[6] stereochemical path encountered in conjugate additions to alkyl hex-2-enopyranosid-4-uloses, namely, *trans* addition to the anomeric alkoxy group.

Compounds **2**–**5** oxidized spontaneously in the air to the corresponding nitroxyl free-radicals, the e.s.r. spectra of which presented the small a_{H-2} hyperfine coupling constants expected[1,7] from an equatorial nitroxyl vicinal to another large equatorial group.

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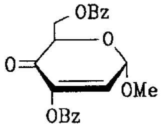

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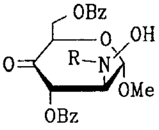

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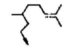
5 R = 

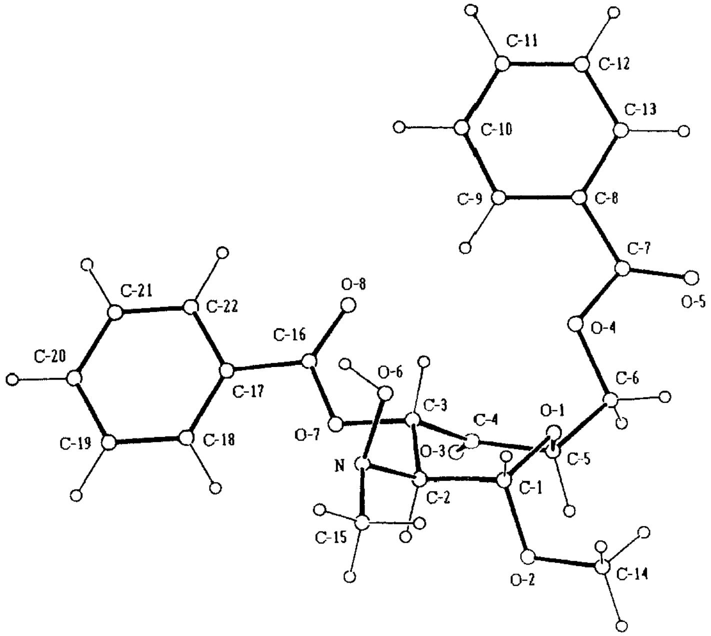


Fig.1. Crystal structure of compound **2**

EXPERIMENTAL

General methods. — See ref. 8. Optical rotations were obtained for solutions in chloroform. Column chromatography was conducted on silica gel (Merck, 70–230 mesh). N.m.r. data are collected in Tables II and III.

*Crystallographic data**. — The data are summarized in Table IV. Selected bond lengths, bond angles, and torsional angles are reported in Table V. Data were collected at room temperature on a Nonius CAD4 difractometer (Mo-K_a). The structure was solved by a direct method (MULTAN 87)[9] and refined by full-matrix least squares

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*Crystallographic data have been deposited with the Cambridge Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, Great Britain.

TABLE I

Preparation of hydroxylamines **2**–**5**

Compound	*Reaction solvent*	*Equiv. of R-NHOH*	*Reaction time (h)*	*Temp. (°)*	*Yield (%)*
2	10:1 EtOH–H_2O	2.3	4	25	81
3	EtOH	3	5	70	82
4	6:1 EtOH–H_2O	1.1	4	25	80
5	THF	1.1	2	25	86

TABLE II

^{1}H-N.m.r. data of compounds **2**–**5** ($CDCl_3$)

Compound	*Chemical shifts (δ)*				*Coupling constants (Hz)*	
	H-1	*H-2*	*H-3*	*H-5,6,6*	$J_{1,2}$	$J_{2,3}$
2	5.40	3.08	6.17	4.64–4.80	4.0	12.0
3	5.30	4.07	6.47	4.67–4.83	4.0	11.7
4	5.55	3.16	6.20	4.55–4.85	4.0	11.5
5	5.41	3.11	6.19	4.60–4.80	4.0	12.0

TABLE III

^{13}C-N.m.r. data of compounds **2**–**5** ($CDCl_3$)

Compound	*C-1*	*C-2*	*C-3*	*C-5*	*C-4*	*C-6*	*OMe*	*N–C*
2^a	98.00	70.33	73.58 ——	73.84	203.20	63.37	54.97	44.87
	*J*176.3	*J*135.6	*J*159.4, *J*141.8			*J*149.2	*J*145.8	*J*139.0
3	100.36	63.36	72.74 ——	73.10	202.86	62.60	54.64	
4	98.06	67.87	73.61	73.61	203.07	63.23	54.97	60.66
5	98.08	68.78	73.42 ——	73.71	200.88	63.25	54.79 ——	54.79

^{a}$CDCl_3$ + $(CD_3)_2SO$.

analysis (XTAL2.4)[10]. All co-ordinates of the hydrogen atoms were calculated, with the exception of that belonging to the hydroxyl group which was observed.

The pyranose ring adopted a quasi perfect boat conformation with minimum values of asymmetry parameters[11] ΔC_s(O-1) = 0.045(3) and ΔC_s(C-1–C-2) = 0.039(2). The hydroxyl group is involved in a hydrogen bond with one of the carbonyl groups [(O-6···O-5)1 − *x*, 1/2 − *y*, 1/2 − z = 2.796(6) Å)].

*Methyl 3,6-di-*O*-benzoyl-2-deoxy-2-(*N*-hydroxy-*N*-methylamino)-α-*D-arabino-*hexopyranosid-4-ulose* (**2**). — Prepared as indicated in Table I from **1** (1 g); extraction (dichloromethane) of the reaction mixture yielded **2**, m.p. 110.4–112.3°, $[\alpha]_D^{22}$ +193° (*c* 0.9); ν_{max}^{KBr} 3420 (OH), 1750, and 1720 (C=O) cm^{-1}; λ_{max}^{EtOH} 202 (ε 9700), 231 (25,400), 274

TABLE IV

Summary of crystal data, intensity measurement, and structure refinement for **2**

Formula	$C_{22}H_{23}NO_8$	μ (mm^{-1})	0.093
Molecular weight	429.4	$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.58
Crystal system	Orthorhombic	No. of measured reflections	1994
Space group	$P2_12_12_1$	No. of observed reflections	1447
Crystal size (mm)	0.13 × 0.22 × 0.30	Criterion for observed	$[F_o] > 4\sigma(F_o)$
a (Å)	11.7810(10)	No. of parameters	280
b (Å)	13.4710(12)	Refinement (on F)	Full-matrix
c (Å)	13.9249(15)	Weighting scheme	$\omega = 1/\sigma^2(F)$
V (Å^3)	2209.9(4)	Max. and average Δ/σ	0.081, 0.014
Z	4	Max, and min. $\Delta\rho$ (eÅ^{-3})	0.26, −0.27
D_c (g.cm^{-3})	1.29	S	1.80
F_{000}	904	R, ωR (%)	5.2, 3.8

TABLE V

Selected bond lengths (Å), bond angles (°), and torsional angles (°) for **2**

O-1–C-1	1.436(7)	O-7–C-3	1.430(7)
O-1–C-5	1.405(7)	O-7–C-16	1.355(8)
O-2–C-1	1.401(7)	O-8–C-16	1.196(9)
O-2–C-14	1.420(8)	N–C-2	1.452(8)
O-3–C-4	1.213(8)	N–C-15	1.459(8)
O-4–C-6	1.449(8)	C-1–C-2	1.547(8)
O-4–C-7	1.332(7)	C-2–C-3	1.544(8)
O-5–C-7	1.207(8)	C-3–C-4	1.508(9)
O-6–N	1.453(7)	C-4–C-5	1.535(9)
C-1–O-1–C-5	112.8(4)	C-4–C-5–O-1	110.6(5)
O-1–C-1–C-2	112.7(4)	C-2–N–O-6	106.7(4)
C-1–C-2–C-3	109.1(4)	C-2–N–C-15	112.7(5)
C-2–C-3–C-4	107.7(5)	O-6–N–C-15	105.5(5)
C-3–C-4–C-5	113.1(5)		
C-2–C-1–O-1–C-5	−55.5(6)	C-2–C-3–O-7–C-16	158.1(5)
O-1–C-1–C-2–C-3	−5.3(7)	C-3–O-7–C-16–O-8	1.3(9)
C-1–C-2–C-3–C-4	55.9(6)	O-7–C-16–C-17–C-18	−4.0(9)
C-2–C-3–C-4–C-5	−52.1(6)	C-4–C-5–C-6–O-4	46.1(7)
C-3–C-4–C-5–O-1	−4.2(7)	C-5–C-6–O-4–C-7	169.4(5)
C-4–C-5–O-1–C-1	60.3(6)	C-6–O-4–C-7–C-8	171.2(5)
O-1–C-1–O-2–C-14	62.2(6)	O-4–C-7–C-8–C-9	−11.5(9)
C-1–C-2–N–O-6	53.8(6)		

(1600), and 282 nm (1300). Mass spectrum: m/z 350 (1), 311 (0.2), 277 (0.2), 260 (2), 246 (0.1), 229 (0.1), 218 (1), 204 (0.4), 175 (3), 156 (0.6), 122(4), 105 (100), 97 (0.6), 85 (27), 51 (11). E.s.r. of the corresponding nitroxyl (diglyme, 20°): g 2.0061; a_N 14.4 G, a_{Me} 12.8 G, a_{H-2} 1.6 G, a_{H-3} 0.9 G, and a_{H-1} 0.6 G.E.s.r. of the nitroxyl corresponding to (3-^{2}H)-**2** (diglyme, 30°): a_N 14.4 G, a_{Me} 12.7 G, a_{H-2} 1.75 G, and a_{H-1} 0.7 G.

Anal. Calc for $C_{22}H_{23}NO_8$ (429.43): C, 61.53; H, 5.40; N, 3.26. Found: C, 61.33; H, 5.45; N, 3.42.

*Methyl 3,6-di-O-benzoyl-2-deoxy-2-(N-hydroxy-N-phenylamino)-α-*D-arabino-*hexopyranosid-4-ulose* (**3**). — Prepared as indicated in Table I from **1** (1.14 g); filtration of the mixture and recrystallization (EtOH) of the resulting solid yielded **3**, m.p. 175.2–176.4° (dec.), $[\alpha]_D^{25}$ +147° (*c* 1); ν_{max}^{KBr} 3480 (OH), 1740 and 1720 (C=O) cm^{-1}; λ_{max}^{EtOH} 205 (ε 22 900), 230 (30 700), 273 (4700), and 281 nm (4200). Mass spectrum; *m/z* 351 (1), 280 (0.7), 232 (0.7), 200 (9), 199 (1), 175 (2), 162 (1), 149 (2), 134 (2), 122 (20), 105 (100), 93 (7), 85 (16), 77 (23), 65 (7). E.s.r. of the corresponding nitroxyl (diglyme, 90°): *g* 2.0056, a_N 10.8 G, a_{Ph} 2.6, 2.6, 1.6, 1.6, and 0.85 G, $a_{H\text{-}2}$ 1.6 G, $a_{H\text{-}1}$ 0.85 G and $a_{H\text{-}3}$ 0.85 G.

Anal. Calc. for $C_{27}H_{25}NO_8$ (491.50): C, 65.98; H, 5.13; N, 2.85. Found: C, 65.97; H, 5.26; N, 3.05.

*Methyl 3,6-di-O-benzoyl-2-deoxy-2-(N-benzyl-N-hydroxyamino)-α-*D-arabino-*hexopyranosid-4-ulose* (**4**). — Prepared as indicated in Table I from **1** (0.19 g); extraction (dichloromethane) of the reaction mixture and recrystallization (isopropyl ether–hexane) yielded **4**, m.p. 102.7–104.1°, $[\alpha]_D^{23}$ +139.5° (*c* 0.4); $\nu_{max}^{CCl_4}$ 3460 (OH), 1750 and 1720 (C=O) cm^{-1}. Mass spectrum: *m/z* 375 (0.3), 350 (0.8), 281 (1), 218 (0.9), 207 (3), 175 (2), 149 (9), 122 (13), 105 (100), 91 (31), 77 (42), and 51 (18). E.s.r. of the corresponding nitroxyl (diglyme, 40°): *g* 2.0062, a_N 14.3 G, a_{CH_2} 10.7 and 8.2 G, $a_{H\text{-}2}$ 1.6 G, $a_{H\text{-}1}$ 0.8 G, and $a_{H\text{-}3}$ 0.8 G.

Anal. Calc. for $C_{28}H_{27}NO_8$ (505.53): C, 66.53; H, 5.38; N, 2.77. Found: C, 66.54; H, 5.38; N, 2.74.

*Methyl 3,6-di-O-benzoyl-2-deoxy-2-(N-hydroxy-N-3,7-dimethyloct-6-enylamino)-α-*D-arabino-*hexopyranosid-4-ulose* (**5**). — Obtained, as described in Table I, from **1** (0.4 g) and *N*-(3,7-dimethyloct-6-enyl)hydroxylamine (6.2 g), obtained (56%) by reduction[12] of citronellal oxime[13] with sodium cyanoborohydride. Chromatographic separation (ethyl acetate–hexane, 1:3) of the reaction mixture gave **5**, isolated as a syrup, $[\alpha]_D^{21}$ +132° (*c* 1.1); ν_{max}^{film} 3450 (OH), 1750 and 1720 (C=O) cm^{-1}. Mass spectrum: *m/z* 350 (0.6), 260 (1), 218 (1), 171 (2), 154 (5), 138 (2), 122 (8), 105 (100), 95 (9), 86 (23), 83 (9), 81 (14), 77 (26), 69 (31), 67 (11), 55 (17), 51 (11), 46 (57).

Anal. Calc. for $C_{31}H_{39}NO_8$ (553.66): C, 67.25; H, 7.10; N, 2.53. Found: C, 67.36; H, 7.30; N, 2.43.

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