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Note

O-Glycosylhydroxylamines: a new class of monosaccharide*.

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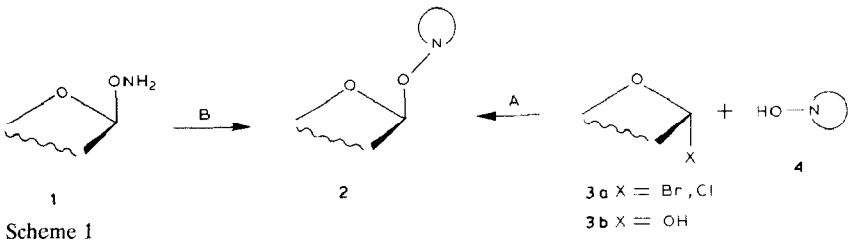
The synthesis of nucleoside analogs having a C-O-N-bond (**2**) are of continuing interest in our laboratory[1–7]. These can be obtained either by route A or B (Scheme 1). Method A involves the alkylation[1–4] of *N*-hydroxyheterocycles **4** with glucofuranosyl halides **3a** or a coupling of *N*-hydroxyheterocycles with sugars **3b** having a "free" hydroxyl group[1–3,5–8] under Mitsunobu reaction[9] conditions.



Scheme 1

Method B employs the *O*-hydroxylamine **1** for starting material and involves a step-by-step synthesis of the pyrimidine or purine ring[1,10]. In comparison to method A, process B allows greater flexibility in the structural modification of the base moiety, assures that one obtains the desired glycosylic linkage (depending on the configuration of the starting anomer), and bypasses the usually required protection–deprotection steps of the amino-, and/or other reactive groups, when they are present in the molecule.

Previously we have reported reactions of *N*-hydroxyphthalimide with alcohols[11], with steroids[12], and with 1,2:3,4-di-*O*-isopropylidene-α-D-galacto-pyranose and 2,3:5,6-di-*O*-isopropylidene-α-D-mannopyranose [6] under Mitsunobu

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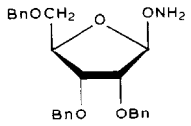
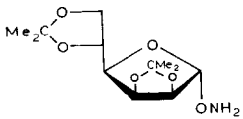
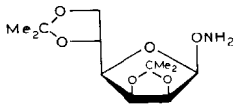
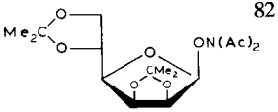
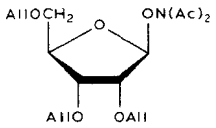
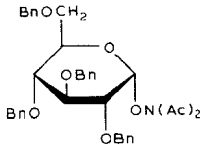
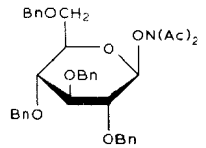
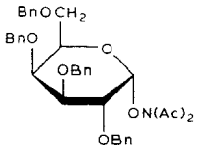
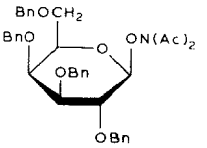
TABLE I

PHYSICOCHEMICAL DATA FOR COMPOUNDS **1** AND **6**

Substrate	*Product*		*Yield* [%]	*M.p. (°C)/* $[\alpha]_D$ *(CHCl₃)*	*I.r. data* *(cm⁻¹, CCl₄)*	*¹H-n.m.r. data* *(δ, CCl₄)*
α,β-5a[a]	**β-1a**[b]		80	105–106 +36.5° (*c* 2)	3300 (ν_{asNH}) 3240 (ν_{symNH}) (in Nujol)	5.2 (s, 1 H, H-1), 4.8 (bs, 2 H, exchangeable with D_2O, ONH_2), 4.5–4.7 (m, 6 H, $CH_2C_6H_5$), 4.3 (m, 1 H, H-4), 4.1 (dd, 1 H, $J_{3,4}$ 7.0 Hz, $J_{2,3}$ 4.5 Hz, H-3), 3.9 (d, $J_{2,3}$ 4.5 Hz, H-2), 3.7 (dd, 1 H, $J_{5,5'}$ 11.0 Hz, $J_{4,5}$ 3.8 Hz, H-5), 3.5 (dd, 2 H, $J_{5,5'}$ 11.0 Hz, $J_{4,5'}$ 4.2 Hz, H-5′
α,β-5b[a]	**α-1b**		7	oil	3300 (ν_{asNH}) 3260 (ν_{symNH})	(δ, $CDCl_3$): 5.2 (bs, 2 H, exchangeable with D_2O, ONH_2), 5.0 (s, 1 H, H-1), 3.8–4.7 (m, 6 H, H-2,3,4,5,6,6′), 1.3–1.5 (m, 12 H, CH_3)
	β-1b		69	oil	3300 (ν_{asNH}) 3260 (ν_{symNH})	(δ, $CDCl_3$): 5.4 (bs, 2 H, exchangeable with D_2O, ONH_2), 5.0 (d, 1 H, $J_{1,2}$ 3.2 Hz, H-1), 4.6–4.8 (m, 2 H, H-3,4), 4.3–4.5 (m, 1 H, H-5), 4.1 (m, 2 H, H-6,6′), 3.6 (dd, 1 H, $J_{1,2}$ 3.2 Hz, $J_{2,3}$ 7.8 Hz, 1 H, H-2), 1.4–1.6 (m, 12 H, CH_3)
β-5b	**β-6b**		82	oil −124.0° (*c* 2)	1730 ($\delta_{C=O}$) 925, 865	(δ, $CDCl_3$): 5.0 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.8 (dd, 1 H, $J_{3,4}$ 3.6 Hz, $J_{4,5}$ 5.6 Hz, H-4), 4.6 (dd, 1 H, $J_{2,3}$ 6.0 Hz, $J_{3,4}$ 3.6 Hz, H-3), 4.3 (dd, 1 H, $J_{5,6}$ 12.2 Hz, $J_{4,5}$ 5.6 Hz, H-5), 3.8–4.0 (m, 2 H, H-6,6′), 3.5 (dd, 1 H, $J_{1,2}$ 3.5 Hz, $J_{2,3}$ 6.0 Hz, H-2), 2.4 (bs, 6 H, NAc), 1.3–1.5 (m, 12 CH_3)

β-5c	**β-6c**		80	oil −74.6° (*c* 3)	1730 ($\delta_{C=O}$) 930, 865	5.6–6.1 (m, 3 H, $CH_2CH{=}CH_2$), 5.0–5.5 (m, 7 H, H-1, $CH_2CH{=}CH_2$), 3.8–4.4 (m, 9 H, H-2,3,4, $CH_2C_6H_5$), 3.4–3.7 (m, 2 H, H-5,5'), 2.4 (bs, 6 H, NAc)
α-5d	**α-6d**		58	oil +53.6° (*c* 4)	1740 ($\delta_{C=O}$) 700	(δ, $CDCl_3$): 5.0 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.3–4.9 (m, 9 H, $CH_2C_6H_5$, H-4), 3.4–4.0 (m, 5 H, H-2,3,5,6,6'), 2.3 (bs, 6 H, NAc)
β-5d	**β-6d**		68	oil −33.8° (*c* 3)	1730 ($\delta_{C=O}$) 690	4.4–5.2 (m, 10 H, $CH_2C_6H_5$ H-1,4), 3.5–3.7 (m, 5 H, H-2,3,5,6,6'), 2.3 (bs, 6 H, NAc)
α-5e	**α-6e**		63	oil +67.6° (*c* 1)	1730 ($\delta_{C=O}$) 690	4.4–5.0 (m, 10 H, $CH_2C_6H_5$, H-1,4), 3.9–4.2 (m, 3 H, H-2,3,5), 3.6 (m, 1 H, H-6), 3.3 (m, 1 H, H-6'), 2.2 (bs, 6 H, NAc)
β-5e	**β-6e**		67	oil −26.4° (*c* 1)	1730 ($\delta_{C=O}$) 630	4.3–5.2 (m, 10 H, $CH_2C_6H_5$, H-1,4), 3.3–3.9 (m, 5 H, H-2,3,5,6,6'), 2.3 (bs, 6 H, NAc)

[a]Anomeric mixture (α:$\beta \cong$ 1:10, by ^{1}H-n.m.r.) as obtained by Mitsunobu reaction, prior to separation by chromatography. [b]Preliminary data for **β-1a** is reported in ref. 7.

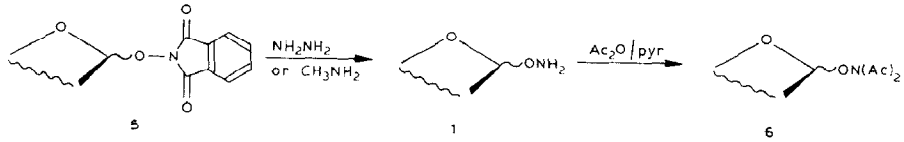
TABLE II

ELEMENTAL ANALYSES FOR COMPOUNDS **1** AND **6**

	β-1a $C_{26}H_{29}NO_5$	*α-1b* $C_{12}H_{21}NO_6$	*β-1b* $C_{12}H_{21}NO_6$	*β-6b* $C_{16}H_{25}NO_8$	*β-6c* $C_{18}H_{27}NO_7$	*α-6d* $C_{38}H_{41}NO_8$	*β-6d* $C_{38}H_{41}NO_8$	*α-6e* $C_{38}H_{41}NO_8$	*β-6e* $C_{38}H_{41}NO_8$
Calc.									
C	71.70	52.35	52.35	53.48	58.52	71.34	71.34	71.34	71.34
H	6.71	7.69	7.69	7.01	7.37	6.46	6.46	6.46	6.46
N	3.22	5.09	5.09	3.90	3.79	2.19	2.19	2.19	2.19
Found									
C	71.64	52.08	52.14	53.36	58.24	71.27	71.08	71.62	71.52
H	6.63	7.50	7.58	7.05	7.37	6.56	6.58	6.35	6.50
N	3.31	5.24	5.17	3.87	3.64	2.28	2.26	2.14	1.97

reaction conditions. Our studies also showed that, when reacted with hydrazine[13,14] or with methyl- or butyl-amine, these *O*-phthalimido derivatives yielded the corresponding *O*-hydroxylamine derivatives. Thus *O*-alkylhydroxylamines[11], steroidoxyamines[12], and 6-[(amino)oxy]-6-deoxy-isopropylidene-α-D-galactopyranose[15] were obtained.

Recently we described[7] a synthesis of *O*-glycosyl-*N*-hydroxyphthalimides **5** from *N*-hydroxyphthalimide and protected gluco- and galacto-pyranoses or manno- and ribo-furanoses in the presence of triphenylphosphine and diethyl azodicarboxylate. Herein is presented a synthesis of new *O*-glycosylhydroxylamines **1** and their bis-acetylated derivatives **6**, prepared from precursors **5** by hydrazinolysis (Scheme 2).



Scheme 2

Treatment of *O*-glycosyl-*N*-hydroxyphthalimides **5** with two equivalents of hydrazine or methylamine (see Experimental) lead to the corresponding *O*-glycosylhydroxylamines **1** in good yields. These compounds can be isolated or used in crude form for the further synthesis of C-O-N-analogs of nucleosides[1,10]. *O*-Furanosylhydroxylamines, particularly the crystalline *O*-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)hydroxylamines (β-**1a**), are fairly stable and can be isolated as free amines, whereas the acetylated derivatives of *O*-pyranosylhydroxylamines are the preferred form for isolation and storage.

In summary, *O*-glycosylhydroxylamines constitute a new group of compounds which are derivatives of sugars and hydroxylamine. They serve as useful building blocks for the synthesis of C-O-N-analogs of nucleosides of a specified anomeric configuration. They also exibit interesting biological properties. Preliminary studies[16] show that some are active against *Herpes simplex* type 1 and *Coxackie* B_4 viruses *in vitro*.

All structures of *O*-glycosylhydroxylamines and their acetyl derivatives were confirmed by i.r. and ^{1}H-n.m.r. spectroscopy (Table I) and by elemental analyses (Table II).

EXPERIMENTAL

Melting points are uncorrected. ^{1}H-n.m.r. spectra for solutions in CCl_4 or $CDCl_3$ were recorded with a JEOL JNM-4H-100 spectrometer using Me_4Si as the internal standard. The spectra were interpreted by first-order analysis, and the assignments were supported by homonuclear selective decoupling when necessary. I.r. spectra were recorded with a Unicam SP-200 spectrometer. Optical rotations

were measured with a Perkin–Elmer 141 MC spectropolarimeter. The mass spectrum was obtained with a LKB 2091 mass spectrometer. Flash chromatography was carried out with columns of Silica Gel-60 (Merck, 230-400 mesh ASTM). Hydrazine hydrate (100% reagent) was purchased from PZChem. Gliwice, Poland. Nonaqueous solutions obtained during workup procedures were dried over magnesium sulfate and concentrated under reduced pressure at ≤40°.

O-*(2,3,5-Tri-*O*-benzyl-β-*D*-ribofuranosyl)hydroxylamine* (**β-1a**). — Hydrazine hydrate (0.25 mL of 100% reagent, 5 mmol) was added to a solution of *O*-2,3,5-tri-*O*-benzyl-D-ribofuranosyl-*N*-hydroxyphthalimide[7] (**α,β-5a**; 1.3 g, 2.3 mmol) in tetrahydrofuran (10 mL), and the mixture was heated under reflux for 10 min, cooled to room temperature (phthalazine precipitated), and diluted with a cold solution of sodium bicarbonate (3%). The mixture was extracted with ethyl ether, and the extract was washed with water, dried, and concentrated. Recrystallization of the crude product from hexane gave **β-1a** (0.8 g, 80%); *m/z*: 436 ($M^+ + 1$). For physicochemical data see Table I; for elemental analyses see Table II.

O-*2,3:5,6-Di-*O*-isopropylidene-α-*D*-mannofuranosyl)hydroxylamine* (**α-1b**) *and* O-*(2,3:5,6-di-*O*-isopropylidene-β-*D*-mannofuranosyl)hydroxylamine* (**β-1b**). — A 33% solution of methylamine in ethanol (1.2 mL) was added to a solution of *O*-(2,3:5,6-di-*O*-isopropylidene-D-mannofuranosyl)-*N*-hydroxyphthalimide [7] (**α,β-5b**; 3.49 g, 8.6 mmol) in chloroform. After being stirred for 15 min at room temperature, the volatiles in the reaction mixture was co-evaporated with ethanol and hexane until the phthalic acid derivative precipitated, and the resulting crystalline mass was removed by filtration. The material in the filtrate was purified by chromatography (1:1→1:2 hexane–ethyl acetate) to give **α-1b** (0.16 g, 7%). For physicochemical data, see Table I, for elemental analyses, see Table II.

Eluted next was **β-1b** (1.6 g, 69%). For physicochemical data, see Table I, for elemental analyses, see Table II.

General procedure for the preparation of N,N-*diacetyl-*O*-glycosylhydroxylamines* **6b–6e**. — Hydrazine hydrate (0.1 mL of 100% reagent, 2 mmol) was added to a solution of *O*-glycosyl-*N*-hydroxyphthalimide[7] (**5b–5e**) in tetrahydrofuran, and the reaction mixture was stirred for 15 min at room temperature. After cooling to 0°, the resulting crystalline material was removed by filtration, and the filtrate was treated with an excess of acetic anhydride–pyridine mixture containing a catalytic amount of 4-dimethylaminopyridine and kept for 1 h at 0°. Co-evaporation with toluene, followed by chromatography (hexane–ethyl acetate), yielded products **6b–6e**. For physicochemical data, see Table I; for elemental analyses, see Table II.

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