Note

Michael additions of thiols to levoglucosenone*

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(Received February 10th, 1986; accepted for publication, May 10th, 1986)

There has been interest in producing carbohydrate derivatives containing sulfur substituted at positions other than C-1, because of their utility as synthetic intermediates¹⁻³ or target compounds^{4,5}, and their usefulness in mechanistic studies⁶⁻⁸. Levoglucosenone (1, 1,6-anhydro-3,4-dideoxy- β -D-glycero-hex-3-eno-pyranos-2-ulose), obtained from the pyrolysis of cellulose⁹, is well suited as a starting material for addition reactions because of its α,β -unsaturated carbonyl functionality. Michael addition of thiols to levoglucosenone consistently produced sulfur-containing carbohydrate derivatives which were readily isolated in high yields.



Addition of 1-butanethiol to levoglucosenone produced 2 (1,6-anhydro-4-S-butyl-3-deoxy-4-thio- β -D-erythro-hexopyranos-2-ulose) in quantitative yield. The steric hindrance of the 1,6-anhydro bridge prevented the 4-equatorial (e) product from forming, and only the 4-axial (a) product was obtained. The pyranose ring of 2 can exist in two possible conformations, ${}^{1}C_{4}$ or a boat. The ¹H-n.m.r. spin-spin coupling-constants, $J_{3a,4}$ and $J_{3e,4}$, indicate that the pyranose ring possesses the ${}^{1}C_{4}$ conformation (slightly distorted due to the 2-carbonyl). In every case, $J_{3a,4}$ was measured to be \sim 7 Hz (see Table III), and $J_{3e,4} < 1$ Hz (often

^{*}This work is an extension of a project initiated by the late Dr. Fred Shafizadeh.

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observed only as broadening of the H-4 and H-3e signals). This is consistent with dihedral angles of $\sim 30^{\circ}$ between H-3a and H-4, and $\sim 90^{\circ}$ between H-3e and H-4, as measured on a Dreiding model of **2**. With the pyranose ring in a boat conformation, the dihedral angle between H-3a and H-4 is $\sim 180^{\circ}$, while that between H-3e and H-4 is $\sim 50^{\circ}$, which would result in coupling constants of ~ 10 and ~ 3 Hz, respectively, according to the Karplus equation¹⁰. The same pyranose conformation and configuration at C-4 were found in compounds **3** through **9**.

Additions of 1-hexanethiol, 1-decanethiol, and 1-dodecanethiol to levoglucosenone gave the expected addition-products **3**, **4**, and **5** in 89, 99, and 89% yields respectively, providing a convenient method of attaching long hydrocarbon chains to a carbohydrate-derived structure.

Two branched-chain thiols, 2-methyl-1-propanethiol and 2-methyl-2propanethiol, were also successfully added to levoglucosenone, yielding 1,6anhydro-3-deoxy-4-S-isobutyl-4-thio- β -D-erythro-hexopyranos-2-ulose (6) and 1,6-anhydro-4-S-tert-butyl-3-deoxy-4-thio- β -D-erythro-hexopyranos-2-ulose (7), isolated in 86 and 82% yield, respectively. Steric hindrance by the tert-butyl group evidently slowed the reaction, which required 3 h for completion, compared with <1 h for the other thiols.

The addition of benzenethiol to levoglucosenone has already been reported⁹, giving the adduct in 85% yield. The addition of a saturated, cyclic thiol was attempted with cyclohexanethiol, and resulted in an 82% yield of the crystalline addition-product **8**, namely, 1,6-anhydro-4-S-cyclohexyl-3-deoxy-4-thio- β -D-erythro-hexopyranos-2-ulose. Therefore, both saturated and aromatic rings can be added to levoglucosenone in this manner.

The possibility of cross-linking two levoglucosenone molecules through the use of a dithiol was now investigated. 1,2-Ethanedithiol was chosen, and its reaction with levoglucosenone yielded two products. The structure of one of the products





Compound	І-Н	H-3a	Н-3е	H-4	Н-5	H-fexo	<i>H-6</i> endo	СН	CH ₂	СН3
7	5.11(s)	3.11(dd)	2.62(m)	3.38(d)	4.75(m)	4.02(dd)	4.05(d)	1	2.62	0.92(t)
3	5.10(s)	3.06(dd)	2.58(m)	3.34(d)	4.73(m)	4.00(dd)	4.04(d)	I	2.58	0.89(t)
4	5.14(s)	3.05(dd)	2.52(m)	3.29(d)	4.74(m)	4.00 ^b	4.04 ^b	I	2.52 2.52	0.88(t)
Ń	5.14(s)	3.05(dd)	2.52(m)	3.29(d)	4.74(m)	4.00 ^b	4.04 ^b	1	2.52	0.88(t)
v	5.10(s)	3.09(dd)	2.50(m)	3.32(d)	4.74(m)	4.00(dd)	4.04(d)	1.78(m)	2.50	(P)66'0
70	5.11(s)	3.17(dd)	2.59(dm)	3.30(dm)	4.76(m)	4.00(ddd)	4.07(dd)	ł	1	1.35(s)
ž	5.16(s)	3.12(dd)	2.54(dm)	3.45(d)	4.76(m)	4.04(brd)	4.09(dd)	2.81(m)	2.02-1.22	I
6	5.14(s)	3.11(dd)	2.52(dm)	3.40(d)	4.76(m)	4.01(dd)	4.05(d)		2.85	ł
				I VQ	141		a state - to -		- HM OLC +- P-F	

¹H-n.m.r. values (δ , 90 MHz) for michael addition products of levoglucosenone⁴

TABLE I

 $^{\alpha}$ CUCl₃ as solvent, with tetramethylsilane as the internal reference. o AB pattern with wing resonances not visible. 'Spectra recorded at 270 MHz.

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¹³C-N.M.R. VALUES (8; 22.5 MHz) FOR MICHAEL ADDITION PRODUCTS OF LEVOGLUCOSENONE⁴.

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Compound	С-1	C-2	C-3	C-4	C-5	C-6	Other				
							c	СН	CHS	CH ₂	CH ₃
7	101.6	199.3	38.4	45.7	76.7	67.9				31.5, 31.2, 22.0	13.7
3	101.6	198.1	38.5	45.8	76.7	67.8				31.5, 29.5, 22.5, 31.4,	14.0
P	101 6	107 8	78 4	157	7.47	67.0				28.5 31 0 20 5 20 2 20 0	14 1
•	0.404	0.177	1.00			225				31.5, 29.5, 29.2, 22.7	
5	101.6	197.8	38.4	45.7	76.7	67.9				32.0, 29.7, 29.5, 29.3,	14.1
										28.9, 31.5, 29.6, 29.4,	
										29.2, 22.7	
9	101.6	197.9	38.4	46.2	76.6	67.8		28.6		40.6	22.0
۲ ۲	101.4	198.1	41.0	43.6	78.9	67.8	43.8				31.1
90	101.6	197.9	39.1	44.2	77.0	67.8			44 .2	33.8, 25.9, 25.7	
6	101.6	197.6	38.5	45.4 46.2	76.8	67.9			4.04	31.4	
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^aCDCl₃ as solvent, with tetramethylsilane as the internal reference.

Compound	J _{3a,3e}	J _{3a,4}	J _{óendo, óexo}	J _{5,6exo}		
2	16.3	7.4	ھـــ	1.4		
3	16.6	7.2	5.1	1.3		
4	16.2	7.0	a	b		
5	16.4	7.2	#	b		
6	16.6	7.1	~6	1.7		
7	16.4	7.3	8.0	~3		
8	16.8	7.2	7.5	<i>b</i>		
9	16.9	7.4	@	~1		

TABLE III

¹H-N.M.R. SPIN-SPIN COUPLING-CONSTANTS (Hz) FOR MICHAEL ADDITION PRODUCTS OF LEVOGLUCOSENONE

"Appeared as singlets, due to disappearance of wing peaks. "Could not be detected.

(9), obtained in 47% yield, was determined, by ¹H- and ¹³C-n.m.r. and i.r. spectroscopy, to contain two levoglucosenone molecules, both bonded to the thiol through the C-4, axial position. Its symmetry is indicated by the n.m.r. spectra, in which the proton or carbon signals for the two levoglucosenone molecules are magnetically equivalent. However, integration of the ¹H-n.m.r. signals for H-1 and the thiol $-CH_2$ protons gave a 1:2 ratio, not the 1:4 ratio which would exist if only one levoglucosenone molecule had reacted. Another product was isolated that could not be identified. It was somewhat unstable, decomposing slowly at room temperature to yield very polar secondary products, as shown by thin-layer chromatography. Its ¹H- and ¹³C-n.m.r. spectra indicated that three levoglucosenone molecules may be involved in the structure. A product resulting from monoaddition was not detected.

These successful, high-yield reactions indicate the synthetic utility of levoglucosenone, and the ease of adding sulfur nucleophiles to the C-4 position. This provides an opportunity for the synthesis of sulfur-containing carbohydrates having the sulfur at a position other than C-1.

EXPERIMENTAL

General methods. — To a solution of levoglucosenone in chloroform at room temperature were added 1 mol. equiv. (or a slight excess) of the thiol and a catalytic amount of triethylamine ($\sim 2\%$ of the mass of levoglucosenone). The reactions were monitored by thin-layer chromatography and, upon completion, the reaction solutions were eluted through a silica column with 1:1 hexane-ethyl acetate in order to isolate the products. Solids isolated were recrystallized from hexane or hexane-ethyl acetate, and oils were distilled under vacuum. Melting points were determined in a Fisher–Johns hot-stage melting-point apparatus, and are uncorrected. Infrared spectra were recorded with a Nicolet MX-1 Fourier-transform infrared spectrometer. Nuclear magnetic resonance spectroscopy was performed with either a Jeol FX-90Q 90-MHz or a Bruker 270-MHz instrument.

1,6-Anhydro-4-S-butyl-3-deoxy-4-thio-β-D-erythro-hexopyranos-2-ulose. — The reaction was complete within 5 min, and yielded 100% of the product (2, R = butyl) as an oil from 1.45 g (12 mmol) of levoglucosenone; ν_{max}^{neat} 2959, 2929, and 2873 (C–H stretches), 1754, 1735 (C=O), and 1114 cm⁻¹ (C–O–C).

Anal. Calc. for $C_{10}H_{16}O_3S$: C, 55.53; H, 7.46; S, 14.82. Found: C, 55.64; H, 7.62; S, 14.65.

1,6-Anhydro-3-deoxy-4-S-hexyl-4-thio-β-D-erythro-hexopyranos-2-ulose. — The reaction was complete within 45 min, to yield 89% of the product (3, R = hexyl) as an oil from 1.09 g (9 mmol) of levoglucosenone; ν_{max}^{neat} 2958, 2928, 2871, 2856 (C–H stretches), 1752, 1736 (C=O), and 1114 cm⁻¹ (C–O–C).

Anal. Calc. for C₁₂H₂₀O₃S: C, 58.99; H, 8.25; S, 13.12. Found: C, 59.07; H, 8.46; S, 13.17.

1,6-Anhydro-4-S-decyl-3-decxy-4-thio-β-D-erythro-hexopyranos-2-ulose. — Reaction was complete in 1 h, to yield the product (4, R = decyl) as a crystalline solid from 1.00 g (8 mmol) of levoglucosenone; m.p. 34–35°; $\nu_{\text{max}}^{\text{KBr}}$ 2952, 2919, 2850 (C–H stretches), 1754, 1732 (C=O), and 1111 cm⁻¹ (C–O–C).

Anal. Calc. for C₁₆H₂₀O₃S: C, 63.96; H, 9.39; S, 10.67. Found: C, 64.26; H, 9.54; S, 11.00.

1,6-Anhydro-3-deoxy-4-S-dodecyl-4-thio- β -D-erythro-hexopyranos-2-ulose. — Reaction was complete in 5 min, and yielded the product (5, R = dodecyl) as a crystalline solid in 89% yield from 1.12 g (9 mmol) of levoglucosenone; m.p. 44– 45°; $\nu_{\text{max}}^{\text{KBr}}$ 2953, 2917, 2850 (C-H stretches), 1753, 1732 (C=O), and 1110 cm⁻¹ (C-O-C).

Anal. Calc. for C₁₈H₃₂O₃S: C, 65.81; H, 9.82; S, 9.76. Found: C, 66.00; H, 9.98; S, 9.91.

1,6-Anhydro-3-deoxy-4-S-isobutyl-4-thio- β -D-erythro-hexopyranos-2-ulose. — Reaction was complete within 20 min, and yielded 86% of the product (**6**, R = *i*-butyl) as a crystalline solid from 1.37 g (11 mmol) of levoglucosenone; m.p. 28-28.5°; $\nu_{\rm max}^{\rm KBr}$ 2972, 2954, 2908, 2868 (C–H stretches), 1753, 1732 (C=O), and 1112 cm⁻¹ (C–O–C).

Anal. Calc. for $C_{10}H_{16}O_3S$: C, 55.53; H, 7.46; S, 14.82. Found: C, 55.60; H, 7.57; S, 14.63.

l,6-Anhydro-4-S-tert-butyl-3-deoxy-4-thio-β-D-erythro-hexopyranos-2-ulose. — Reaction was not complete in 2 h; therefore, an additional amount of 2-methyl-2-propanethiol (for a total of 1.3 mol. equiv.) was added, and reaction was then complete in an additional 1 h. The product (7, R = tert-butyl) was isolated as a crystalline solid in 82% yield from 1.18 g (9 mmol) of levoglucosenone; m.p. 67-68°; ν_{max}^{KBr} 2969, 2955, 2942, 2898, 2964 (C-H stretches), 1751, 1732 (C=O), and 1111 cm⁻¹ (C-O-C).

Anal. Calc. for $C_{10}H_{16}O_3S$: C, 55.53; H, 7.46; S, 14.82. Found: C, 55.46; H, 7.59; S, 14.75.

1,6-Anhydro-4-S-cyclohexyl-3-deoxy-4-thio- β -D-erythro-hexopyranos-2ulose. — Reaction was complete in 1 h, to yield the product (8, R = cyclohexyl) as a crystalline solid from 0.90 g (7 mmol) of levoglucosenone; m.p. 56–57°; $\nu_{\text{max}}^{\text{KBr}}$ 2927, 2851 (C–H stretches), 1751, 1731 (C=O), and 1112 cm⁻¹ (C–O–C).

Anal. Calc. for C₁₂H₁₈O₃S: C, 59.47; H, 7.48; S, 13.24. Found: C, 59.46; H, 7.59; S, 13.43.

Preparation of the symmetrical dimer 9. — Levoglucosenone (1.00 g, 8 mmol) in chloroform (10 mL) was treated with 1,2-ethanedithiol (0.70 mL, 1 mol. equiv.) and triethylamine. Reaction was complete within 30 min, and t.l.c. showed two products, R_F 0.14 and 0.33, which were separated by elution through a silica column. The symmetrical dimer 9 (R_F 0.14) was obtained as a crystalline solid (0.60 g, 43%); m.p. 88–90°; ν_{max}^{KBr} 2970, 2910 (C–H stretches), 1753, 1735 (C=O), and 1109 cm⁻¹ (C–O–C).

Anal. Calc. for C₁₄H₁₈O₆S₂: C, 48.54; H, 5.24; S, 18.51. Found: C, 48.37; H, 5.35; S, 18.20.

ACKNOWLEDGMENTS

This work was supported by the National Science Foundation, Research Grant PFR 80-23854. The author is also grateful to the Rocky Mountain Laboratory (NIAID) for the use of the 90-MHz n.m.r. spectrometer.

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