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X-RAY STRUCTURAL AND N.M.R.-SPECTRAL STUDIES OF METHYL α-L-EVALOPYRANOSIDE: REASSIGNMENT OF ANOMERIC CONFIGURATION FOR THE METHANOLYSIS PRODUCT OF METHYL 6-DEOXY-3-*C*-METHYL-α-L-MANNOFURANOSIDE

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ABSTRACT

The methanolysis product of methyl 6-deoxy-3-*C*-methyl-α-L-mannofuranoside has been reassigned as methyl 6-deoxy-3-*C*-methyl-α-L-mannopyranoside by X-ray crystallographic and n.m.r.-spectral analyses. The crystals of methyl α-L-evalopyranoside are monoclinic, space group *C*2, with cell dimensions: a = 12.913(2), b = 8.052(1), c = 9.766(2) Å, *B* = 105.13(2)°. The pyranoside ring exists in the $^1C_4$ conformation, with the methoxyl and 3-*C*-methyl groups axial. Nuclear Overhauser effects were measured for selected proton resonances in the ^{1}H-n.m.r. spectrum. Irradiation of the 3-*C*-methyl and 5-*C*-methyl group proton signals resulted in enhancements for H-2, H-4, H-5, and the methoxyl group hydrogen atoms, but not for H-1.

INTRODUCTION

In a recent Note[1] describing the synthesis of L-nogalose from L-rhamnose, we reported the conversion of methyl 6-deoxy-3-*C*-methyl-α-L-mannofuranoside (**1**) into methyl 6-deoxy-3-*C*-methyl-β-L-mannopyranoside (methyl β-L-evalopyranoside; **2**) by treatment with acidic methanol. The assignment of the β-L-configuration to **2** was made on the basis of (*1*) the ^{13}C-n.m.r. spectrum of **2**, which was identical with that reported[2] for an enantiomeric methyl D-evalopyranoside isolated from the antibiotic flambamycin and suggested[3] to be the β anomer, and (*2*) the discrepancy between other physical constants of **2** and those reported[3] for methyl α-D-evalopyranoside synthesized from D-mannose. Since the publication of our results, two groups have reported[4,5] syntheses of glycosides of nogalose. We were struck by the correlation of spectral and physical data reported for methyl α-L-evalopyranoside (**3**), an intermediate in both syntheses, with those of our product **2**, assumed to possess the opposite anomeric configuration. In view of the utility of evalose as a synthetic intermediate[6], and the possibility of error in our initial assign-

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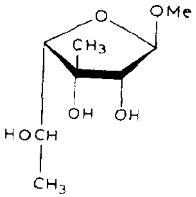
ment, we decided to analyze the structure of the methanolysis product of **1** by X-ray crystallography. In addition, ^{1}H- and ^{13}C-n.m.r.-spectral data were re-examined, and nuclear Overhauser effects (n.O.e.) were measured for selected proton resonances. The results of these studies are discussed herein.



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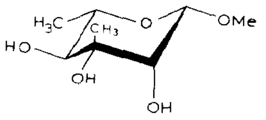

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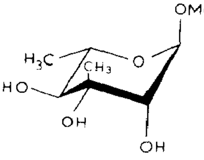

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EXPERIMENTAL

The crude methanolysis product was recrystallized from ether–methanol, giving the pure compound, the crystallographic parameters of which are collected in Table I. Preliminary photographic evidence revealed 2/*m* Laue symmetry, and systematic absences allowed any of the *C*-centered monoclinic space-groups *C*2, *C*m, or *C*2/m. Given the incompatibility of *m*-symmetry in the lattice with the proposed structure, *C*2 was initially chosen, and later confirmed by the appropriateness of the final structure. No correction for absorption effects was used ($T_{min}/T_{max} = 0.94$).

All non-hydrogen atom locations were obtained by direct methods (SOLV). Subsequent difference Fourier syntheses located all hydrogen atoms. Final refinement contained a model with all non-hydrogen atoms anisotropic and all hydrogen atoms isotropic.

All calculations used the SHELXTL (5.1) program library (Nicolet Corp., Madison, WI).

Atomic coordinates* are given in Table II, and bond distances and bond angles in Tables III and IV, respectively. Torsion angles are listed in Table V.

All n.m.r. spectra were recorded with a Varian XL-200 spectrometer. The ^{1}H-n.m.r. spectra were obtained at 200.06 MHz for solutions in $CDCl_3$, with a 4-s acquisition time, giving 0.125 Hz per point. The H-4 and H-5 resonances were computer-simulated by using Varian spin-simulation software. The H-1 and H-6 resonances were included in the spin set, giving a 0.19-Hz r.m.s. error for 13 lines for H-4 and H-5. Spectra were also recorded at 0.251 Hz per point for solutions in $CDCl_3$ containing 20% of CD_3SOCD_3 for better solubility. This mixed solvent was used for n.O.e. difference spectroscopy. N.O.e. enhancements were obtained on a

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*A list of structure factors has been deposited with, and can be obtained from, Elsevier Science Publishers B.V., BBA Data Deposition, P.O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/402/*Carbohydr. Res.*, 185 (1989) 61–67.

TABLE I

CRYSTALLOGRAPHIC DATA FOR METHYL α-L-EVALOPYRANOSIDE

(a) Crystal parameters

Formula	$C_8H_{16}O_5$	V (Å^3)	980.2
Formula weight	192.20	Z	4
Crystal system	monoclinic	D (calc); g.cm^{-3}	1.302
Space group	$C2$	Temp. (°C)	23
a (Å)	12.913(2)[a]	Color	colorless
b (Å)	8.052(1)	Size (mm)	0.36 × 0.39 × 0.42
c (Å)	9.766(2)	μ (MoKα) (cm^{-1})	1.01
β (degrees)	105.13(2)		

(b) Data collection

Diffractometer Nicolet R3m	Octants collected	$\pm h,\ +k,\ +l$
Radiation MoKα	Reflections collected	1255
Wavelength (Å) 0.71073	Independent reflections	1197
Monochromator graphite	Observed reflections ($3\sigma F_0$)	1122
Scan method $\theta/2\theta$	R (int) (%)	3.03
Scan limits, deg $4<2\theta<55$	Standard reflections	3 standards/97 reflections
Scan speed, deg.min^{-1} var. 4–15	Decay	<1%

(c) Refinement

$R(F)$ (%)	3.93	Δ/σ (final)	0.103
$R(wF)$ (%)	4.46	d (ρ) eÅ^{-3}	0.28
GOF	1.374	N_o/N_v	6.2
g[b]	0.001		

[a]Unit-cell parameters from the least-squares fit of 25 reflections (21° $\leq 2\theta \leq$ 30°). [b]$w^{-1} = \sigma^2(F_0) + F^{02}$.

nitrogen-purged sample at 30° with the decoupler gated on for a 15-s presaturation period, followed by a 2-s acquisition time. All spectra were referenced to internal tetramethylsilane. Both proton-coupled and -decoupled ^{13}C-n.m.r. spectra were obtained at 50.31 MHz for solutions in dry pyridine, with tetramethylsilane as the internal standard. Sharp locking was obtained by using a 4-mm (o.d.) coaxial insert containing C_6D_6.

RESULTS AND DISCUSSION

The molecular structure of the methyl evalopyranoside obtained by methanolysis of **2** is shown in Fig. 1. There are two short intermolecular hydrogen-bonds: O-2---H-O3, 2.04 Å, and O-3---H-O4, 1.98 Å. The pyranoside ring is in the $^1C_4$(L) conformation, with the anomeric methoxyl and 3-*C*-methyl groups axial.

The α-L-configuration for **3** was also consistent with the results of n.O.e. difference spectroscopy. Irradiation of the 3-*C*-methyl and 5-*C*-methyl group proton resonances, which overlap, resulted in enhancement of the signals for H-2 (13%), H-4 (8%), H-5 (19%), and the methoxyl group (2%), but not for H-1 (0%).

TABLE II

ATOMIC COORDINATES ($\times 10^4$) AND ISOTROPIC THERMAL PARAMETERS ($Å^2 \times 10^3$)

	x	y	z	U
C-1	7505(2)	576	7406(2)	38(1)[a]
C-2	7621(2)	1966(3)	6395(2)	33(1)
C-3	8793(2)	2474(3)	6563(2)	31(1)[a]
C-4	9489(2)	928(3)	6628(2)	32(1)[a]
C-5	9323(2)	−312(3)	7719(2)	36(1)[a]
C-6	9954(2)	−1894(4)	7748(4)	53(1)[a]
O-1	7688(1)	1268(3)	8765(2)	48(1)[a]
C-1′	7403(3)	186(5)	9768(4)	67(1)[a]
O-2	7143(1)	1368(3)	5008(2)	44(1)[a]
O-3	8854(1)	3309(2)	5292(2)	39(1)[a]
C-3′	9198(2)	3611(4)	7834(3)	43(1)[a]
O-4	10600(1)	1332(3)	6953(2)	44(1)[a]
O-5	8202(1)	−771(2)	7366(2)	39(1)[a]
HO-2[b]	719(2)	197(4)	452(3)	41(7)
HO-3	869(2)	427(4)	534(3)	49(7)
HO-4	1064(3)	205(5)	623(3)	48(7)
H-1	687(2)	13(4)	717(3)	49(8)
H-1′A	772(3)	−98(7)	969(4)	74(11)
H-1′B	668(4)	−18(8)	951(5)	114(15)
H-1′C	763(3)	73(6)	1066(3)	80(11)
H-2	727(2)	286(3)	661(2)	21(5)
H-3′A	912(3)	307(5)	875(3)	60(9)
H-3′B	885(3)	453(5)	772(3)	53(8)
H-3′B	976(3)	402(6)	780(3)	66(10)
H-4	927(2)	36(4)	576(2)	29(6)
H-6A	981(4)	−268(10)	829(6)	116(16)
H-6B	981(3)	−244(6)	678(4)	77(11)
H-6C	1069(3)	−166(6)	809(3)	72(10)
H-5	951(2)	15(3)	862(2)	24(5)

[a]Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor. [b]Hydrogen atom coordinates $\times 10^3$.

TABLE III

BOND LENGTHS (Å)

C-1–C-2	1.525(3)	C-1–O-1	1.402(3)
C-1–O-5	1.416(2)	C-1–H-1	0.87(3)
C-2–C-3	1.534(3)	C-2–O-2	1.418(3)
C-2–H-2	0.90(2)	C-3–C-4	1.528(3)
C-3–O-3	1.433(3)	C-3–C-3′	1.521(3)
C-4–C-5	1.516(3)	C-4–O-4	1.423(3)
C-4–H-4	0.94(2)	C-5-6	1.509(4)
C-5–O-5	1.445(3)	C-5–H-5	0.93(2)
C-6–H-6A	0.88(7)	C-6–H-6B	1.01(4)
C-6–H-6C	0.94(4)	O-1–C-1′	1.424(5)
C-1′–H-1′A	1.05(5)	C-1′–H-1′B	0.95(5)
C-1′–H-1′C	0.95(3)	O-2–HO-2	0.69(3)
O-3–HO-3	0.81(3)	C-3′–H-3′A	1.02(4)
C-3′–H-3′B	0.86(4)	C-3′–H-3′C	0.81(4)
O-4–HO-4	0.93(3)		

TABLE IV

BOND ANGLES (DEGREES)

C-2–C-1–O-1	107.5(1)	C-2–C-1–O-5	112.0(2)
O-1–C-1–O-5	112.3(2)	C-2–C-1–H-1	112.1(18)
O-1–C-1–H-1	108.7(19)	O-5–C-1–H-1	104.3(21)
C-1–C-2–C-3	112.7(2)	C-1–C-2–O-2	106.1(2)
C-3–C-2–O-2	111.3(2)	C-1–C-2–H-2	107.0(16)
C-3–C-2–H-2	107.7(14)	O-2–C-2–H-2	112.0(13)
C-2–C-3–C-4	109.9(2)	C-2–C-3–O-3	108.0(2)
C-4–C-3–O-3	104.7(2)	C-2–C-3–C-3′	111.6(2)
C-4–C-3–C-3′	112.5(2)	O-3–C-3–C-3′	109.9(2)
C-3–C-4–C-5	112.1(2)	C-3–C-4–O-4	111.8(2)
C-5–C-4–O-4	108.3(2)	C-3–C-4–H-4	108.8(16)
C-5–C-4–H-4	104.2(17)	O-4–C-4–H-4	111.8(16)
C-4–C-5–C-6	113.2(2)	C-4–C-5–O-5	108.5(2)
C-6–C-5–O-5	106.9(2)	C-4–C-5–H-5	110.8(16)
C-6–C-5–H-5	108.2(15)	O-5–C-5–H-5	109.1(15)
C-5–C-6–H-6A	115(4)	C-5–C-6–H-6B	112.4(23)
H-6A–C-6–H-6B	103(5)	C-5–C-6–H-6C	109(3)
H-6A–C-6–H-6C	107(4)	H-6B–C-6–H-6C	110(3)
C-1–O-1–C-1′	113.6(2)	O-1–C-1′–H-1′A	108.5(24)
O-1–C-1′–H-1′B	115(3)	H-1′A–C-1′–H-1′B	94(4)
O-1–C-1′–H-1′C	107(3)	H-1′A–C-1′–H-1′C	116(3)
H-1′B–C-1′–H-1′C	116(4)	C-2–O-2–HO-2	109.0(23)
C-3–O-3–HO-3	108.5(22)	C-3–C-3′–H-3′A	111.4(20)
C-3–C-3′–H-3′B	110.6(19)	H-3′A–C-3′–H-3′B	108(3)
C-3–C-3′–H-3′C	109.2(27)	H-3′A–C-3′–H-3′C	121(3)
H-3′B–C-3′–H-3′C	96(4)	C-4–O-4–HO-4	103.2(19)
C-1–O-5–C-5	113.6(2)		

TABLE V

SOME TORSIONAL ANGLES (DEGREES)

O-1–C-1–C-2–C-3	74.1	O-2–C-2–C-3–C-3′	161.5
O-1–C-1–C-2–O-2	−163.8	C-2–C-3–C-4–C-5	−51.2
O-5–C-1–C-2–C-3	−49.7	C-2–C-3–C-4–O-4	−173.0
O-5–C-1–C-2O-2	72.4	O-3–C-3–C-4–C-5	−167.0
C-2–C-1–O-1–C-1′	168.4	O-3–C-3–C-4–O-4	71.3
O-5–C-1–O-1–C-1′	−68.0	C-3′–C-3–C-4-5	73.8
C-2–C-1–O-5–C-5	58.4	C-3′–C-3–C-4–O-4	−48.0
O-1–C-1–O-5–C-5	−62.6	C-3–C-4–C-5–C-6	176.7
C-1–C-2–C-3–C-4	46.1	C-3–C-4–C-5–O-5	58.2
C-1–C-2–C-3–O-3	159.7	O-4–C-4–C-5–C-6	−59.5
C-1–C-2–C-3–C-3′	−79.4	O-4–C-4–C-5–O-5	−178.0
O-2–C-2–C-3–C-4	−72.9	C-4–C-5–O-5–C-1	−62.2
O-2–C-2–C-3–O-3	40.7	C-6–C-5–O-5–C-1	175.3

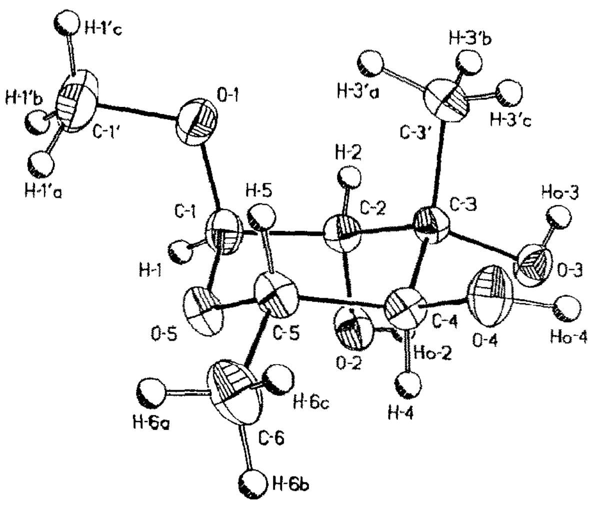

Fig. 1. Structure of compound **3**. [Hydrogen atoms are depicted with spheres having an arbitrary radius, and the non-hydrogen atoms, with 40%-probability ellipsoids.]

TABLE VI

^{1}H-N.M.R. CHEMICAL SHIFTS (δ) AND COUPLING CONSTANTS (Hz) OF METHYL α-L-EVALOPYRANOSIDE (**3**)

Solvent	*H-1* ($J_{1,2}$)	*H-2*	*H-4* ($J_{4,5}$)	*H-5* ($J_{1,5}$)	*H-6* ($J_{5,6}$)	*CH_3-3*	*OCH_3*
$CDCl_3$	4.70 (1.35)	3.60	3.50 (9.66)	3.64 (0.61)	1.32 (6.03)	1.34	3.38
1:4 CD_3SOCD_3–$CDCl_3$	4.61 (1.46)	3.48	3.40 (9.66)	3.53	1.26 (6.02)	1.25	3.33
$CDCl_3$ (lit.[4])	4.69	3.66–3.51 (m, 3 H)			1.31 (6.2)	1.33	3.38
C_5D_5N	5.14	4.26–3.96 (m, 3 H)			1.61 (6.0)	1.84	3.38
C_5D_5N (lit.[7])	4.96 (1.5)	3.91	3.95 (m, 2 H)		1.48 (6.0)	1.67	3.29

TABLE VII

^{13}C-N.M.R. CHEMICAL SHIFTS (δ) FOR METHYL α-L-EVALOPYRANOSIDE (**3**)

Solvent	*C-1*	*C-2, C-4*	*C-3*	*C-5*	*OCH_3*	*CH_3-3*	*C-6*
C_5H_5N	103.0	75.9, 76.0	73.1	68.4	54.8	20.0	18.9
C_5D_5N (lit.[2])	103.0	76.1, 76.1	73.2	68.5	54.8	20.0	18.9

The large value for H-2 reflects the error in separating its enhancement from H-5. Chemical shifts for ^{1}H- and ^{13}C-n.m.r. spectra and the *J* values for some of the proton resonances are given in Tables VI and VII, respectively, along with the n.m.r. data reported for methyl α-L-evalopyranoside synthesized[4] by Parker and Meschwitz. ^{13}C-N.m.r. shifts for the glycoside isolated from the antibiotic flambamycin are also listed (for comparison).

From the results of this study it is clear that the product of methanolysis of **1** is methyl α-L-evalopyranoside (**3**), and not the corresponding β-L anomer.

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