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Note

X-ray crystal structure analysis of 4,7,8,9-tetra-*O*-acetyl-*N*-acetyl-2,3-dehydro-2-deoxy-4-epi-neuraminic acid methyl ester

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Abstract

X-ray crystallographic analysis was performed on a single crystal of 4,7,8,9-tetra-*O*-acetyl-*N*-acetyl-2,3-dehydro-2-deoxy-4-epi-neuraminic acid methyl ester. The pyranoid ring adopts the $^5H_6$ conformation.

Keywords: Sialic acid; 4-Epimer; X-ray analysis

The best inhibitors of sialidase known thus far are 2,3-dehydro-2-deoxy-*N*-acetylneuraminic acid (Neu2en5Ac) and some of its analogues. Its diastereomer 5-acetamido-2,6-anhydro-2,3,5-trideoxy-D-*glycero*-D-*talo*-non-2-enonic acid (4-*epi*-Neu2en5Ac) and its analogues are significantly weaker inhibitors [1]. However, von Itzstein et al. [2] reported that derivatives of 4-*epi*-Neu2en5Ac having a large substituent at the 4-position possess potent antiviral activities. A great deal of interest has centered on the stereochemistry of these compounds, since their conformation may well affect their biological activities. The crystal structure of Neu2en5Ac has been established by X-ray diffraction analysis by Furuhata et al. [3].

Herein, we present the crystal and molecular structure of 4,7,8,9-tetra-*O*-acetyl-*N*-acetyl-2,3-dehydro-2-deoxy-4-epi-neuraminic acid methyl ester (methyl 4,7,8,9-tetra-*O*-acetyl-5-acetamido-2,6-anhydro-2,3,5-trideoxy-D-*glycero*-D-*talo*-non-2-enoate (**1**)).

1. Results and discussion

Initially we intended to obtain crystals of 4-*epi*-Neu2en5Ac or its methyl ester, but both were difficult to crystallize from several solvents. Fortunately, methyl 4,7,8,9-tetra-*O*-acetyl-4-*epi*-Neu2en5Ac methyl ester, prepared from 4-*epi*-Neu2en5Ac ester [4,5] by acetylation in pyridine, yielded crystals from 1:1 acetone–2-propanol, suitable for X-ray crystallographic analysis.

All measurements were made on a Rigaku AFC7R diffractometer with graphite-mono-

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chromated Mo Kα radiation. The results are summarized in Table 1. The atomic coordinates of the non-hydrogen atoms are listed in Table 2. The ORTEP plot for compound **1** is shown in Fig. 1 and the puckering of the molecule is shown in Fig. 2. The pyranoid ring adopts a $^5H_6$ conformation.

Table 1
Crystal data and structure refinement for compound **1**

Empirical formula	$C_{23}H_{35}NO_{13}$
Formula weight	533.53
Crystal color, habit	colorless, prismatic
Crystal dimensions	$0.20 \times 0.20 \times 0.30$ mm
Crystal system	monoclinic
Lattice type	primitive
Number of reflections used for unit cell determination (2θ range) (°)	19 (13.8-21.3)
Omega scan peak width at half-height (°)	0.11
Lattice parameters	
a (Å)	9.333(2)
b (Å)	9.462(1)
c (Å)	15.813(2)
β (°)	99.56(1)
V (Å^3)	1377.2(4)
Space group	$P2_1$ (# 4)
Z	2
D_{calc} (g cm^{-3})	1.287
F_{000}	568.00
μ(Mo Kα) (cm^{-1})	1.06
Temperature (°C)	20
Scan type	ω–2θ
$2\theta_{max}$ (°)	55.0
Number of reflections measured	
Total	3552
Unique	3353
R_{int}	0.024
Corrections	Lorentz-polarization absorption (transmission factors: 0.9638–1.0000); secondary extinction (coefficient: 1.81925e-06)
Reflection/parameter ratio	5.41
Residuals: R; R_w	0.051; 0.054
Goodness of fit indicator	1.73
Max shift/error in final cycle	0.08
Maximum peak in final difference map (e Å^{-3})	0.21
Minimum peak in final difference map (e Å^{-3})	−0.17
Index ranges	$0 \le h \le 12$, $0 \le k \le 12$, $-19 \le l \le 19$

Table 2
Fractional atomic coordinates and equivalent thermal parameters

Atom	x	y	z	B_{eq}
O-1	0.0995(4)	0.9707	0.6564(2)	4.30(9)
O-2	0.0402(5)	1.1960(6)	0.4776(3)	6.1(1)
O-3	0.1790(4)	1.0049(6)	0.5130(2)	4.8(1)
O-4	−0.3773(5)	1.2723(7)	0.6887(3)	7.0(1)
O-5	0.2608(4)	1.0641(6)	0.7056(2)	4.52(9)
O-6	0.00892(5)	1.1380(6)	0.9428(2)	5.8(1)
O-7	0.2617(6)	0.7993(7)	0.9403(3)	7.6(1)
O-8	0.2649(4)	0.8847(6)	0.8080(2)	4.23(9)
O-10	0.2425(4)	0.5847(6)	0.7823(2)	4.50(10)
O-11	0.4010(5)	0.6627(7)	0.5262(3)	6.6(1)
O-12	0.2662(5)	0.5702(6)	0.6162(3)	5.3(1)
O-13	0.2088(6)	0.2283(6)	0.1129(3)	7.5(1)
N	−0.0668(5)	1.0019(6)	0.8533(3)	4.2(1)
C-1	0.0271(5)	1.0789(7)	0.6089(3)	3.7(1)
C-2	−0.0734(6)	1.1560(7)	0.6336(4)	4.2(1)
C-3	−0.1195(6)	1.1375(7)	0.7179(4)	4.5(1)
C-4	−0.0133(6)	1.0447(7)	0.7752(3)	3.9(1)
C-5	0.0279(6)	0.9186(7)	0.7247(3)	4.0(1)
C-6	0.0798(6)	1.1020(8)	0.5255(4)	4.0(1)
C-7	0.2341(7)	1.0191(9)	0.4339(4)	5.9(2)
C-8	−0.3808(7)	1.1460(9)	0.6907(4)	4.9(2)
C-9	−0.5152(7)	1.0617(9)	0.6728(4)	6.3(2)
C-10	−0.0135(7)	1.0538(7)	0.9320(3)	4.3(1)
C-11	−0.0834(7)	1.0011(8)	1.0034(4)	5.8(2)
C-12	0.3172(7)	0.8670(8)	0.8937(4)	5.0(2)
C-13	0.4585(8)	0.950(1)	0.9168(4)	7.6(2)
C-14	0.1320(6)	0.8123(7)	0.7748(4)	3.8(1)
C-15	0.1620(6)	0.6850(7)	0.7218(3)	3.9(1)
C-16	0.2519(6)	0.7104(8)	0.6523(4)	4.7(2)
C-17	0.1863(8)	0.4568(7)	0.7873(4)	4.8(2)
C-18	0.2951(7)	0.3612(8)	0.8386(5)	5.9(2)
C-19	0.3444(7)	0.5621(8)	0.5528(4)	4.9(2)
C-20	0.3461(8)	0.4150(9)	0.5203(5)	6.5(2)
C-21	0.3404(10)	0.172(1)	0.2462(5)	9.1(3)
C-22	0.283(1)	0.122(1)	0.11626(6)	10.4(3)
C-23	0.296(1)	−0.006(1)	0.1339(7)	12.7(4)

2. Experimental

General methods.—^{1}H NMR spectra were measured with a Bruker AMX-300 instrument at 300 MHz. The optical rotations was determined with a Perkin–Elmer B25 polarimeter in a 1 dm tube at the D line of sodium at rt. The melting point was uncorrected.

Methyl 4,7,8,9-tetra-O-*acetyl-2,5-dehydro-2-deoxy-4*-epi-*Neu2en5Ac ester.*—To a solution of 4-*epi*-Neu2en5Ac (5.0 g, 0.016 mmol) in pyridine (50 mL) was added Ac_2O (31 μL,

0.33 mmol) and the mixture was heated at rt for 14 h, poured into ice–water, stirred and extracted with $CHCl_3$. The extract was washed with acidified water to pH 7, dried and evaporated to give **1** as a colorless oil. Crystallization from acetone–2-propanol gave crystals of **1**. Mp 75–77°C, $[\alpha]_D^{20}$ −12.6° (*c* 2.0, $CHCl_3$), ^{1}H NMR ($CDCl_3$) δ 6.18 (d, 1 H, $J_{3,4} = 5.6$ Hz, H-3), 5.83(br, 1 H, NH), 5.44 (dd, 1 H, $J_{7,8} = 4.1$, $J_{7,6} = 2.1$ Hz, H-7), 5.27 (ddd, 1 H, $J_{8,9} = 7.7$, $J_{8,9'} = 2.6$ Hz, H-8), 5.13 (dd, 1 H, $J_{4,5} = 4.0$ Hz, H-4), 4.75 (dd, 1 H, $J_{9'9} = 12.4$ Hz, H-9′), 4.55 (dd, 1 H, $J_{5,6} = 10.5$ Hz, H-5), 4.25 (dd, 1 H, H-6), 4.15 (dd, 1 H, H-9), 3.73 (s, 3 H, CO_2CH_3), 2.08, 2.06, 2.05, 2.04 (4s, 12 H, 4OAc), 1.08 (s, 3H, NHAC).

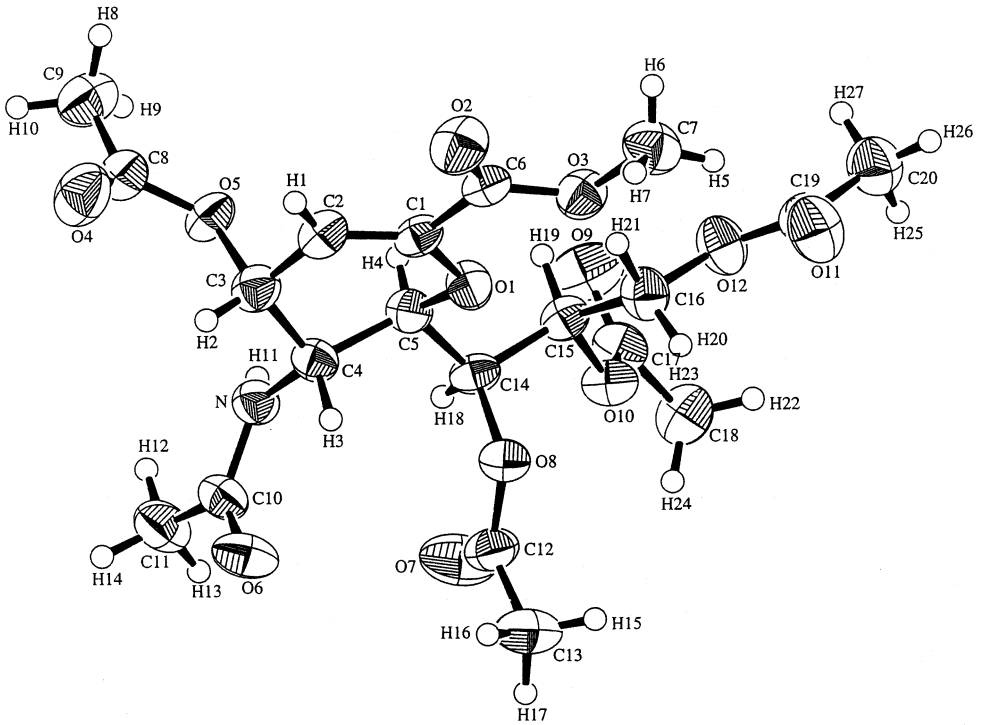

Fig. 1. ORTEP plot for the title compound.

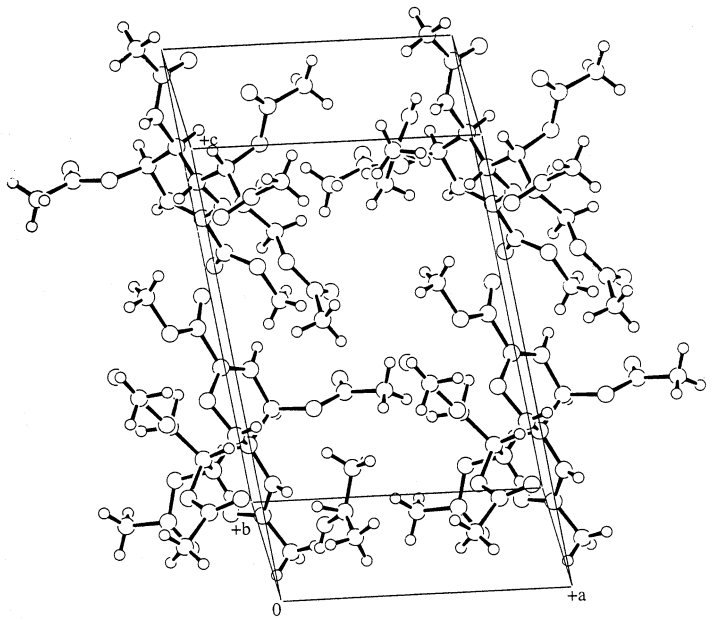

Fig. 2. Arrangement of the molecules in the unit cell.

3. Supplementary material

Tables of atomic coordinates, bond lengths and bond angles have been deposited with the Cambridge Crystallographic Data Center. These may be obtained on request from The Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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