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STRUCTURE OF 2-ACETAMIDO-3-AMINO-2,3-DIDEOXY-D-GLUCOFURANURONO-6,3-LACTAM

YOKO SUGAWARA, HITOSHI IWASAKI,
The Institute of Physical and Chemical Research, Wako-shi, Saitama 351-01 (Japan)

NACHIKO SUZUKI,
The Institute of Medical Science, The University of Tokyo, Shirokanedai, Minato-ku, Tokyo 108 (Japan)

AND SATOSHI OKUDA
Chemical Laboratory, College of General Education, Nagoya University, Chikusa-ku, Nagoya 464 (Japan)

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ABSTRACT

An X-ray crystallographic analysis of the title compound, an *N*-acetyl derivative of the 2,3-diamino-2,3-dideoxy-D-glucofuranurono-6,3-lactam found in the hydrolyzate of *Pseudomonas aeruginosa* P14 lipopolysaccharide, was performed. The crystals are monoclinic, space group $P2_1$, $a = 11.704(2)$, $b = 5.333(1)$, $c = 7.399(2)$ Å, $\beta = 91.63(2)°$, and $Z = 2$. The structure was solved by direct methods and refined by the block-diagonal least-squares method to a final R value of 0.046 for 796 independent reflections. The dihedral angle between the mean plane through the furanose ring and that through the γ-lactam ring is 106.2(2)°, the furanose ring is $^1T_2$, and the C-3, C-4, C-6, and N-3 atoms of the γ-lactam ring are nearly coplanar. The conformation in aqueous solution is discussed, based on the ^{1}H-n.m.r. data.

INTRODUCTION

Recently, a new 2-amino sugar found in the hydrolyzate of *Pseudomonas aeruginosa* P14 lipopolysaccharide was identified as 2,3-diamino-2,3-dideoxy-D-glucofuranurono-6,3-lactam (**1**), based on n.m.r., i.r., and mass-spectroscopic studies, and on synthesis[1,2]. Although compound **1** was too labile to crystallize, its 2-*N*-acetyl derivative, 2-acetamido-3-amino-2,3-dideoxy-D-glucofuranurono-6,3-lactam (**2**), gave stable crystals. We performed X-ray crystallographic analysis of this compound in order to confirm its molecular identity and to reveal structural characteristics.

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TABLE I

CRYSTAL DATA

Molecular formula	$C_8H_{12}N_2O_5$
Crystal system	monoclinic
Space group	$P2_1$
a (Å)	11.704(2)
b (Å)	5.333(1)
c (Å)	7.399(2)
β (°)	91.63(2)
Volume of unit cell (Å^3)	461.7(2)
Z	2
Dx (Mg m^{-3})	1.555

EXPERIMENTAL

A crystal of synthetic **2**, approximately 0.5 × 0.08 × 0.02 mm, which was crystallized from methanolic solution[2], was used to collect the reflection data. Cell constants were refined by the least-squares procedure on 19 reflections. The crystal data are shown in Table I. X-Ray intensity-data were measured on a Rigaku automated four-circle diffractometer with graphite-monochromated CuKα radiation through the range $2\theta \leqq 128°$ with the $\omega - 2\theta$ scan-mode. They were corrected for Lorentz, polarization, and absorption factors [μ(CuKα) = 1.074 mm^{-1}]. The structure was solved by direct methods using[3] MULTAN78, and refined by the block-diagonal least-squares method, taking account of the anomalous scattering effect. All the hydrogen atoms were located on a difference-Fourier map, and inclusion of H atoms with isotropic temperature-factors gave a final R value of 0.046 for 796 independent reflections [$|F_o| \geqq 3\sigma(F_o)$]. The weighting scheme for the final refinement was: $w = 0.5$ for $|F_o| < 5.0$, $w = 1.0$ for $5.0 \leqq |F_o| < 12.0$, $w = (6.0/|F_o|)^2$ for $12.0 \leqq |F_o|$, and $R_w = 0.053$. No peak higher than 0.24 eÅ^{-3} was observed in the final difference-Fourier map. Calculations were performed with a FACOM M-380 computer of the Institute of Physical and Chemical Research using the UNICS III program system[4]. Atomic scattering-factors and the correction terms for anomalous scattering were taken from International Tables for X-ray Crystallography[5].

RESULTS AND DISCUSSION

Atomic coordinates of non-hydrogen atoms are listed in Table II*, and the molecular structure with the atom-numbering scheme is shown in Fig. 1. Com-

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*Tables of observed and calculated structure-factors, anisotropic thermal parameters of non-hydrogen atoms, and hydrogen-atom positions can be obtained on request from Elsevier Science Publishers B.V., BBA Data Deposition, P.O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/317/*Carbohydr. Res.*, 142 (1985) 195–201.

TABLE II

ATOMIC COORDINATES (× 10^4) AND EQUIVALENT TEMPERATURE FACTORS ($Å^2$)[a]

Atom	x	y	z	B_{eq}
C-1	3430(3)	2399(8)	−844(5)	2.31
C-2	2209(3)	3281(8)	−475(5)	2.24
C-3	2273(3)	3964(8)	1550(5)	2.27
C-4	3533(3)	4670(8)	1901(5)	2.38
C-5	3885(3)	3265(8)	3629(6)	2.71
C-6	3020(3)	1170(9)	3736(5)	2.34
C-7	856(3)	5898(8)	−2212(5)	2.28
C-8	678(4)	8214(9)	−3286(6)	3.15
N-2	1919(3)	5432(7)	−1579(5)	2.53
N-3	2115(3)	1761(7)	2689(5)	2.40
O-1	3502(2)	−166(6)	−411(4)	2.88
O-4	4128(2)	3865(6)	347(4)	2.63
O-5	5001(2)	2272(7)	3658(5)	3.90
O-6	3121(2)	−734(6)	4681(4)	3.05
O-7	65(2)	4403(6)	−1914(4)	3.23

[a] E.s.d. values in parentheses. Equivalent temperature factors are defined by the expression $B_{eq} = 4/3\Sigma_i\Sigma_j a_i a_j B_{ij}$, where a_i values are cell constants.

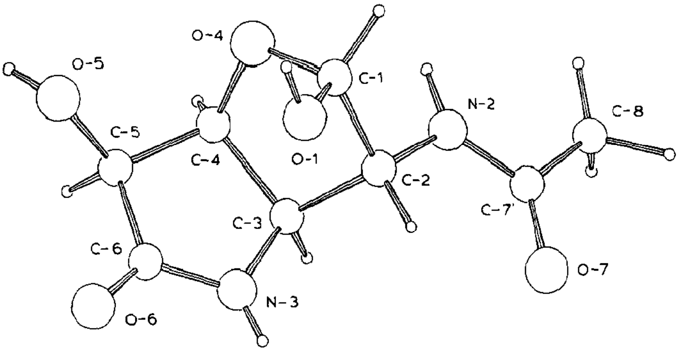

Fig. 1. Molecular structure of 2-acetamido-3-amino-2,3-dideoxy-β-D-glucofuranurono-6,3-lactam (**2**) with the atom-numbering scheme.

pound **2** was shown to consist of fused furanose and γ-lactam rings, which confirms the structure previously proposed by spectroscopic studies[1,2]. Although equal amounts of the α and the β anomers exist in aqueous solution, based on the n.m.r. spectrum[2], this compound exists as the β anomer in this crystal, and the difference-Fourier map gave no evidence of coexistence with the α anomer.

Structure parameters are shown in Fig. 2. They coincide with the standard bond-lengths and -angles of furanosides[6] or peptides[7] within 3σ. The dihedral angle between two ring planes, namely, the mean plane defined by C-1, C-2, C-3, C-4, and O-4 and that defined by C-3, C-4, C-5, C-6, and N-3, is 106.2(2)°. The torsional angles in the furanose and lactam rings are listed in Table III. The furanose ring

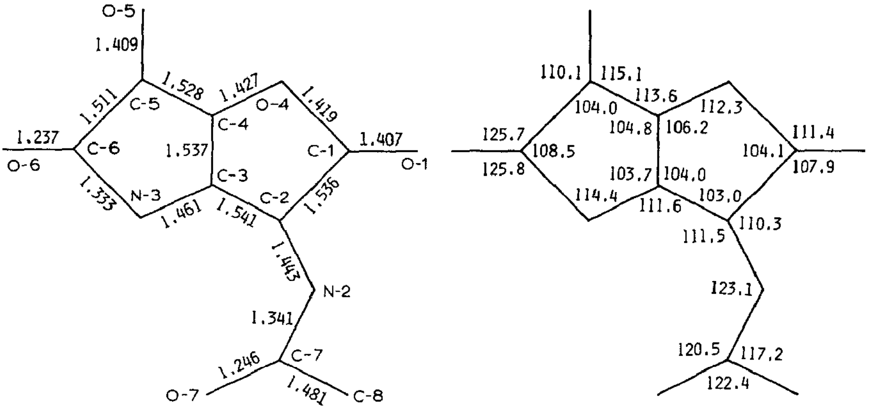

Fig. 2. Bond lengths (Å) and bond angles (degrees) of **2**. The e.s.d. values of the bond lengths are 0.005–0.007 Å and those of the bond angles are 0.3–0.4°.

TABLE III

TORSIONAL ANGLES (DEGREES)[a] IN FURANOSE RINGS AND LACTAM OR LACTONE RINGS OF 2-ACETAMIDO-3-AMINO-2,3-DIDEOXY-β-D-GLUCOFURANURONO-6,3-LACTAM (**2**), β-D-GLUCOFURANURONO-6,3-LACTONE[8] (**3**), 3*R*-(1′ *S*-AMINOCARBOXYMETHYL)-2-PYRROLIDONE-5*S*-CARBOXYLIC ACID[9] (**4**) AND L-PYRROLID-2-ONE-5-CARBOXAMIDE[10] (**5**)

Furanose ring				
	2	**3**		
O-4–C-1–C-2–C-3	−32.2(4)	−37.0(4)		
C-1–C-2–C-3–C-4	27.0(4)	26.8(4)		
C-2–C-3–C-4–O-4	−12.5(4)	−8.1(4)		
C-3–C-4–O-4–C-1	−8.7(4)	−15.8(4)		
C-4–O-4–C-1–C-2	26.1(4)	33.4(4)		
Lactam ring or lactone ring[b]				
	2	**3**	**4**	**5**
X-3–C-3–C-4–C-5	−16.3(4)	−10.1(4)	−31.7(3)	−23.5(5)
C-3–C-4–C-5–C-6	21.2(4)	15.5(4)	30.1(3)	19.8(5)
C-4–C-5–C-6–X-3	−19.1(4)	−16.6(5)	−18.0(3)	−8.6(6)
C-5–C-6–X-3–C-3	9.2(5)	10.6(5)	−3.2(4)	−7.4(6)
C-6–X-3–C-3–C-4	4.8(4)	0.0(4)	22.7(4)	20.3(6)

[a] These values were calculated from the reported atomic coordinates. E.s.d. values in parentheses. [b] X is a nitrogen atom in the lactam ring and an oxygen atom in the lactone ring.

adopts the $^1T_2$ conformation, with C-1 and C-2 being out of the plane defined by C-3, C-4, and O-4 by 0.20(1) and −0.32(1) Å, respectively. The C-6, N-3, C-3, and C-4 atoms of the lactam ring are coplanar within ±0.026 Å, and C-5 and O-6 are out of this plane by −0.33(1) and 0.13(1) Å, respectively. The *N*-acetyl group attached to C-2 adopts a trans–gauche$^-$ orientation [φ(C-1–C-2–N-2–C-7) = 147.7(4)° and φ(C-3–C-2–N-2–C-7) = −98.4(4)°].

It is interesting to compare the structure of **2** with that of β-D-glucofuranurono-6,3-lactone (**3**), which consists of fused furanose and lactone rings[8] (Table III). The conformation of **3** resembles that of **2** in the following points. The dihedral angle between the mean plane through the furanose ring and that through the γ-lactone ring is calculated to be 102.9(2)° from the atomic coordinates reported. The furanose ring adopts the $^1T_2$ conformation. The C-6, O-3, C-3, and C-4 atoms of the γ-lactone ring are coplanar, showing good correspondence to the structure of the γ-lactam ring of **2**. The C-5, C-6, O-6, X-3, and C-3 atoms of the γ-lactam (X; nitrogen) or γ-lactone (X; oxygen) are expected to be coplanar because of the double-bond character of the amide or ester linkage. In the case of the γ-lactam derivative of 3*R*-(1′*S*-aminocarboxymethyl)-2-pyrrolidone-5*S*-carboxylic acid[9] (**4**) or L-pyrrolid-2-one-5-carboxamide[10] (**5**), for example, four atoms corresponding to C-5, C-6, N-3, and C-3 of **2** are nearly coplanar, whereas those corresponding to C-6, N-3, C-3, and C-4 are not (Table III). These common features of **2** and **3** are presumably caused by constraint from the fused-ring structure.

The hydrogen-bonding parameters and the crystal structure of **2** are shown in Table IV and Fig. 3, respectively. There is no intramolecular hydrogen bond. The O-1 atom is hydrogen bonded to O-4 as a proton donor and to N-2 as a proton acceptor, although the atomic distance between O-1 and N-2 is somewhat longer for a hydrogen bond as compared with the common values[11] of 2.87–3.07 Å. In addition, a very weak hydrogen bond appears to exist between O-1 and O-5, and a "three-center" type of hydrogen bond[12] might be formed by O-1, O-4, O-5, and HO-1. The O-5 and N-3 atoms are proton donors to the carbonyl oxygen atoms of O-6 and O-7, respectively. Oxygen and nitrogen atoms other than O-1 and O-5 participate in one hydrogen bond each.

Next discussed is the conformation in aqueous solution based on ^{1}H-n.m.r. data. The dihedral angles (degrees) between the vicinal H atoms, the positions of which were obtained from the difference-Fourier map, are as follows (the values in brackets are those based on the calculated hydrogen coordinates): H-1–C-1–C-2–H-2 99(4) [87], H-2–C-2–C-3–H-3 −82(4) [−88], H-3–C-3–C-4–H-4 −10(4)

TABLE IV

HYDROGEN BOND PARAMETERS[a]

D · · · A	*Symmetry*	*Translation*			*D · · · A (Å)*	*D-H (Å)*	*H · · · A (Å)*
		a	*b*	*c*			
O-1–HO-1 · · · O-4	2	1	−1	0	2.820(4)	0.91(7)	2.01(7)
O-1–HO-1 · · · O-5	2	1	−1	0	3.308(5)	0.91(7)	2.59(7)
N-2–HN-2 · · · O-1	1	0	1	0	3.098(5)	0.91(6)	2.30(6)
O-5–HO-5 · · · O-6	2	1	0	1	2.705(5)	0.88(5)	1.86(5)
N-3–HN-3 · · · O-7	2	0	−1	0	2.887(5)	0.78(6)	2.13(6)

[a] E.s.d. values in parentheses. Symmetry codes are: (1) x, y, z; (2) $-x, y + 1/2, -z$.

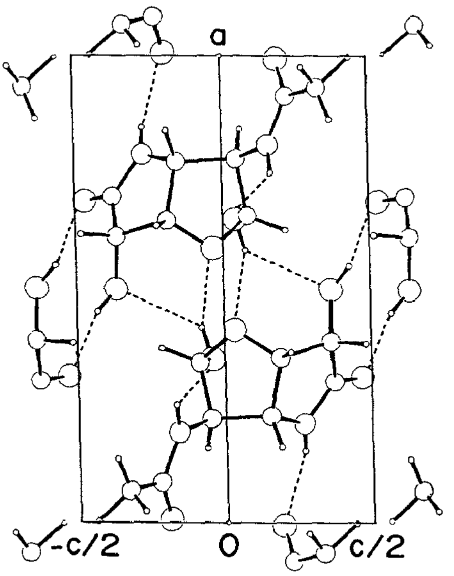

Fig. 3. Projection of the crystal structure of **2** down the *b* axis.

[−14], and H-4–C-4–C-5–H-5 21 (4) [24]. The spin-coupling constants[2] from the ^{1}H-n.m.r. spectrum of the α anomer in D_2O solution are $J_{1,2}$ 4.8, $J_{2,3}$ 2.1, $J_{3,4}$ 4.8, and $J_{4,5}$ 6.2 Hz, and those of the β anomer are $J_{1,2}$ <0.5, $J_{2,3}$ <0.5, $J_{3,4}$ 4.8, and $J_{4,5}$ 6.2 Hz. As the spin-coupling constant is in proportion to $\cos^2\varphi$ (φ: dihedral angle)[13], the H-1–C-1–C-2–H-2 and H-2–C-2–C-3–H-3 angles of the β anomer should be near 90°. From this result, the ring-puckering structures of the furanose ring of the β anomer in the crystal and in solution would appear approximately equal. The difference between $J_{1,2}$ of the α anomer and the β anomer originates, of course, from the different anomeric configuration. By neglecting substitution effects on the coupling constants, H-2–C-2–C-3–H-3 of the α anomer is roughly estimated to be 120° from the Karplus equation[13]. Therefore C-1–C-2–C-3–C-4 would be nearly equal to 0°. In other words, the C-1, C-2, C-3, and C-4 atoms of the furanose ring of the α anomer would be nearly coplanar as compared with those of the β anomer. The $J_{3,4}$ and $J_{4,5}$ values of the α anomer and the β anomer are equal, which suggests that the ring structure of lactam ring of the two forms in solution is similar.

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