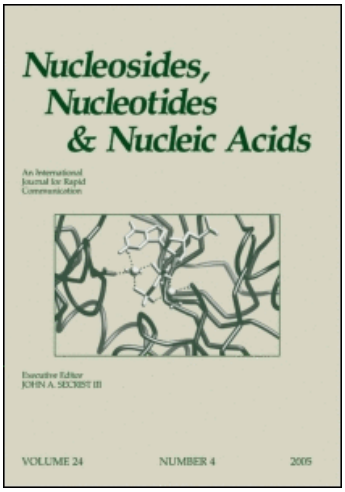

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The Structure of 2' (R)-Mercapto-2'-deoxyneplanocin A (Nucleosides and Nucleotides 48.)

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THE STRUCTURE OF 2'(R)-MERCAPTO-2'-DEOXYNEPLANOCIN A (NUCLEOSIDES AND NUCLEOTIDES 48.)

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ABSTRACT

The molecular and crystal structure of 2'(R)-mercapto-2'-deoxyneplanocin A, $C_{11}H_{13}N_3O_2S$ M.W.=279.32, has been determined by X-ray analysis. The space group is $P2_12_12_1$ with a=10.322(1), b=22.870(2), c=5.273(1)Å and z=4. The structure was solved by direct method, and least-squares refinement using 1806 reflections with $|F_o| > 3\sigma(F)$ led to the final R value of 0.045. The sugar C(2') atom is displaced by 0.35Å opposite to the base N(9), *i.e.*, C(2')-exo conformation and the torsion angle about the N(9)-C(1) bond is 26.3(4)° (anti conformation).

INTRODUCTION

Neplanocin A (1), isolated from the culture filtrate of *Ampullariella regularis* A11079, is an antitumor nucleo-

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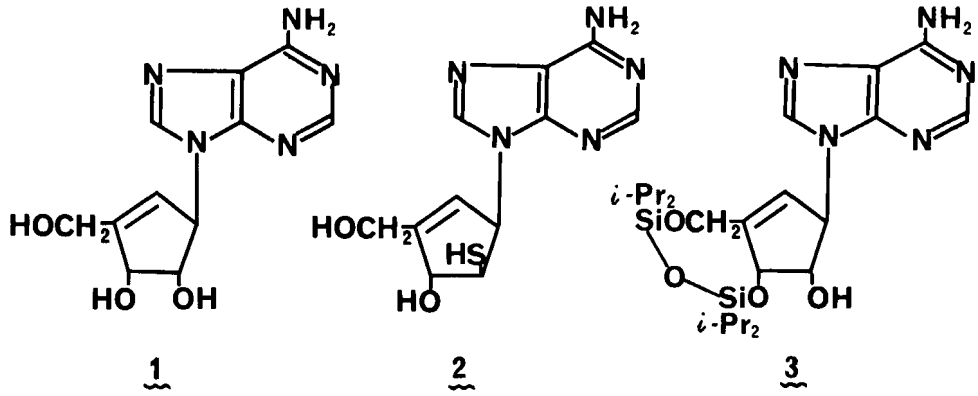

1 2 3

FORMULA 1

side antibiotic and possesses a unique cyclopentenetriol in place of the ribose moiety of adenosine.[1] The absolute structure was established by a chemical degradation study and X-ray analysis as shown in FORMULA 1.[2] Modification at 2'-position of neplanocin A (1) is expected to improve the biological activities by analogy to araC and araA.[3] A facile and versatile procedure for manipulation at the 2'-position of neplanocin A (1) and purine ribosides has been reported by the present authors.[4] Among various derivatives of 1, 2'(R)-mercapto-2'-deoxyneplanocin A (2) was isolated as a single crystal.[4] This compound was considerably more stable than the reported 2'-mercaptans of ribo configuration.[5] Therefore it was interesting to elucidate the structure and conformational features of 2. In this paper we wish to report the X-ray structure study of 2'(R)-mercapto-2'-deoxyneplanocin A (2).

EXPERIMENTAL AND STRUCTURAL DETERMINATION

Neplanocin A (1) was first converted to 3',6'-O-protected neplanocin A (3), and then triflation and substitution at the 2'-position were carried out. Removal of the silyl protecting group and the acetyl group by a usual manner were performed to afford 2. Colorless single crystals of 2 were grown from ethanol solution.[4] (m.p. 236° dec., Analysis. Calcd for $C_{11}H_{13}N_5O_2S$: C;47.30, H;4.69, N;25.08, S;11.48%.

TABLE 1. Crystal data of 2'(R)-SH-2'-deoxyneplanocin A

$C_{11}H_{13}N_5O_2S$	M.W. = 279.32		
Orthorhombic	$P2_12_12_1$,	z=4,	Dcal=1.490 g/cm^3
a=10.322(1),	b=22.870(2),		c=5.273(1) Å
U=1244.8(2) Å^3			

Found: C;47.37, H;4.53, N;25.05, S;11.31%) Preliminary oscillation and Weissenberg photographs indicated unambiguously the space group to be $P2_12_12_1$.

A sample of approximate dimensions 0.55 x 0.29 x 0.12 mm was mounted on a Rigaku automated four-circle diffractometer. Integrated intensities of the independent reflections for 2θ less than 60° were measured with the ω-2θ scan mode at the ω scan rate of 2° min^{-1} by use of graphite-monochromated Mo$K\alpha$ (λ=0.71069Å) radiation. The scan width in ω was $(0.9 + 0.3\tan\theta)^\circ$ with stationary background counts of 15s duration on either side of the peak. No remarkable intensity variation was observed for the five monitoring reflections during the data collection. The intensities were corrected for the Lorentz and polarization effects. No corrections were made for absorption or extinction. A total of 2124 independent reflections were obtained, of which 1806 reflections with $|Fo| > 3\sigma(F)$ were used for the structure determination. The crystal data are given in TABLE 1.

The structure was solved by the direct method using the MULTAN 78 program.[6] An E-map calculated with a phase set having the highest figure-of-merit revealed all the non-hydrogen atoms. Their positional and anisotropic thermal parameters were refined by the block-diagonal least-squares calculations. A difference Fourier map revealed all the hydrogen atom; they were refined isotropically. In the final least-squares cycle the weighting scheme, $1/w = \sigma^2(F) + 0.0005|Fo|^2$, was used. The final residual indices were: R=0.045 and $Rw = [\Sigma w(|Fo| - |Fc|)^2/\Sigma w|Fo|^2]^{\frac{1}{2}}$ =0.054.*

* The list of the atomic parameters can be obtained from the authors on request

RESULTS AND DISCUSSION

The bond lengths and angles are given in TABLES 2 and 3. The values are consistent with the chemical structure described above. FIG.1 shows the molecular structure. The crystal structure of 2 viewed along the *c*-axis is shown in FIG.2. The molecules are linked to each other by hydrogen bonds to make a three-dimensional network.

The adenine ring is planar within ±0.03 Å. The N(6) atom deviated from the adenine plane by 0.09 Å. The bond lengths and angles of the adenine moiety are in satisfactory agreement with those of 1 and adenosine.

In the cyclopentene ring the bond lengths and angles are in the expected range and the C(4')= C(5') bond distance is 1.323(4) Å. The C(3') atom is in the plane of C(1'), C(4') and C(5'), whereas the C(2') atom is displaced by 0.35 Å opposite to the N(9). Although there is no classification for the puckering of the cyclopentene ring as exists for the furanose ring in nucleosides or nucleotides, we may apply the same approach to 2. Therefore, in the present cyclopentene ring the puckering is designated as the C(2')-exo conformation. The puckerings in 1[2] and 3',6'-O-(tetraisopropyldisiloxane-1,3-diyl)neplanocin A 3[7] are C(2')-exo-C(3')-endo

TABLE 2. Bond lengths(Å) of 2'(R)-SH-2'-deoxyneplanocin A

Bond		Bond	
N(1)-C(2)	1.344(4)	C(1')-C(2')	1.546(4)
N(1)-C(6)	1.352(4)	C(1')-C(5')	1.504(4)
C(2)-N(3)	1.327(4)	C(1')-N(9)	1.477(4)
N(3)-C(4)	1.341(4)	C(2')-S(2')	1.801(3)
C(4)-C(5)	1.390(4)	C(2')-C(3')	1.537(4)
C(4)-N(9)	1.373(3)	C(3')-O(3')	1.430(4)
C(5)-C(6)	1.415(4)	C(3')-C(4')	1.515(4)
C(5)-N(7)	1.385(3)	C(4')-C(5')	1.323(4)
C(6)-N(6)	1.340(4)	C(4')-C(6')	1.488(4)
N(7)-C(8)	1.315(4)	C(6')-O(6')	1.429(4)
C(8)-N(9)	1.375(3)		

TABLE 3. Bond angles(°) of 2'(R)-SH-2'-deoxyneplanocin A

Bond		Bond	
C(2)-N(1)-C(6)	119.0(2)	C(1')-N(9)-C(8)	128.6(2)
N(1)-C(2)-N(3)	129.1(3)	C(2')-C(1')-C(5')	101.0(2)
C(2)-N(3)-C(4)	110.5(3)	C(2')-C(1')-N(9)	112.9(2)
N(3)-C(4)-C(5)	127.7(3)	C(5')-C(1')-N(9)	109.8(2)
N(3)-C(4)-N(9)	126.6(3)	C(1')-C(2')-S(2')	119.0(2)
C(5)-C(4)-N(9)	105.7(2)	C(1')-C(2')-C(3')	103.8(2)
C(4)-C(5)-C(6)	116.1(2)	C(3')-C(2')-S(2')	113.0(2)
C(4)-C(5)-N(7)	111.1(2)	C(2')-C(3')-O(3')	113.8(2)
C(6)-C(5)-N(7)	132.8(3)	C(2')-C(3')-C(4')	101.5(2)
N(1)-C(6)-C(5)	117.6(3)	C(4')-C(3')-O(3')	115.1(2)
N(1)-C(6)-N(6)	119.0(3)	C(3')-C(4')-C(5')	111.0(2)
C(5)-C(6)-N(6)	123.4(2)	C(3')-C(4')-C(6')	121.1(2)
C(5)-N(7)-C(8)	103.4(2)	C(5')-C(4')-C(6')	127.8(3)
N(7)-C(8)-N(9)	114.3(2)	C(1')-C(5')-C(4')	111.8(2)
C(4)-N(9)-C(8)	105.6(2)	C(4')-C(6')-O(6')	109.5(2)
C(1')-N(9)-C(4)	125.7(2)		

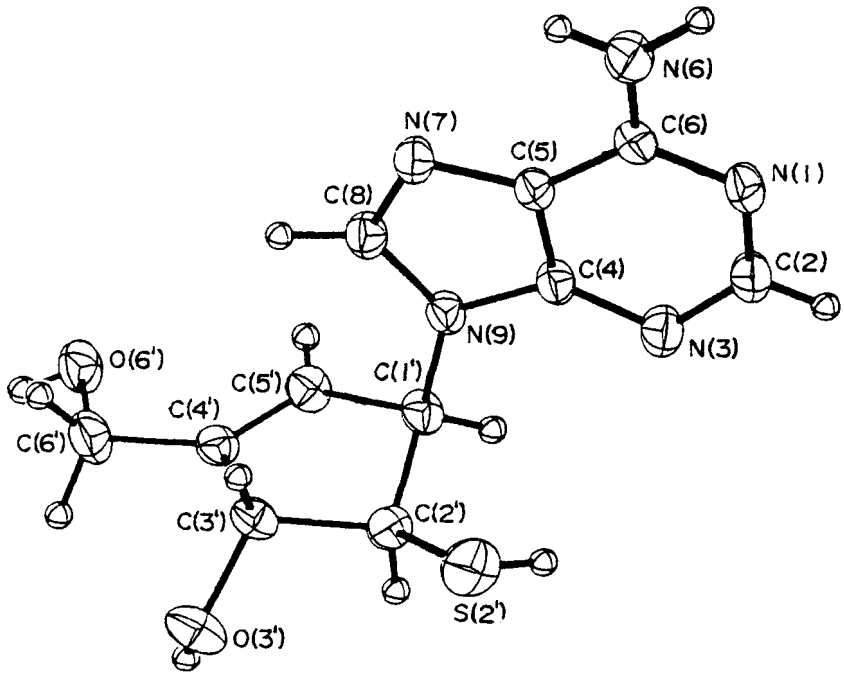

FIG.1 A drawing of molecular structure of 2'(R)-SH-2'-deoxyneplanocin A.

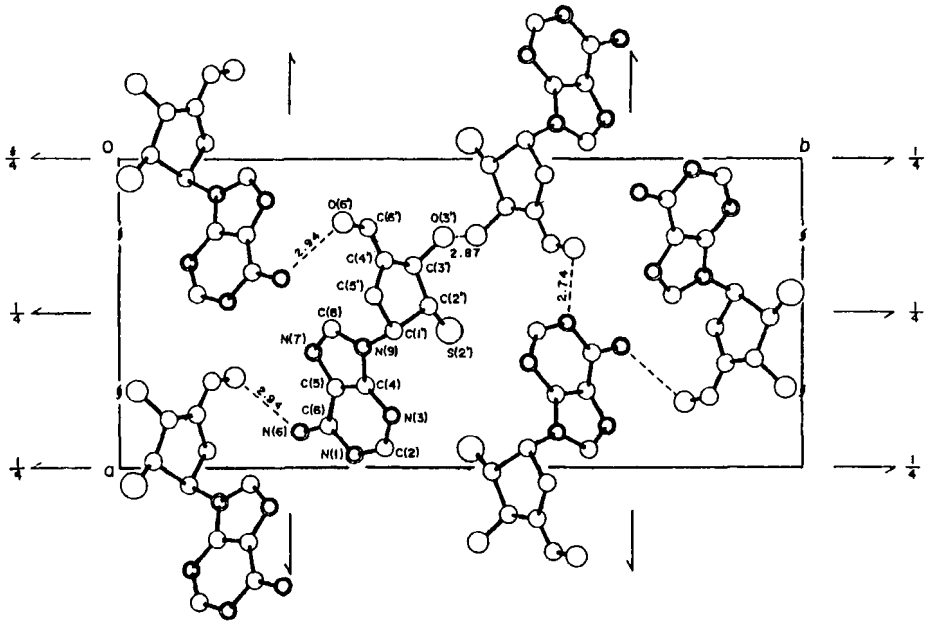

FIG. 2 Crystal structure of 2'(R)-SH-2'-deoxyneplanocin A

and C(2')-endo, respectively. The C(2')-exo conformation of 2 may be attributed to the (R)-configuration at the 2'-position.

The interplanar angle between the adenine plane and the mean cyclopentene plane is 85.1°. The torsion angle about the N(9)-C(1') bond, ϕ[C(8)-N(9)-C(1')-C(5')], is 26.3(4)°, which lies in the range described as *anti*. The corresponding torsion angle in 1 is 61.3(3)°, and in 3 two independent molecules were involved in its crystals having 34.4(7)° and 33.0(7)°, respectively.

Since the CD spectra of 2 and other 2'(R)-substituted neplanocin As were very similar[4], the overall structure of these 2'(R)-substituted derivatives were assumed to be almost identical. The apparent chemical stability of the 2'-mercaptan group of 2 as compared with those in the usual nucleosides may be attributed to the difference of the "sugar moiety" itself.

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