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Structure of 8,2′-Anhydro-8-mercapto-9-β-D-arabinofuranosylhypoxanthylyl(3′-5′)-8,2′-anhydro-8-mercapto-9-β-D-arabinofuranosyladenine (I^spA^s) Hexahydrate*†

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Abstract. $C_{20}H_{20}N_9O_9PS_2.6H_2O$, triclinic, $P\bar{1}$, $M_r = 733{\cdot}6$, $a = 14{\cdot}324\ (5)$, $b = 11{\cdot}130\ (3)$, $c = 5{\cdot}794\ (1)$ Å, $\alpha = 97{\cdot}40\ (3)$, $\beta = 87{\cdot}42\ (3)$, $\gamma = 120{\cdot}05\ (4)°$, $Z = 1$, $D_m = 1{\cdot}630\ (1)$, $D_x = 1{\cdot}536$ Mg m^{-3}. The final R value is 0·066 for 2697 observed reflections. The molecular conformation is a folded form, with (g^+,t) torsion angles around P–O bonds, which is stabilized by hydrophobic interactions between sugar and base moieties and by intermolecular base stacking.

Introduction. It has been reported that the nucleic acid with high-*anti* orientation possesses an interesting tendency to form a left-handed duplex by CD measurement (Uesugi, Yasumoto, Ikehara, Fang & Ts'o, 1972) and energy calculations (Fujii & Tomita, 1976). In the previous paper, we reported the molecular structure of A^spA^s [8,2′-*S*-cyclo-2′-thioadenvlyl(3′-5′)-8,2′-*S*-cyclo-2′-thioadenosine] which did not have the left-handed stacking form but had a new type of stable non-helical 'bent' form (Fujii, Hamada, Miura, Uesugi, Ikehara & Tomita, 1982).

I^spA^s was synthesized by condensation of 8,2′-*S*-cycloinosine and 8,2′-*S*-cycloadenosine 5′-monophosphate (Ikehara, Uesugi & Shida, 1980). By slow evaporation of an aqueous solution of I^spA^s in the refrigerator, prismatic transparent crystals were obtained. The intensity data (using a crystal 0·74 × 0·52 × 0·33 mm, sealed in a quartz capillary with some mother liquor) were collected on a Rigaku Denki automatic four-circle diffractometer with Cu $K\alpha$ radiation. The ω scanning technique was employed at a rate of 8° min^{-1}.

The structure was solved by the direct method employing the program *MULTAN* 78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978). An E map derived from the set with the highest combined figure of merit showed many peaks corresponding to one P atom, two S atoms and some light atoms. Successive Fourier syntheses revealed the remaining non-hydrogen atoms, including six water molecules. After refinements with anisotropic temperature parameters, a difference Fourier synthesis showed all H-atom positions, except those of the water molecules. Final refinement, by a block-diagonal least-squares method with anisotropic thermal parameters for non-hydrogen atoms and with isotropic thermal parameters for H atoms, reduced R and R_w to 0·066 and 0·089, respectively. The atomic scattering factors in *International Tables for X-ray Crystallography* (1974) were used. All the computations were performed on an ACOS-700 computer of the Crystallographic Research

* (6a*S*, 7*R*, 8*R*, 9a*R*)-4-Amino-6a,7,8,9a-tetrahydro-7-hydroxyfuro[2′,3′:4,5]thiazolo[3,2-*e*]purin-3-ium-8-ylmethyl (6a*S*, 7*R*,8*R*,9a*R*)-3,4,6a,7,8,9a-hexahydro-8-hydroxymethyl-4-oxofuro[2′,3′:4,5]thiazolo[3,2-*e*]purin-7-yl phosphate hexahydrate. (The abbreviation I in I^spA^s stands for inosine – 9-β-D-ribofuranosylhypoxanthine.)

† Structure of a Dinucleoside Monophosphate Having a High-*anti* Configuration. II.

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Center, Institute of Protein Research, Osaka University, with *UNICS* (1973).

Discussion. The atomic coordinates are given in Table 1.* The protonated N(1) site of the adenine moiety (formed by dissociation of the phosphate group) is confirmed by an H-atom peak on the difference Fourier map. The bond distances and angles (Fig. 1) are generally in agreement with those of related compounds. The molecular conformation is shown in Fig. 2. The related torsion angles are listed in Table 2. The torsion angle χ, defining the base–sugar orientation, is in the high-*anti* region, *i.e.* 126·1 (7)° for the cycloinosine and 127·1 (7)° for the cycloadenosine part. It is a common feature that, in cyclonucleotides or cyclonucleosides, the χ values depend on the sugar puckering, because the normal envelope form of the sugar moiety is distorted by the additional fused ring [C(8)–N(9)–C(1′)–C(2′)–S]. As noted in a previous paper (Fujii, Hamada, Miura, Uesugi, Ikehara & Tomita, 1982), the

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36883 (19 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Final fractional coordinates* (× 10^4) *and equivalent isotropic thermal parameters for non-hydrogen atoms, with their estimated standard deviations in parentheses*

$B_{eq} = \frac{1}{3}\sum_i\sum_j B_{ij}a^*_i a^*_j \mathbf{a}_i.\mathbf{a}_j$.

	x	*y*	*z*	B_{eq}(Å^2)
N(1) (I)	10367 (5)	7989 (5)	2833 (12)	3·4 (2)
C(2) (I)	9801 (6)	8501 (8)	1971 (14)	4·4 (3)
N(3) (I)	8896 (4)	8356 (6)	2712 (10)	3·1 (2)
C(4) (I)	8557 (5)	7577 (6)	4546 (11)	2·9 (2)
C(5) (I)	9055 (5)	7020 (7)	5579 (11)	3·1 (3)
C(6) (I)	10045 (6)	7189 (7)	4747 (12)	3·5 (3)
O(6) (I)	10610 (5)	6765 (7)	5441 (11)	4·8 (3)
N(7) (I)	8445 (4)	6266 (6)	7369 (10)	3·0 (2)
C(8) (I)	7613 (5)	6409 (6)	7345 (10)	2·9 (2)
N(9) (I)	7612 (4)	7192 (5)	5695 (9)	2·5 (2)
C(1′) (I)	6670 (5)	7367 (7)	5523 (11)	3·0 (3)
C(2′) (I)	5952 (5)	6742 (6)	7549 (11)	2·5 (3)
C(3′) (I)	5669 (5)	7996 (7)	9094 (11)	3·2 (3)
C(4′) (I)	6768 (6)	9277 (7)	7957 (13)	3·2 (3)
C(5′) (I)	7793 (9)	10212 (9)	9305 (19)	5·4 (4)
O(1′) (I)	6948 (4)	8781 (5)	5643 (9)	3·2 (2)
S (I)	6452 (1)	5817 (2)	9080 (3)	2·9 (1)
O(3′) (I)	4923 (4)	7848 (6)	9016 (9)	4·0 (3)
O(5′) (I)	8461 (5)	9600 (7)	9413 (13)	5·6 (3)
P	4087 (2)	7197 (2)	11037 (3)	3·0 (1)
O (*L*) (I)	4321 (5)	6250 (6)	12168 (10)	4·4 (3)
O (*R*) (I)	2998 (5)	6622 (8)	9987 (13)	5·0 (3)
N(1) (A)	9366 (5)	13544 (7)	12629 (14)	3·6 (3)
C(2) (A)	8932 (7)	12788 (8)	14421 (17)	4·0 (4)
N(3) (A)	7973 (5)	12437 (7)	15286 (12)	3·8 (3)
C(4) (A)	7473 (5)	12965 (7)	14170 (12)	3·2 (3)
C(5) (A)	7854 (6)	13735 (6)	12285 (13)	3·0 (3)
C(6) (A)	8870 (5)	14083 (6)	11495 (13)	2·8 (3)
N(6) (A)	9356 (5)	14844 (7)	9779 (13)	3·8 (3)
N(7) (A)	7121 (5)	14099 (6)	11601 (11)	3·1 (2)
C(8) (A)	6337 (5)	13528 (6)	13006 (11)	2·9 (3)
N(9) (A)	6486 (5)	12803 (6)	14599 (10)	3·2 (2)
C(1′) (A)	5674 (5)	12213 (7)	16300 (14)	3·3 (3)
C(2′) (A)	4695 (7)	12308 (7)	15482 (13)	3·8 (3)
C(3′) (A)	3877 (6)	10793 (8)	14482 (17)	3·3 (3)
C(4′) (A)	4188 (6)	9985 (7)	15940 (12)	3·5 (3)
C(5′) (A)	3847 (6)	8531 (7)	14831 (13)	3·6 (3)
O(1′) (A)	5315 (4)	10788 (5)	16331 (12)	3·5 (2)
S (A)	5127 (2)	13535 (2)	13369 (4)	3·7 (1)
O(3′) (A)	2839 (6)	10455 (8)	14689 (22)	4·4 (3)
O(5′) (A)	4385 (5)	8599 (5)	12694 (10)	4·4 (3)
O(*W*1)	2970 (8)	4531 (13)	15304 (20)	9·9 (7)
O(*W*2)	3515 (7)	3711 (8)	9029 (15)	6·7 (5)
O(*W*3)	11921 (6)	8043 (9)	−382 (13)	6·1 (5)
O(*W*4)	393 (12)	1488 (14)	7526 (36)	10·1 (8)
O(*W*5)	2280 (11)	998 (14)	10405 (35)	9·9 (7)
O (*W*6)	11139 (10)	14192 (15)	9967 (44)	10·0 (7)

Table 2. *Torsion angles* (°) *with their estimated standard deviations in parentheses*

Notation	Designation	I^{s}p	pA^s
χ	C(8)–N(9)–C(1′)–O(1′)	126·1 (7)	127·1 (7)
ψ	C(3′)–C(4′)–C(5′)–O(5′)	69·2 (11)	61·3 (9)
ψ'	O(3′)–C(3′)–C(4′)–C(5′)	133·0 (8)	80·6 (11)
ω	O(3′)–P–O(5′)–C(5′)		181·7 (6)
ω'	C(3′)–O(3′)–P–O(5′)	90·7 (8)	
φ'	C(4′)–C(3′)–O(3′)–P	211·9 (6)	
φ	C(4′)–C(5′)–O(5′)–P		185·7 (6)
Furanose ring			
τ_0	C(4′)–O(1′)–C(1′)–C(2′)	18·0 (8)	−8·3 (9)
τ_1	O(1′)–C(1′)–C(2′)–C(3′)	−8·1 (8)	−14·6 (9)
τ_2	C(1′)–C(2′)–C(3′)–C(4′)	−4·4 (7)	28·8 (8)
τ_3	C(2′)–C(3′)–C(4′)–O(1′)	15·0 (8)	−35·0 (8)
τ_4	C(3′)–C(4′)–O(1′)–C(1′)	−21·2 (8)	28·3 (9)
Pseudorotation parameters*			
P		248·2	32·7
τ_m		21·8	33·6

* *P*, τ_m: Altona & Sundaralingam (1972).

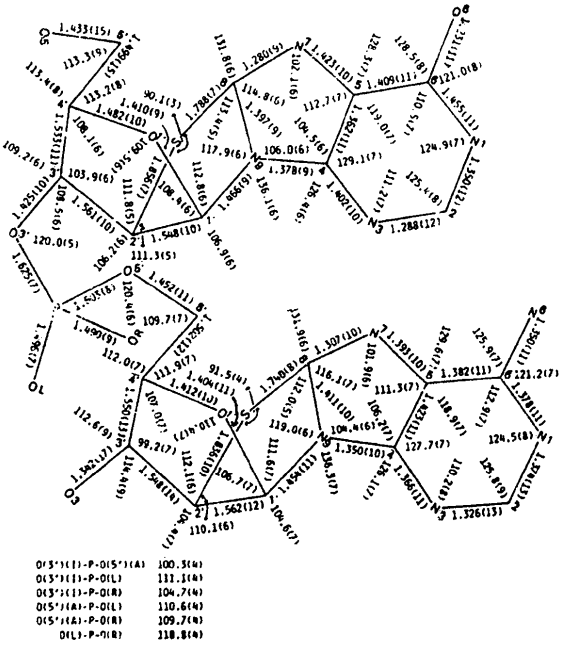

Fig. 1. Bond lengths (Å) and bond angles (°) with their estimated standard deviations in parentheses.

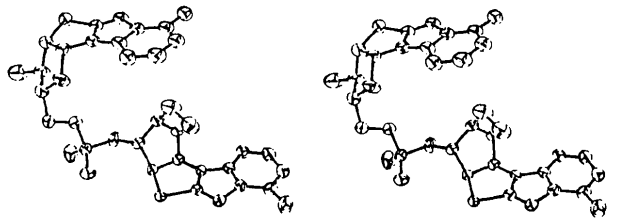

Fig. 2. A stereoview of the molecular conformation.

displacements of C(1′) and C(2′) from the base plane change with the sugar puckering, and the twist angle C(8)–N(9)–C(1′)–C(2′) is 7·2 (8)° for cycloinosine and 12·1 (9)° for cycloadenosine. The sugar puckerings at the cycloinosine site and at the cycloadenosine site are C(4′)-*endo* and C(3′)-*endo*, respectively. The displacements of C(4′) of the cycloinosine site and of C(3′) of the cycloadenosine site from the least-squares planes through the other four atoms in the sugar rings are 0·278 (12) and 0·544 (14) Å, respectively. However, the C(4′)-*endo* form is considerably distorted from the envelope form and, as shown in Table 2, the pseudorotation phase angle is 248° (Altona & Sundaralingam, 1972), corresponding to C(4′)-*endo*–O(1′)-*exo*. The C(3′)-*endo* puckering at the cycloadenosine site was first found in cyclonucleosides and cyclonucleotides. The torsion angles (ω',ω) are (g^+,t): 90·7 (8), 181·7 (6)°, and differ from the (g^-,t) found in A^spA^s or the (g^-,g^-) frequently found in other crystalline dinucleoside monophosphates. A previous energy calculation of a dinucleoside monophosphate with high-*anti* conformation indicated that it was possible to construct a stable conformation with (g^+,t) (Fujii & Tomita, 1976). It is interesting to note that a similar (g^+,t) conformation was found in the GpC fragment in Z_{II}-DNA where (ω',ω) are (55, 146°) (Wang, Quigley, Kolpak, van der Marel, van Boom & Rich, 1981). We have already noted that there are two distinct torsional regions around the C(3′)–O(3′) bond, *i.e.* $\varphi' = 192$ and 254° in the case of 8,2′-*S*-cycloadenosine monophosphate (A^sp) (Miyamae, Tanaka, Hamada, Fujii & Tomita, 1982); two A^spA^s molecules ($\varphi' = 209°$ and $\varphi' = 210°$) and the present I^spA^s molecule [$\varphi' = 211·9$ (6)°] have values corresponding to the former region. These φ' values are shifted to a value which is 20° larger than that in cyclonucleotides having the phosphate linkage on the 3′ site; for instance, in A^sp. The torsion angles $\varphi =$ 185·7 (6)° and $\psi = 61·3$ (9)° are normal.

The I^spA^s molecule takes a folded form. As shown in Fig. 2, the hypoxanthine and adenine base planes are almost parallel and the sugar moiety faces inwards. The dihedral angle between the two base planes is 3·9° and the average base–base distance is 6·7 Å. The hydrophobic interaction between the hydroxymethyl group and the adenine ring may stabilize this folded form. In the Z-DNA conformation (CpG fragment), the contact between O(1′) and the guanine base may also stabilize the Z-DNA molecule (Wang, Quigley, Kolpak, Crawford, van Boom, van der Marel & Rich, 1979).

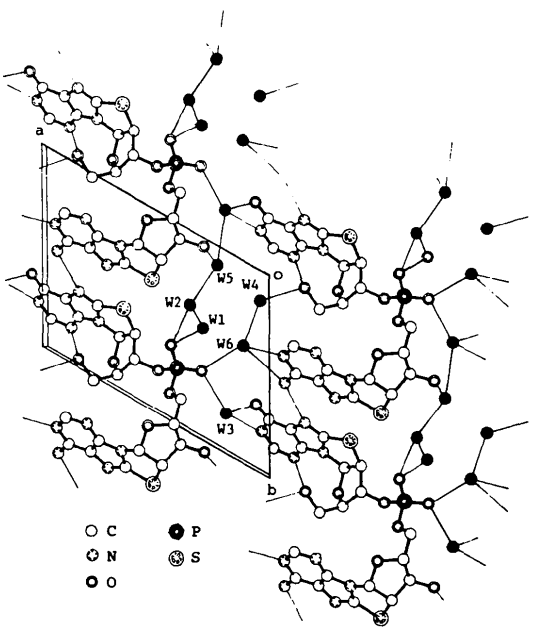

Fig. 3. The molecular packing.

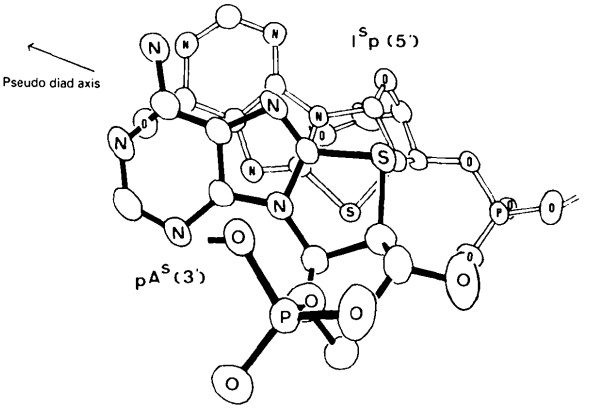

Fig. 4. Intermolecular base stacking.

The molecular packing is shown in Fig. 3 and hydrogen-bond distances are listed in Table 3. There is only one hydrogen bond between bases [N(6) (A)···N(7) (I)]. The other hydrogen bonds are observed between the I^spA^s molecule and water or between water and water. There is a strong intermolecular base stacking between base moieties of adenine and hypoxanthine with the average distance 3·4 Å as shown in Fig. 4. The overlappings occur mainly between imidazole rings and between the fused

Table 3. *Hydrogen-bond distances* (Å) *with their standard deviations in parentheses*

Donor	Acceptor		Donor	Acceptor	
N(1) (I)	O(*W*3)^{i}	2·857 (12)	O(*W*2)	O(*L*)^{i}	2·898 (13)
O(5′) (I)	N(3) (I)^{ii}	2·805 (11)	O(*W*2)*	O(*W*5)^{i}	2·843 (23)
N(1) (A)	O(*W*6)^{i}	2·757 (28)	O(*W*3)	O(6) (I)^{iv}	2·934 (12)
N(6) (A)	N(7) (I)^{iii}	3·017 (10)	O(*W*3)	O(*R*)^{v}	2·737 (13)
N(6) (A)	O(*W*6)^{i}	2·995 (28)	O(*W*4)	O(5′) (I)^{vi}	2·802 (23)
O(3′) (A)	O(*W*5)^{iii}	2·937 (25)	O(*W*5)	O(*W*3)^{vii}	3·039 (23)
O(*W*1)	O(*L*)^{i}	2·794 (15)	O(*W*6)	O(*R*)^{viii}	2·680 (28)
O(*W*1)*	O(*W*2)^{ii}	2·791 (17)	O(*W*6)	O(*W*4)^{viii}	2·849 (34)

Symmetry code: (i) x,y,z; (ii) $x,y,1+z$; (iii) $x,\ 1+y,z$; (iv) $x,y,-1+z$; (v) $1+x,y,-1+z$; (vi) $-1+x,-1+y,z$; (vii) $-1+x,-1+y,\ 1+z$; (viii) $1+x,\ 1-y,z$.

* H atoms were not located; the assignment as donor or acceptor could be reversed.

rings involving the S atom. This stacking is very similar to that of A^spA^s and therefore it may be a common feature in molecular packing of *S*-cyclonucleosides or cyclonucleotides.

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Non-ionized 5a-Epi-6-oxatetracycline* Free Base

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Abstract. $C_{20}H_{20}N_2O_8.C_4H_{10}O$, triclinic, $P\bar{1}$, $a=9{\cdot}864\ (1)$, $b=11{\cdot}129\ (1)$, $c=11{\cdot}713\ (1)$ Å, $\alpha=80{\cdot}967\ (8)$, $\beta=85{\cdot}335\ (9)$, $\gamma=70{\cdot}310\ (7)°$ at 297 (1) K; $Z=2$, $\rho_{calc}=1{\cdot}36$ g cm^{-3}. Racemic 5a-epi-6-oxatetracycline free base cocrystallizes with one molecule of diethyl ether. A total of 3498 reflections ($\sin\theta/\lambda_{max}=0{\cdot}590$ Å^{-1}) contributed to refinement of 436 variables to give standard residues: $R=0{\cdot}040$, $R_w=0{\cdot}053$, $\sigma=1{\cdot}30$ with $w=(\sigma^2|F|+0{\cdot}0125|F_o|+0{\cdot}0001|F_o|^2+0{\cdot}000005|F|^3)^{-1}$. The title compound is a totally synthetic tetracycline analog. The molecular structure in the crystal is that of a non-ionized free base displaying a short intramolecular hydrogen bond, $d(O\cdots H)=1{\cdot}23\ (3)$ Å and $\angle(O\text{–}H\cdots O)=165\ (3)°$, in the *A*-ring chromophore. The conformation is very similar to that of other 5a-epitetracycline derivatives.

Introduction. Numerous tetracycline derivatives are broad spectrum antibiotics that have found extensive application in human and veterinary medicine. The crystal structure of the title compound (I) was undertaken to identify unequivocally the relative configuration of atom C(5a) and to examine further the effects of the introduction of a heteroatom into the ring

* (5a*β*,6a*α*,7*α*,10a*α*)-(±)-7-(Dimethylamino)-5a,6,6a,7,10a-pentahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-10*H*-benzo[*b*]xanthene-9-carboxamide.

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