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A Structural Study of 3′-Deoxytubercidin and 3-Deaza-3′-deoxyadenosine

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Abstract. 3′-Deoxytubercidin (3′-dTu), $C_{11}H_{14}N_4O_3$, $M_r = 250{\cdot}26$, monoclinic, $P2_1$, $a = 5{\cdot}299\ (1)$, $b = 9{\cdot}945\ (3)$, $c = 11{\cdot}107\ (1)$ Å, $\beta = 100{\cdot}75\ (1)°$, $V = 575{\cdot}13$ Å^3, $Z = 2$, $D_x = 1{\cdot}445$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54184 Å, $\mu = 86{\cdot}2$ mm^{-1}, $F(000) = 264$, $T = 298$ K. Final $R = 0{\cdot}030$ for 1266 observed reflections with $I \geq 1{\cdot}5\sigma(I)$. 3-Deaza-3′-deoxyadenosine (3′-ddA), $C_{11}H_{14}N_4O_3$, $M_r = 250{\cdot}26$, orthorhombic, $P2_12_12_1$, $a = 5{\cdot}826\ (1)$, $b = 9{\cdot}075\ (2)$, $c = 21{\cdot}887\ (3)$ Å, $V = 1157{\cdot}27$ Å^3, $Z = 4$, $D_x = 1{\cdot}436$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54184 Å, $\mu = 85{\cdot}6$ mm^{-1}, $F(000) = 528$, $T = 298$ K. Final $R = 0{\cdot}030$ for 1075 observed reflections with $I \geq 1{\cdot}5\sigma(I)$. 3-Deaza-3′-deoxyadenosine (3′-ddA) and 3′-deoxytubercidin (3′-dTu) are analogues of the nucleoside 3′-deoxyadenosine (3′-dA). The sugar pucker for both structures is the C3′-*endo* conformation. For 3′-dTu the C4′—C5 bond conformation is *gauche*(+)–*trans* whereas for 3′-ddA it is *gauche*(+)–*gauche*(−). Where the substitutions of N by C have been made in the purine bases, the relevant bond lengths have increased by 0·05 Å and the bond angles by 3° compared with adenosine, which causes significant deviation from the usual planar purine-ring structure.

Introduction. The title structures are analogues of cordycepin, the nucleoside antitumour antibiotic 3′-deoxyadenosine (3′-dA) (Radwan & Wilson, 1980). This has been shown to inhibit the growth of human tumour cells in culture (Rich, Meyers, Weinbaum, Cory & Suhadolnik, 1965). 3′-dA primarily inhibits RNA synthesis and, as a consequence, blocks DNA and protein synthesis in cells. Its mode of action involves incorporation into the 3′-end of an RNA molecule and this prevents further elongation, thereby acting as a chain terminator (Suhadolnik, 1979). A major problem associated with the clinical use of these nucleoside antitumour antibiotics is that the enzyme adenosine deaminase (ADAase) (Montgomery, 1970) causes deamination of purine antimetabolites and hence limits their activity. The aim of the structural studies detailed in this paper is to examine compounds potentially active in chain termination of RNA that are, at the same time, resistant to ADAase, although without being an inhibitor (Montgomery, Thomas, Zell, Einspahr & Bugg, 1985), which causes other toxic effects produced by excess adenosine (Plagemann & Wohlhueter, 1981). Syntheses are described elsewhere (Serafinowski, 1987).

3-Deaza-3′-deoxyadenosine (3′-ddA) has a C atom substituted for the N atom at the 3-position of the adenine base; 3′-deoxytubercidin (3′-dTu) has a C atom substituted for an N atom at position 7. The substitutions of a C for an N atom in these nucleoside antibiotics have electronic effects which are manifested in changes in bond geometry. These are discussed in this paper and compared with the crystal structures of the parent nucleosides adenosine (Lai & Marsh, 1972), 2′-deoxyadenosine (Watson, Sutor & Tollin, 1965),

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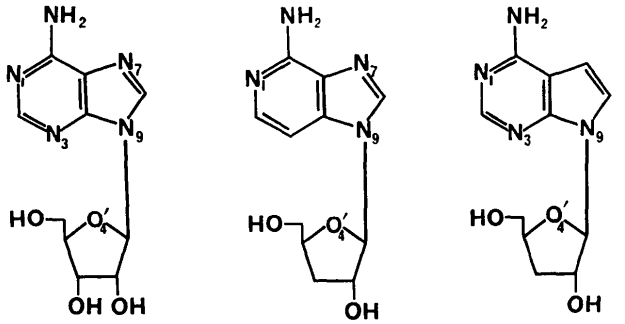
3′-deoxyadenosine (Radwan & Wilson, 1980) and other related nucleosides.



Experimental. *3′-dTu.* Recrystallization from ethanol/water solution produced colourless rectangular crystals. A specimen of dimensions 0·2 × 0·2 × 0·1 mm was used. Cell dimensions were obtained from least-squares refinement of 25 θ values measured on an Enraf–Nonius diffractometer; Ni-filtered Cu $K\alpha$ radiation was used ($\lambda = 1{\cdot}54178$ Å). Intensity data collected with an ω–2θ scan technique and a max. scan time of 120 s per reflection, for $1{\cdot}5 \le \theta \le 72°$ and $0 \le h \le 6$, $0 \le k \le 12$, $-13 \le l \le 13$, 1325 unique reflections were measured, of which 1266 had $I \ge 1{\cdot}5\sigma(I)$.

3′-ddA. Recrystallization from ethanol/water solution produced colourless cubic crystals. A crystal of dimensions 0·2 × 0·2 × 0·2 mm was used. Cell dimensions were obtained from least-squares refinement of 25 θ values measured on an Enraf–Nonius diffractometer; Ni-filtered Cu $K\alpha$ radiation was used. Intensity data collected with an ω–2θ scan technique and a max. scan time of 120 s per reflection, for $1{\cdot}5 \le \theta \le 70°$ and $0 \le h \le 7$, $0 \le k \le 11$, $0 \le l \le 26$, 1299 unique reflections, of which 1075 had $I \ge 1{\cdot}5\sigma(I)$.

Three intensity standards were monitored every 200 reflections during the data collection for both structures and showed no statistically significant crystal decay. An empirical absorption correction was applied to both data sets (Walker & Stuart, 1983). The structures were solved by direct methods with *MULTAN*82 (Main *et al.*, 1982). H atoms were located in difference Fourier syntheses, and their positional and isotropic thermal parameters refined on F by full-matrix least-squares methods, together with non-H-atom positional and anisotropic thermal parameters. For 3′-dTu, the final R was 0·030 and wR was 0·028, for 3′-ddA, the final R was 0·030 and wR 0·029. For both structures, unit weights were found to be appropriate. Scattering factors were taken from *International Tables for X-ray Crystallography* (1974). Calculations were performed on a VAX 11/750 computer using the *SDP* system (Frenz, 1980). For both 3′-dTu and 3′-ddA, max. Δ/σ was 0·01, and observed range of $\Delta\rho$ was within $\pm 0{\cdot}15$ e Å^{-3}.

Discussion. The molecular structures of 3′-dTu and 3′-ddA are shown in Fig. 1. Atomic parameters and bond distances and angles are given in Tables 1 and 2.* The adenine-base analogues show significant deviations from the usual planar purine-ring structures (Table 2), this being most prominent for 3′-dTu. For this structure the C7 and N1 atoms are 0·05 Å below the mean plane and the N6 atom is 0·06 Å above. With 3′-ddA the C3 and N6 atoms are 0·04 Å above the mean plane and N1 is 0·04 Å below it. These deviations are significantly greater than those for other modified nucleosides, such as tubercidin (Stroud, 1973) and togacamycin monohydrate (Prusiner & Sundaralingam, 1978).

* Lists of H-atom parameters, anisotropic thermal parameters, H-bond distances and structure factors have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44034 (20 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

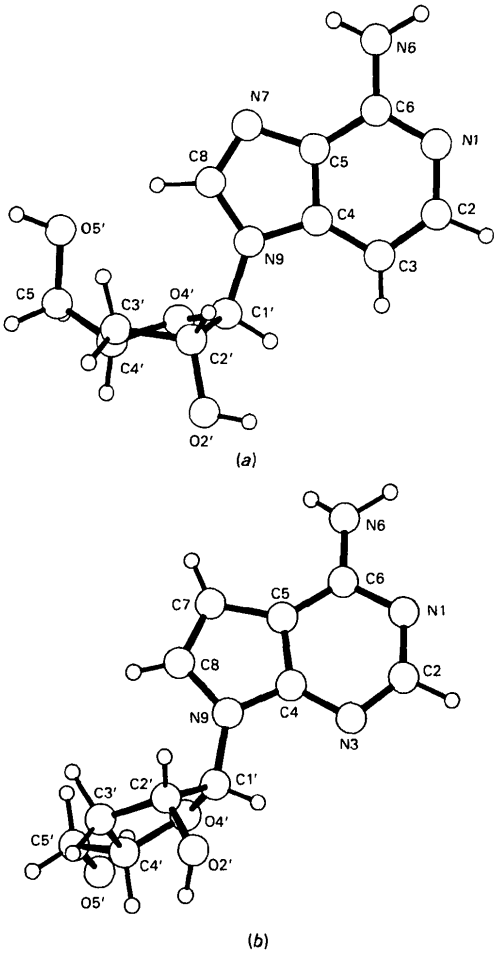


Fig. 1. Molecular structures of (*a*) 3-deaza-3′-deoxyadenosine, (*b*) 3′-deoxytubercidin.

The bond lengths and angles for both structures are in good agreement with those of adenosine, apart from where the substitutions have been made (Table 2). The overall effect is that the relevant bond lengths in both structures have increased by 0·05 Å and the bond angles by 3° compared with adenosine.

In both structures the sugar pucker may generally be described as being in the C3′-*endo* conformational range. The pseudorotational phase angle *P* for 3′-dTu is 25·7 (9)° and for 3′-ddA it is 7·7 (4)° (Altona & Sundaralingam, 1972).

The glycosidic angle for 3′-dTu is −106·4 (2)° and for 3′-ddA it is −126·1 (2)°. Thus they are both in an *anti* conformation (Fig. 1 and Table 3). This is in accord with the majority of nucleosides in the solid state. It can be seen that both structures have values for the glycosidic angles similar to tubercidin (Altona &

Table 1. *Non-H-atom positional parameters, with e.s.d.'s in parentheses*

B is in Å^2 and is defined as $\frac{1}{3}(B_{11} + B_{22} + B_{33})$.

	x	*y*	*z*	*B* (Å^2)
3′-dTu				
N1	0·1100 (4)	0·037	0·1943 (2)	3·22 (4)
C2	0·0982 (5)	0·0205 (3)	0·0842 (2)	3·06 (5)
N3	−0·0622 (3)	0·0037 (2)	0·0190 (2)	2·76 (4)
C4	−0·2411 (4)	0·0958 (2)	0·0031 (2)	2·35 (4)
C5	−0·2575 (4)	0·1633 (2)	0·1049 (2)	2·51 (4)
C6	−0·0621 (5)	0·1338 (2)	0·2053 (2)	2·86 (4)
N6	−0·0371	0·1961 (3)	0·3145 (2)	4·28 (5)
C7	−0·4777 (5)	0·2494 (3)	0·0796 (2)	2·83 (4)
C8	−0·5813 (4)	0·2317 (3)	−0·0398 (2)	2·84 (4)
N9	−0·4394 (3)	0·1377 (2)	−0·0921 (2)	2·53 (4)
C1′	−0·4654 (4)	0·1068 (3)	−0·2211 (2)	2·67 (4)
C2′	−0·7340 (5)	0·0595 (3)	−0·2841 (2)	3·20 (5)
C3′	−0·8434 (5)	0·1804 (3)	−0·3572 (2)	3·42 (5)
C4′	−0·6083 (4)	0·2526 (3)	−0·3861 (2)	2·63 (4)
O4′	−0·4088 (4)	0·2247 (2)	−0·2831 (1)	3·56 (3)
O2′	−0·7142 (4)	−0·0565 (2)	−0·3583 (2)	4·45 (4)
C5′	−0·6387 (5)	0·4020 (3)	−0·3989 (2)	3·80 (6)
O5′	−0·4104 (4)	0·4679 (2)	−0·4165 (1)	4·01 (4)
3′-ddA				
C2	0·6111 (5)	0·4395 (3)	0·4785 (1)	2·59 (5)
C6	0·9350 (5)	0·4535 (3)	0·4169 (1)	2·30 (5)
O4′	0·4058 (3)	−0·0264 (2)	0·32519 (8)	2·54 (3)
C3	0·5372 (5)	0·3063 (3)	0·4563 (1)	2·34 (5)
N1	0·8040 (4)	0·5117 (2)	0·46106 (9)	2·49 (4)
C4	0·6805 (5)	0·2437 (3)	0·4123 (1)	2·10 (5)
N7	0·9882 (4)	0·2311 (2)	0·3484 (1)	2·86 (5)
N6	1·1188 (4)	0·5299 (3)	0·3964 (1)	3·28 (5)
N9	0·6727 (4)	0·1127 (2)	0·38029 (9)	2·17 (4)
C5	0·8762 (5)	0·3149 (3)	0·3923 (1)	2·13 (5)
C3′	0·6129 (6)	−0·2360 (3)	0·3554 (1)	2·89 (5)
C8	0·8614 (5)	0·1124 (3)	0·3429 (1)	2·84 (5)
C4′	0·4423 (5)	−0·1797 (3)	0·3090 (1)	2·50 (5)
C2′	0·5617 (5)	−0·1445 (3)	0·4118 (1)	2·51 (5)
C5′	0·5119 (7)	−0·1877 (4)	0·2432 (1)	3·95 (7)
O2′	0·3743 (4)	−0·2086 (2)	0·44395 (8)	3·29 (4)
C1′	0·4883 (5)	0·0035 (3)	0·3841 (1)	2·17 (5)
O5′	0·7272 (5)	−0·1168 (3)	0·2331 (1)	4·74 (5)

Table 2. *Bond distances* (Å), *bond angles* (°) *and deviations* (Å) *of atoms from least-squares planes*

Atomic names in parentheses signify where a substitution has been made relative to adenosine.

		3′-dTu	3′-ddA
N1	C2	1·339 (6)	1·356 (6)
N1	C6	1·348 (6)	1·339 (6)
C2	N3 (C3)	1·316 (6)	1·373 (6)
N3 (C3)	C4	1·353 (5)	1·394 (6)
C4	C5	1·391 (6)	1·382 (6)
C4	N9	1·367 (5)	1·381 (5)
C5	C6	1·404 (6)	1·411 (6)
C5	C7 (N7)	1·432 (7)	1·388 (5)
C6	N6	1·346 (6)	1·352 (5)
C7 (N7)	C8	1·349 (6)	1·312 (5)
C8	N9	1·393 (6)	1·370 (5)
N9	C1′	1·447 (5)	1·464 (5)
C1′	C2′	1·538 (6)	1·535 (5)
C1′	O4′	1·419 (5)	1·402 (4)
C2′	C3′	1·505 (7)	1·518 (5)
C2′	C2′	1·433 (6)	1·423 (5)
C3′	C4′	1·524 (6)	1·510 (7)
C4′	C4′	1·432 (5)	1·451 (6)
C4′	C5′	1·498 (7)	1·499 (6)
C5′	O5′	1·421 (6)	1·426 (5)

			3′-dTu	3′-ddA
C2	N1	C6	118·0 (4)	119·1 (4)
N1	C2	N3 (C3)	129·0 (5)	125·8 (4)
C2	N3 (C3)	C4	111·4 (4)	114·6 (4)
N3 (C3)	C4	C5	126·7 (4)	121·5 (4)
N3 (C3)	C4	N9	125·1 (4)	132·9 (4)
C5	C4	N9	108·3 (4)	105·6 (4)
C4	C5	C6	115·3 (4)	119·8 (4)
C4	C5	C7 (N7)	107·4 (4)	110·6 (4)
C6	C5	C7 (N7)	137·2 (4)	129·7 (4)
N1	C6	C5	119·3 (4)	119·2 (4)
N1	C6	N6	117·1 (4)	119·3 (4)
C5	C6	N6	123·6 (5)	121·5 (4)
C5	C7 (N7)	C8	106·4 (4)	104·4 (4)
C7 (N7)	C8	N9	110·2 (4)	113·3 (3)
C4	N9	C8	107·8 (4)	106·2 (4)
C4	N9	C1′	124·8 (4)	125·3 (4)
C8	N9	C1′	126·6 (4)	128·4 (3)
N9	C1′	C2′	115·1 (4)	114·2 (3)
N9	C1′	O4′	108·3 (4)	109·3 (3)
C2′	C1′	O4′	107·1 (4)	106·9 (3)
C1′	C2′	C3′	103·4 (4)	102·2 (3)
C1′	C2′	O2′	110·3 (4)	109·8 (3)
C3′	C2′	O2′	113·3 (4)	109·2 (3)
C2′	C3′	C4′	104·0 (4)	103·5 (4)
C3′	C4′	O4′	104·5 (4)	104·9 (4)
C3′	C4′	C5′	114·2 (5)	116·9 (5)
O4′	C4′	C5′	108·6 (4)	108·7 (3)
C1′	O4′	C4′	110·9 (4)	111·0 (3)
C4′	C5′	O5′	113·0 (5)	111·3 (4)

Deviations from least-squares planes: e.s.d.'s *ca* 0·002 Å; the atoms marked with an asterisk were used to calculate the mean planes

3′-dTu

Purine ring; $\chi^2 = 3328$

N1*	−0·054	C5*	−0·018	C8*	−0·11
C2*	−0·030	C6*	9·065	N9*	0·028
N3*	0·041	N6*	0·064	C1′	0·273
C4*	0·020	C7*	−0·045		

3′-ddA

Purine ring; $\chi^2 = 1051$

N1*	−0·047	C5*	−0·004	C8*	−0·012
C2*	−0·005	C6*	−0·008	N9*	0·002
C3*	0·033	N6*	0·043	C1′	0·0080
C4*	0·011	N7*	−0·014		

Table 3. *Comparison of torsion angles* (°) *for modified nucleosides*

	3-dTu	3-dA	A	2′-dA	araA	3′-dA	3′-dTu	3′-ddA
O4′–C1′–N9–C4	253·6	233·9	188·6	182·7	204·8	205·6	246·5	191·8
O5′–C5′–C4′–O4′	59·3	64·3	60·1	68·1	70·5	62·4	61·9	201·8
O5′–C5′–C4′–C3′	175·5	305·8	176·9	186·9	55·1	180·0	180·0	60·5
Sugar pucker	C3′-*endo*	C3′-*endo*	C3′-*endo*	C3′-*exo*	C3′-*endo*	C3′-*endo*	C3-*endo*	C3′-*endo*

3′-dTu≡, 3′-ddA≡ — This study.
A — Adenosine (Lai & Marsh, 1972).
2′-dA — 2′-Deoxyadenosine (Watson, Sutor & Tollin, 1965).
araA — Adenine arabinofuranoside (Chwang & Sundaralingam, 1974).
3′-dA — 3′-Deoxyadenosine (Radwan & Wilson, 1980).
3-dTu — Tubercidin (Altona & Sundaralingam, 1972).
3-dA — 3-Deazaadenosine (Singh, May, Townsend & Hodgson, 1976).

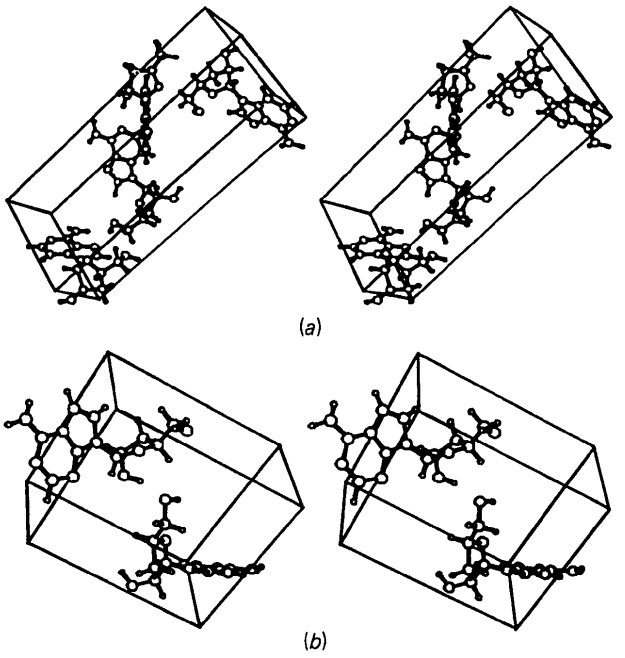


Fig. 2. Unit-cell packing diagrams for (*a*) 3-deaza-3-deoxyadenosine, (*b*) 3′-deoxytubercidin.

Sundaralingam, 1972), which is somewhat higher than for the other related nucleosides. For the majority of modified nucleosides listed in Table 3, including 3′-dTu, the conformation about the C4′—C5′ bond is *gauche*(+)–*trans*. 3′-ddA is exceptional here in having a *gauche*(+)–*gauche*(−) conformation about this bond, which is normally the more stable conformation for nucleosides.

Hydrogen bonding

Fig. 2 shows stereoviews of the packing diagrams of the molecules in their crystal lattice. Hydrogen-bond lengths and angles have been deposited. There is a lack of base–base hydrogen bonds in both crystal lattices as compared with most nucleosides in the solid state.

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Structure of 2-Methoxy-*N*-(4-nitrobenzylidene)-5-pyridylamine

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Abstract. $C_{13}H_{11}N_3O_3$, $M_r = 257{\cdot}2$, monoclinic, $P2_1/n$, $a = 11{\cdot}080\ (2)$, $b = 3{\cdot}376\ (1)$, $c = 14{\cdot}364\ (2)$ Å, $\beta = 112{\cdot}56\ (1)°$, $V = 1231{\cdot}1\ (6)$ Å^3, $Z = 4$, $D_x = 1{\cdot}388$, $D_m = 1{\cdot}385$ g cm^{-3}, λ(Mo $K\alpha$) $= 0{\cdot}71069$ Å, $\mu = 0{\cdot}62$ cm^{-1}, $F(000) = 536$, $T = 293$ K, $R = 0{\cdot}0374$ for 1554 observed reflections. The molecule as a whole is in a nearly planar conformation. The dihedral angle between the plane through C(1), C(7), N(1) and C(8) and the phenyl ring is 3·2 (2)°, and that between the phenyl and pyridine rings is 19·6 (2)°. Bond distances indicate a quinoid resonance contribution throughout the molecule.

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