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The Crystal Structure of 3-Deazacytidine

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$C_{10}H_{14}N_2O_5$, $M_r = 242\cdot2$, orthorhombic, $P2_12_12_1$, $a = 11\cdot046$ (2), $b = 14\cdot103$ (2), $c = 6\cdot918$ (1) Å, $D_x = 1\cdot51$, $D_c = 1\cdot49$ g cm^{-3}, $Z = 4$, $\bar{\mu}$(Mo $K\alpha$) = $1\cdot4$ cm^{-1}. The structure was refined by full-matrix least squares to a final R of $0\cdot035$ [1660 reflexions with $I \geq 3\sigma(I)$; 1846 unique reflexions in the sphere $2\theta \leq 60°$ with Mo $K\alpha$ radiation]. The torsion angle C(2)—N(1)—C(1')—O(1') is $-112\cdot2°$ ($247\cdot8°$); the conformation around C(4')—C(5') is gauche–trans, and the pucker of the ribose ring is $2'$-endo, $3'$-endo.

Introduction

Cellular and viral metabolic processes can be inhibited by chemical modification of natural precursor molecules such as the pyrimidines and purine ribonucleosides. Replacement of C(6) in uridine by N gives rise to an antileukaemic drug (Schwalbe, Saenger & Gassman, 1971). Analogues in which N(3) is replaced

by CH also have cytostatic properties (Robins, Currie, Robins & Bloch, 1969). The title compound (and 3-deazauridine) inhibits the growth of several RNA viruses. herpes simplex and parainfluenza (Sendai). However, the mechanism of this inhibition is not well understood. The crystal structure of 3-deazauridine showed that the base is in the enol (4-hydroxy tautomer) form (Schwalbe & Saenger, 1973). The present work describes the crystal structure of 3-deazacytidine in order to compare the molecular geometries of these two 3-deazapyrimidines.

Crystals of 3-deazacytidine were grown from an ethanolic solution of a sample kindly provided by Dr M. J. Robins of the Chemistry Department, University of Alberta. Preliminary photographs showed the systematic absences $h00$, $h = 2n + 1$; $0k0$, $k = 2n + 1$; $00l$, $l = 2n + 1$; accurate cell parameters and intensities were collected from a crystal $0.48 \times 0.51 \times 0.45$ mm with Mo $K\alpha$ radiation on a Picker FACS-1 diffractometer. The details of the data collection have been described (Hutcheon & James, 1974). The density was measured by flotation in a mixture of chlorobenzene and carbon tetrachloride.

Intensities for 3592 reflexions (hkl and $\bar{h}kl$) in the range $3° \leq 2\theta \leq 60°$ were measured, and equivalent reflexions averaged after the application of empirical absorption corrections (North, Phillips & Matthews, 1968). 1846 reflexions (R, based on the intensities of equivalent reflexions, 0·021) resulted, and of these 1660 were considered above the threshold $I \geq 3\sigma(I)$, where $\sigma(I) = [P + B + (0.01I)^2]^{1/2}$.

The structure was solved with MULTAN (Main, Germain & Woolfson, 1970). The E map computed with the phase set having $R_{\text{Karle}} = 0.18$ contained peaks interpretable in terms of the molecular structure of 3-deazacytidine. The starting model was refined by full-matrix least squares, minimizing $\Sigma\omega(|F_o| - |F_c|)^2$, where $\omega^{1/2} = |2F_o/\sigma(I)|^{1/2}$.

Incorporation of the H atoms and anisotropic thermal parameters for the non-hydrogen atoms followed by further refinement resulted in a final R ($= \Sigma \|F_o| - |F_c\|/\Sigma |F_o|$) of 0·035.* The scattering factors of Cromer & Mann (1968) were used for C, N and O atoms; the curve for H was the orbitally contracted model given by Mason & Robertson (1966). The program system used was XRAY-70 (Stewart, Kundell & Baldwin, 1970).

Discussion

Fig. 1 is an ORTEP (Johnson, 1965) stereo-drawing of the molecule. Bond distances and angles are shown in Fig. 2. Table 1 contains the atomic parameters. Estimated standard deviations were derived from the diagonal elements of the inverse matrix of the final least-squares cycle.

The ribose ring, crystallographically one of the least studied moieties in nucleoside structures, has a $2'$-endo, $3'$-endo conformation with displacements of 0·81 and 0·25 Å for C(2') and C(3') respectively. The best four-atom plane through the ribose ring and a list of selected atomic displacements from this plane are given in Table 2. The conformation about C(4')—C(5') is the unusual gauche–trans with $\varphi_{OO} = 61.6°$ and $\varphi_{OC} = 180.5°$, which is observed in only one other nucleoside with cytosine as the base (Sherfinski & Marsh, 1973). The conformation around the glycosidic bond is shown in Fig. 3 and the torsion angle C(6)—N(1)—C(1')—O(1') is 67·8°. The conformation of the base is anti but is on
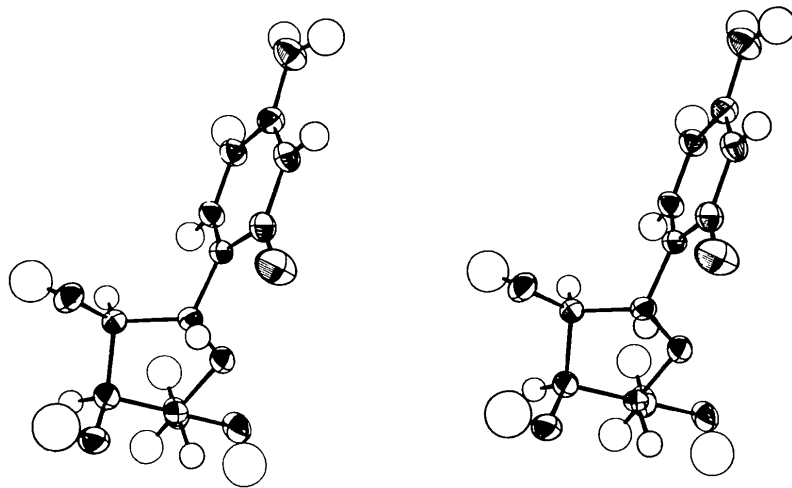
Fig. 1. Stereo-drawing (Johnson, 1965) of 3-deazacytidine. The sugar pucker is ^2E and the conformation around C(4')—C(5') is gauche–trans.
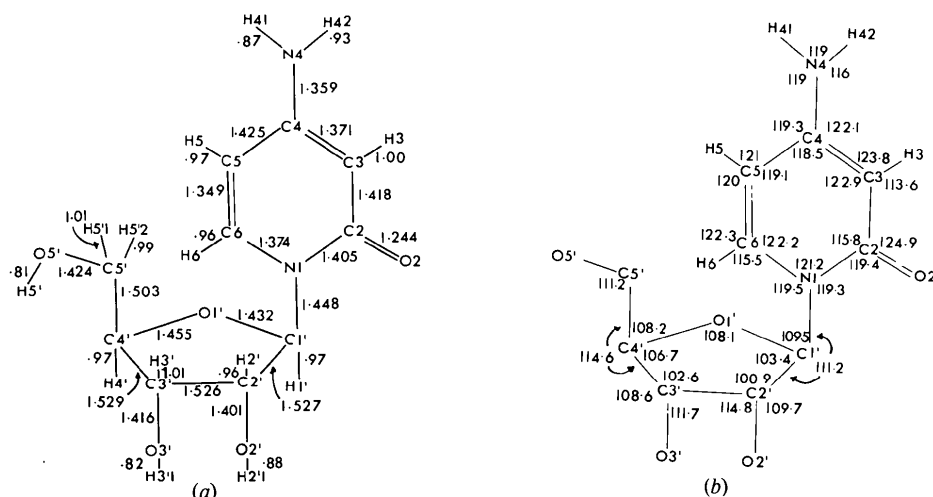
Fig. 2. (a) Bond distances (Å) and (b) bond angles (°) for 3-deazacytidine. The average e.s.d.'s are 0·002 Å and 0·2°: when H atoms are involved, they are 0·02 Å and 0·9°.

Table 1. *Final atomic parameters* ($\times 10^4$, *for* H $\times 10^3$) *for 3-deazacytidine, with e.s.d.'s in parentheses*

	x	y	z
N(1)	3346 (1)	3592 (1)	1955 (2)
C(2)	4001 (1)	3915 (1)	3567 (2)
O(2)	4135 (1)	3383 (1)	4984 (2)
C(3)	4446 (1)	4856 (1)	3443 (2)
C(4)	4278 (1)	5420 (1)	1851 (2)
N(4)	4641 (1)	6340 (1)	1806 (3)
C(5)	3669 (1)	5030 (1)	217 (3)
C(6)	3240 (1)	4135 (1)	316 (3)
C(1')	2771 (1)	2670 (1)	2029 (3)
C(2')	1450 (1)	2644 (1)	1381 (2)
O(2')	710 (1)	3019 (1)	2838 (2)
C(3')	1281 (1)	1586 (1)	1008 (2)
O(3')	1072 (1)	1080 (1)	2745 (2)
C(4')	2513 (1)	1291 (1)	198 (2)
O(1')	3361 (1)	2041 (1)	703 (2)
C(5')	2543 (1)	1162 (1)	−1958 (3)
O(5')	3715 (1)	881 (1)	−2595 (2)
H(3)	484 (1)	508 (1)	466 (2)
H(41)	461 (1)	665 (1)	72 (3)
H(42)	521 (1)	651 (1)	271 (3)
H(5)	363 (1)	538 (1)	−98 (3)
H(6)	286 (1)	383 (1)	−76 (2)
H(1')	287 (1)	246 (1)	335 (2)
H(2')	131 (1)	297 (1)	18 (2)
H(2'1)	5 (2)	325 (1)	229 (3)
H(3')	62 (1)	147 (1)	3 (2)
H(3'1)	46 (2)	130 (1)	324 (3)
H(4')	278 (1)	70 (1)	77 (2)
H(5'1)	196 (1)	64 (1)	−234 (3)
H(5'2)	234 (1)	175 (1)	−267 (3)
H(5')	385 (1)	32 (2)	−240 (4)

Table 2. *Least-squares planes*

Deviations are in Å. Atoms or distances denoted by an asterisk are those determining the plane.

	Plane I		Plane II	Plane III
N(1)*	−0·032	C(1')	−0·035*	0·000*
C(2)*	0·019	C(2')	0·624	0·810
C(3)*	0·009	C(3')	0·032*	0·251
C(4)*	−0·023	C(4')	−0·053*	0·000*
C(5)*	0·010	O(1')	0·056*	0·000*
C(6)*	0·018	C(5')	1·027	1·033
O(2)	0·046	O(5')	0·871	0·722
N(4)	−0·120	N(1)	0·596	0·541
C(1')	−0·142	O(2')	0·296	0·599
		O(3')	−1·276	−0·985
χ^2	957·7		4020·6	−

Equations of least-squares planes in direct space

$$Px + Qy + Rz = S$$

Plane	P	Q	R	S (Å)
I	9·506	−4·939	−2·559	0·938
II	−2·431	7·917	−5·519	0·355
III	−3·679	7·735	−5·306	−0·031

the high side of the observed range for pyrimidine nucleosides: cytidine (Furberg, Petersen & Rømming, 1965) 18°; cytidinium nitrate (Guy, Nassimbeni, Sheldrick & Taylor, 1976) 16·4°; uridine (Green, Rosenstein, Shiono, Abraham, Trus & Marsh, 1975) 18·3° for

molecule A, 24·3° for molecule B; arabinosyl cytosine HCl (Sherfinski & Marsh, 1973) 26·7°; arabinosyl cytosine (Tougard & Lefebvre-Soubeyran, 1974) 28·8°; 3-deazauridine (Schwalbe & Saenger, 1973) 52·3°; 2'-deoxycytidine (Young & Wilson, 1975) 21·2° for molecule I, 42·2° for molecule II; and 6-azacytidine (Singh & Hodgson, 1974) 99·1°.

The 3-deazacytosine ring is not particularly planar (Table 2, $\chi^2 = 958$). In addition there is clearly an alternation of single and double bonds (Fig. 2). Both these observations indicate a loss of aromatic character on substituting the N(3) of cytosine by CH. A similar ob-

Table 3. *Hydrogen-bond distances and angles*

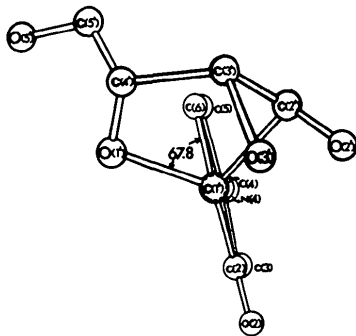| Bond type A—H···B	A···B	A—H	H···B	Angle (°) A—H···B	Symmetry of acceptor
N(4)—H(41)···O(2')	2·916 (2)	0·87 (2)	2·08 (2)	161	2,‖c
N(4)—H(42)···O(1')	2·970 (2)	0·93 (2)	2·06 (2)	166	2,‖b
O(3')—H(3'1)···O(2)	2·761 (2)	0·82 (2)	1·96 (2)	165	2,‖a
O(2')—H(2'1)···O(5')	2·700 (2)	0·88 (2)	1·93 (2)	145	2,‖a
O(5')—H(5')···O(3')	2·785 (2)	0·81 (2)	1·98 (2)	172	2,‖c

Fig. 3. Perspective drawing of 3-deazacytidine showing the torsion angle C(6)—N(1)—C(1')—O(1'). The projection direction is approximately parallel to the C(1')→N(1) vector.

servation was made regarding the 3-deazauricil moiety of 3-deazauridine (Schwalbe & Saenger, 1973). C(5)—C(6) [1·349 (3) Å] has almost pure double-bond character but C(3)—C(4) [1·371 (3) Å] is closer to an aromatic bond. The aromatic character of the uracil ring is also disrupted in 2,2'-anhydro-2-hydroxy-1-(β-D-*arabino*-pentofuranosyl)-4-pyridone (Hutcheon & James, 1977).

Although it may appear from Fig. 4 that there is a high degree of base stacking in the structure, there is not. Rather the structure has an extensive hydrogen-bonding network which is summarized in Table 3. The exocyclic N(4) acts as a hydrogen-bond donor in two cases, one to O(2') of a neighbouring molecule, and rather surprisingly to O(1') of the ribose ring in a second neighbouring molecule. This relatively rare occurrence of the ribose ring O(1') acting as a hydrogen-bond acceptor has been noted by Sprang & Sundaralingam (1973) in 2-chloro-1-(β-D-ribofuranosyl)-benzimidazole.

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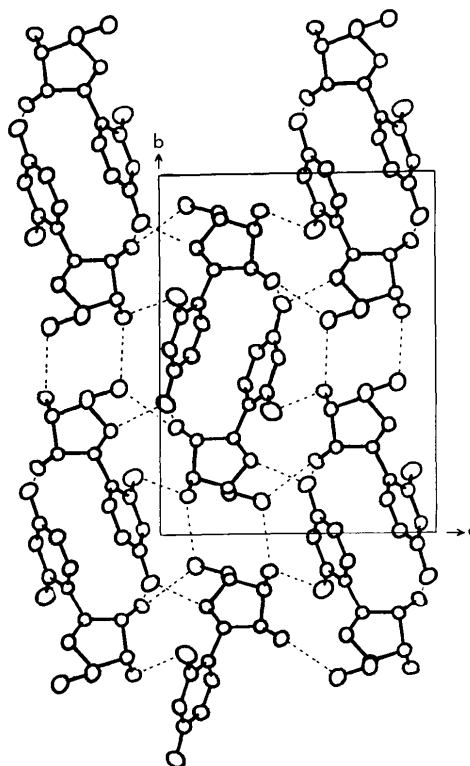

Fig. 4. Molecular packing diagram for 3-deazacytidine. The view is projected down c onto the (001) plane. There is no base stacking in the crystals, but rather an extensive hydrogen-bonding network.

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The Crystal Structure of 2,2'-Anhydro-2-hydroxy-1-(β-D-*arabino*-pentofuranosyl)-4-pyridone

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$C_{10}H_{11}NO_5$, orthorhombic, $P2_12_12_1$, $a = 9.255$ (3), $b = 16.783$ (5), $c = 12.858$ (4) Å, $Z = 8$, $D_c = 1.485$ g cm^{-3}, $\bar{\mu}$(Mo $K\alpha$) = 1.59 cm^{-1}. The structure was determined by direct methods and refined by full-matrix least squares to $R = 0.05$ [1476 reflexions with $I \geq 3\sigma(I)$; 73% of total in the sphere $3° \geq 2\theta \geq 50°$]. There are two molecules in the asymmetric unit; one has the E_4 [C(4')-*exo*] conformation, the other the ^4E [C(4')-*endo*]. Ring fusion has fixed the glycosidic torsion angle (average $\chi_{CN} = 292.0°$) but the torsion angles about C(4')–C(5') are different (molecule A: $\varphi_{OO} = 69.5°$, $\varphi_{OC} = 174.2°$; molecule B: $\varphi_{OO} = 169.9°$, $\varphi_{OC} = 71.8°$).

Introduction

Several 3-deazapyrimidines possess significant anti-tumour activities, although their mechanism of action is not fully elucidated. Implicit in their activity is the lack of an N atom in the 3 position of the pyrimidine ring, thus precluding Watson–Crick base pairing. A comparison of the molecular geometry of the present compound with that of the related 2,2'-anhydro-1-(β-D-*arabino*-furanosyl)uracil (Delbaere & James, 1973) is made in this paper.

Suitable single crystals of the title compound were obtained from Dr M. J. Robins, Chemistry Department, University of Alberta. The compound had been synthesized according to Robins & Currie (1968). The space group was determined from the systematic absences observed on photographs ($h00$, $h = 2n + 1$; $0k0$, $k = 2n + 1$; $00l$, $l = 2n + 1$) and the final cell dimensions and intensities were measured from a crystal

(0.40 × 0.25 × 0.10 mm) with a FACS-1 diffractometer. Details of the data collection are those described in Hutcheon & James (1974). Those reflexions with $\sigma(I)/I > 0.30$ were excluded from the solution and refinement. The standard deviation in intensity was computed from $\sigma(I) = [P + t^2B + (0.01I)^2]^{1/2}$, where P is the total peak count, B the total background count, I the net intensity of the peak and t the ratio of the total peak-scan time to the total background-counting time. No corrections for absorption were applied.

The structure was solved by symbolic addition (Karle & Karle, 1966) and tangent refinement (Karle & Hauptman, 1956). Those Σ_2 relations which resulted from three reflexions on the same axial zone were removed (Karle, 1969). Completion of the initial model was achieved by a series of F_o maps based on partial structural information from the starting E map. Full-matrix least-squares refinement of all the atomic