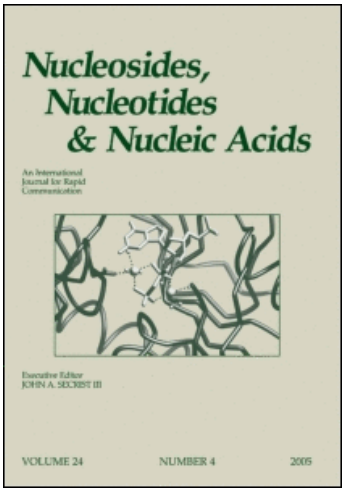

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Crystal Structure of 1-(2',3',5'-Tri -O-Acetyl-β-D-ribofuranosyl)-3-acetoxy-2-pyridone: An Antitumour Agent

A. K. Das[a]; M. Ghosh[a]; A. K. Basak[a]; S. K. Mazumdar[a]; R. A. Palmer[b]
[a] Crystallography and Molecular Biology Division Saha Institute of Nuclear Physics Sector 1, INDIA [b] Department of Crystallography, Birkbeck College Malet Street, London, UK

To cite this Article Das, A. K. , Ghosh, M. , Basak, A. K. , Mazumdar, S. K. and Palmer, R. A.(1990) 'Crystal Structure of 1-(2',3',5'-Tri -O-Acetyl-β-D-ribofuranosyl)-3-acetoxy-2-pyridone: An Antitumour Agent', Nucleosides, Nucleotides and Nucleic Acids, 9: 5, 731 — 744
To link to this Article: DOI: 10.1080/07328319008045202
URL: http://dx.doi.org/10.1080/07328319008045202

NUCLEOSIDES & NUCLEOTIDES, 9(5), 731-744 (1990)

CRYSTAL STRUCTURE OF 1-(2',3',5'-TRI-O-ACETYL-β-D-RIBOFURANOSYL)-3-ACETOXY-2-PYRIDONE AN ANTITUMOUR AGENT

A. K. Das*, M. Ghosh, A. K. Basak, S. K. Mazumdar

Crystallography and Molecular Biology Division

Saha Institute of Nuclear Physics

Sector 1, Block 'AF', Bidhannagar, Calcutta 700064

INDIA

and R. A. Palmer

Department of Crystallography, Birkbeck College

Malet Street, London WC1E7HX, UK

ABSTRACT

1-(2', 3', 5'-Tri-O-acetyl- β- D-ribofuranosyl)- 3 -acetoxy -2-pyridone, crystallised in space group $P2_1$ with Z=2 and cell parameters a=12.446(2), b=10.415(2), c=7.699(2) Å, β=93.30(4)°. The structure was solved by direct methods and refined by full-matrix least-squares to a final R value of 0.051 for 1847 observed reflections. The sugar pucker is

* Correspondence

found to be $^{3}E(C3'$ endo) with $P=17.7^{o}$ and $\chi_{CN}=170.2(2)^{o}$ in the *anti* range. The C4'-C5' conformation is gauche minus. Because of the absence of H-bond donor atoms, the crystal structure is stabilised by a network of C-H---O close contacts. No base stacking is observed..

INTRODUCTION

The antitumor active ribonucleoside of 3-deazapyrimidine derivative, 1- (2',3',5'-Tri-O-acetyl-β-D-ribofuranosyl)-3-acetoxy-2-pyridone is thought to interfere with specific enzymes involved in pyrimidine metebolism in a manner analogous to the action of 3-deazauridine[1]. In this nucleoside a pyridine base attached to the ribofuranose sugar ring replaces the pyrimidine of 3-deazauridine. The influence of such modifications on the stereochemistry of nucleosides and nucleotides and the associated changes in activity are not fully understood. The study reported here is a part of a programme on structure analyses of this type compounds designed to investigate the precise influence of substituents on the molecular conformation. It is to be expected that the absence of NC3) of the base ,which precludes Watson-Crick base pairing and complete lack of H-bonding propensity may affect on the molecular conformation in the crystalline state. The substituents on the sugar moiety may on the other hand directly influence the puckering of the sugar ring by their steric effect.

EXPERIMENTAL

The title compound was synthesized and supplied by Dr. V. E. Marquez of National Institutes of Health, Bethesda, MD. 20205 USA. Colourless plate-like crystals were obtained by slow evaporation from a chloroform-hexane solution. The crystal used for X-ray data collection had approximate dimensions of .25x.25x.35mm^3. Systematic absences $(0k0: k=2n+1)$ indicated the space group to be $P2_1$. Intensity data were collected on a Nonius CAD4 diffractometer with monochromated CuKα radiation, λ=1.5418Å. Lattice parameters determined from the θ values for 25 strong reflections are a=12.446(2), b=10.415(2), c=7.699(2) Å, β=93.30(4)°, giving V=996.3(4) Å^3. ρ_c=1.37 g cm^{-3}, Z=2, F(000)=432, μ(CuKα)=8.73 cm^{-1}. A total of 3556 reflections with $-14 \le h \le 14, -3 \le k \le 12, 0 \le l \le 9$ were recorded. Lorentz and polarization corrections were applied but no absorption correction. Of 1854 unique reflections, 1847 had $I \ge 3\sigma(I)$ and were considered to be observed. The structure was solved by direct methods using the program MULTAN 78[2]. Of the 12 phase sets developed, the solution with the highest combined figure of merit (2.287) produced an E-map on which 15 out of 29 non-H atoms were located. The remaining non-H atoms were located from a weighted electron density map. The structure was refined by full-matrix least-squares, first isotropically to R=0.114 and then anisotropically to R=0.074 using the SHELX78[3] program. Of the 21 H atoms, 13 were located on a difference electron density map, and the rest were positioned geometrically. The final R value is 0.051.

Atomic scattering factors for non-H atoms were taken from Cromer and Waber (1965)[4] and for H-atoms from Steward et al (1965)[5]. The quantity minimized was $\Sigma w(|Fo|-|Fc|)^2$ with w=1. Table 1 lists the refined atomic parameters.

RESULTS AND DISCUSSION

Fig.1 is a minimum overlap view of the molecule showing the numbering scheme. The molecular geometry consisting of bond distances and angles and selected torsion angles is listed in Table 2. The bond lengths of the base agree satisfactorily with those of 3-deaza-4-deoxy uridine[6] (mean deviation 0.024Å) and 3-deazauridine[7]. There are no significant differences in bond angles in these structures. The pyridone ring is nearly planar, with a rms deviation of atomic displacements from the ring plane of 0.009Å (Table 3). The C2-O2 bond, 1.225(7)Å, is slightly longer than the expected value for an isolated C=O double bond, 1.207Å, due to conjugation with the ring. This effect is evidenced by the four acetyl carbonyl bond distances C7-O7, 1.194(8), C10'-O10', 1.178(9), C6'-O6', 1.183(8), and C8'-O8', 1.193(9)Å, which are all slightly shorter than the C2-O2 bond length. In the furanose ring C1'-O4', 1.419(7)Å, is significantly shorter than C4'-O4', 1.450(6)Å. Similar differences are frequently observed in this type of sugar ring, as for example in 3'-5'-Di-O-acetylthymidine[8], and are attributed[9] to the delocalisation of electrons from O4' to C1' anti bonding orbitals. A noteable exception to this rule is found in

Table 1. Fractional co-ordinates* and equivalent isotropic thermal parameters($\times 10^3$ Å^2 or $\times 10^2$ Å^2 for H atoms)

	x	y	z	U_{eq}/U_{iso}
N1	0.6486(4)	0.0900(29)	1.0637(6)	35(2)
O2	0.7326(3)	0.1876(28)	1.2991(5)	48(2)
O3	0.5451(4)	0.3179(28)	1.3708(6)	50(2)
O7	0.5436(4)	0.1565(28)	1.5619(6)	58(2)
O2'	0.9376(3)	0.0943(28)	1.0067(6)	43(1)
O3'	0.8926(3)	0.1617(28)	0.6600(5)	42(1)
O4'	0.7393(3)	-.0616(28)	0.8968(5)	38(1)
O5'	0.7440(4)	-.2078(28)	0.5749(6)	45(1)
O6'	0.7148(5)	-.2003(28)	0.2875(6)	72(2)
O8'	0.8218(4)	0.3596(28)	0.6736(7)	59(2)
O10'	0.9921(5)	0.2972(29)	1.0236(12)	97(3)
C2	0.6491(5)	0.1704(29)	1.2101(7)	38(2)
C3	0.5471(5)	0.2279(29)	1.2371(7)	41(2)
C4	0.4558(5)	0.2039(29)	1.1348(8)	47(2)
C5	0.4619(5)	0.1185(29)	0.9938(8)	52(2)
C6	0.5585(5)	0.0636(29)	0.9612(8)	41(2)
C7	0.5467(5)	0.2694(29)	1.5350(8)	43(2)
C8	0.5539(6)	0.3729(29)	1.6673(9)	55(3)
C1'	0.7541(4)	0.0334(29)	1.0281(7)	36(2)

(continued)

Table 1. continued

C2'	0.8283(5)	0.1250(29)	0.9581(8)	36(2)
C3'	0.8076(4)	0.1172(29)	0.7631(7)	33(2)
C4'	0.7984(5)	-.0268(29)	0.7469(7)	33(2)
C5'	0.7384(5)	-.0693(29)	0.5826(8)	41(2)
C6'	0.7320(5)	-.2612(29)	0.4158(8)	44(2)
C7'	0.7379(8)	-.4028(30)	0.4242(10)	68(3)
C8'	0.8881(6)	0.2893(29)	0.6204(9)	52(2)
C9'	0.9744(9)	0.3237(30)	0.5015(20)	85(5)
C10'	1.0120(9)	0.1867(29)	1.0295(9)	53(3)
C11'	1.1195(6)	0.1278(29)	1.0621(11)	72(3)
H51'	0.7693(49)	-.0279(75)	0.4890(82)	5(2)
H52'	0.6569(45)	-.0415(66)	0.5859(70)	4(2)
H11'	0.7808(41)	-.0061(66)	1.1446(71)	3(2)
H21'	0.8038(54)	0.2160(88)	1.0001(88)	7(2)
H41'	0.8821(58)	-.0728(80)	0.7635(91)	6(2)
H6	0.5634	-.0015	0.8528	5
H81	0.5280	0.3522	1.7563	5
H82	0.6445(70)	0.3920(101)	1.6977(110)	10(3)
H83	0.5198	0.4373	1.6323	5
H91'	1.0113(77)	0.2562(98)	0.4748(127)	9(3)
H92'	1.0091(85)	0.3959(122)	0.5913(146)	10(4)
H93'	0.9746(75)	0.4120(104)	0.4204(134)	11(3)
H71'	0.7665	-.4282	0.5174	5
H72'	0.6636(73)	-.4511(100)	0.3934(115)	10(3)
H73'	0.7785	-.4318	0.3506	5

H111'	1.1399	0.1222	1.1607	5
H112'	1.1674	0.1664	1.0114	5
H113'	1.1209	0.0589	1.0167	5
H4	0.3806	0.2495	1.1616	5
H3'	0.7536	0.1587	0.7335	5
H5	0.3908	0.0966	0.9121	5

---

* Absolute configuration may be generated using the transformation $\bar{x}\ \bar{y}\ \bar{z}$.

Table 2 Molecular geometry.

Bond distances.(Å)

N1-C2	1.404(7)	O6'-C6'	1.183(8)
N1-C6	1.362(7)	O8'-C8'	1.193(9)
N1-C1'	1.478(7)	O10'-C10'	1.178(9)
O2-C2	1.225(7)	C2-C3	1.430(8)
O3-C3	1.393(7)	C3-C4	1.368(9)
O3-C7	1.361(7)	C4-C5	1.409(10)
		C5-C6	1.369(9)
O2'-C2'	1.453(7)	C7-C8	1.482(9)
O2'-C10'	1.339(8)	C1'-C2'	1.524(8)
O3'-C3'	1.435(6)	C2'-C3'	1.521(8)
O3'-C8'	1.364(8)	C3'-C4'	1.509(8)
O4'-C1'	1.419(7)	C4'-C5'	1.498(8)
O4'-C4'	1.450(6)	C6'-C7'	1.479(10)
O5'-C5'	1.446(7)	C8'-C9'	1.494(11)
O6'-C6'	1.346(7)	C10'-C11'	1.480(11)

(continued)

Table 2. continued

Bond angles(deg.)			
C6-N1-C1'	121.5(5)	O4'-C1'-C2'	106.8(4)
C2-N1-C1'	115.1(4)	N1-C1'-C2'	110.6(5)
C2-N1-C6	123.4(5)	O2'-C2'-C1'	106.5(5)
C3-O3-C7	115.9(5)	C1'-C2'-C3'	101.1(5)
C2'-O2'-C10'	117.0(5)	O2'-C2'-C3'	108.8(5)
C3'-O3'-C8'	114.6(5)	O3'-C3'-C2'	114.7(5)
C1'-O4'-C4'	110.0(4)	C2'-C3'-C4'	102.2(5)
C5'-O5'-C6'	116.5(5)	O3'-C3'-C4'	109.3(5)
N1-C2-O2	120.1(5)	O4'-C4'-C3'	102.8(5)
O2-C2-C3	126.1(6)	C3'-C4'-C5'	113.3(5)
N1-C2-C3	113.8(5)	O4'-C4'-C5'	110.3(5)
O3-C3-C2	116.3(5)	O5'-C5'-C4'	107.8(5)
C2-C3-C4	123.7(6)	O5'-C6'-O6'	123.0(6)
O3-C3-C4	119.9(6)	O6'-C6'-C7'	125.3(7)
C3-C4-C5	118.6(6)	O5'-C6'-C7'	111.7(6)
C4-C5-C6	119.5(6)	O3'-C8'-O8'	122.8(6)
N1-C6-C5	120.8(6)	O8'-C8'-C9'	126.8(8)
O3-C7-O7	121.8(6)	O3'-C8'-C9'	110.4(8)
O7-C7-C8	126.7(7)	O10'-C10'-C11'	126.7(7)
O3-C7-C8	111.4(6)	O2'-C10'-O10'	123.7(7)
N1-C1'-O4'	109.3(4)	O2'-C10'-C11'	109.7(7)

Selected torsion angles (deg.)

C2-N1-C1'-C2'	-72.6(19)	C6-N1-C1'-O4'	-9.2(24)
C6-N1-C1'-C2'	108.1(19)	C2-N1-C1'-O4'	170.2(16)
O4'-C1'-C2'-C3'	24.9(18)	C2'-C1'-O4'-C4'	-00.5(19)
C1'-C2'-C3'-C4'	-38.9(16)	C2'-C3'-O3'-C8'	-85.2(20)
C2'-C3'-C4'-O4'	39.3(17)	O3'-C3'-C4'-C5'	-79.7(18)
C3'-O3'-C8'-C9'	-175.4(15)	C3'-C4'-C5'-O5'	174.6(14)
O4'-C4'-C5'-O5'	-70.7(18)	C3'-C4'-O4'-C1'	-24.4(19)
C4'-C5'-O5'-C6'	-155.9(16)	C5'-O5'-C6'-C7'	-179.3(16)

Table 3 Least-Squares planes, atomic deviations(Å) and dihedral angles(deg.)

Equations of weighted leaste-squares planes are in the form AX+BY+CZ - D = 0, where X, Y and Z are the orthogonal coordinates in Å. Starred atoms are involved in the calculations of the least-squares planes.

Plane 1 Pyridone ring.

.2474(94)X + .7706(64)Y -.5872(78)Z + 2.2127(982) = 0

C4*	.006(23)	C3*	.006(23)	C2*	-.016(23)
N1*	.014(23)	C6*	-.001(23)	C5*	-.009(23)
O3	.104(22)				

(continued)

Table 3. continued

Plane 2 Sugar ring

-.8842(38) X + .3909(77) Y - .2555(76) Z + 9.8606(504) = 0

O4'*	.063(14)	C1*	.081(14)	C2'*	.211(15)
C3'*	.250(14)	C4'*	.209(15)		

Plane	dihedral angle(deg.)
1-2	76.5(6)

Table 4 Close C-H---O Contacts.

D-H---A	D-H	D---A	H---A	∠ D-H---A
C8'-H82'...O7^{i}	1.060(5)	3.375(31)	2.49(6)	139.7
C8'-H81'...O2^{i}	0.94(6)	3.451(33)	2.70(7)	136.9
C8-H82'...O8'^{ii}	1.15(8)	3.336(9)	2.25(8)	155.1
C1'-H11'...O6'^{ii}	1.020(5)	3.204(32)	2.46(6)	128.3
C7'-H71'...O8'^{iii}	0.82(1)	3.267(33)	2.59(2)	140.0

Symmetry code

i	x,y,z-1
ii	x,y,z+1
iii	x,y-1,z

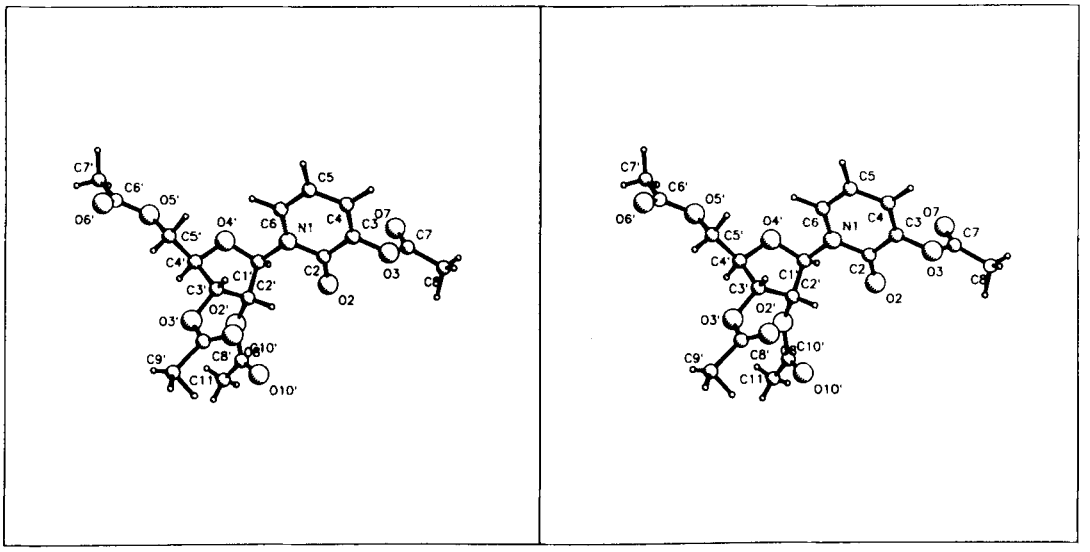

Fig. 1 Stereoview of the molecule.

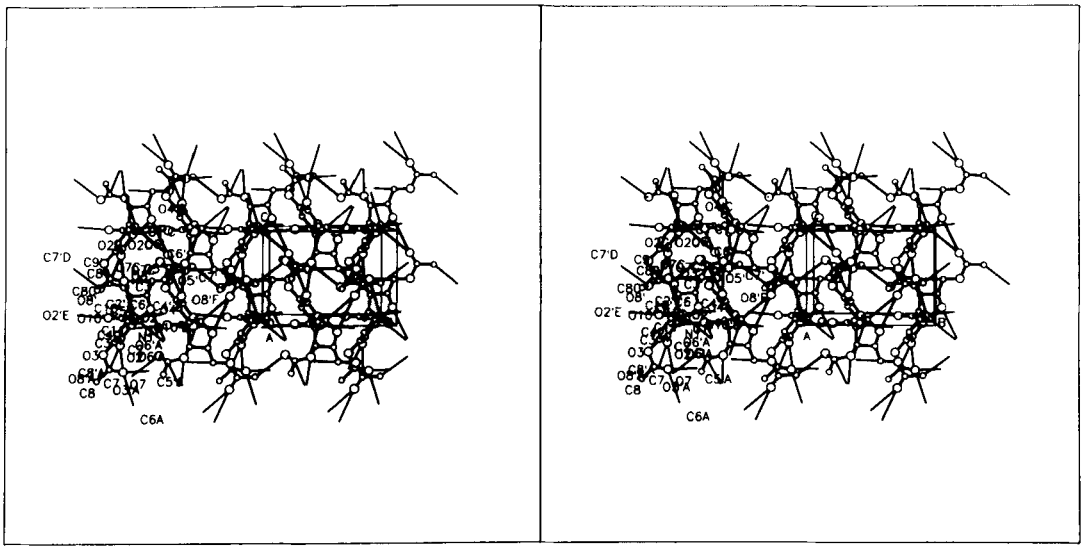

Fig.2 Stereoview of the packing in the unit cell of the title compound.

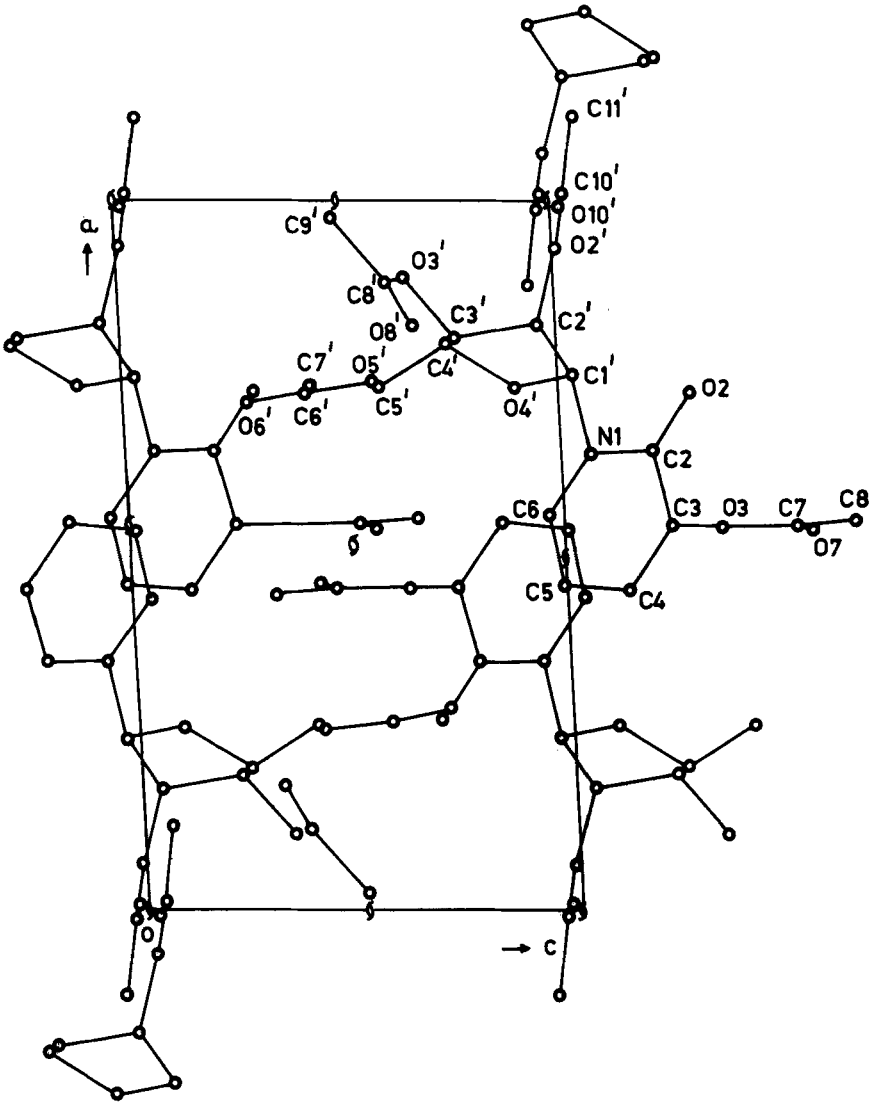

Fig. 3. Packing diagram b-axis projection.

2',3',5'-tri-O-acetyluridine[10] where C1'-O4'=1.432(7) and C4'-O4'=1.430(7) Å.

The glycosidic torsion angle χ_{CN}=C2-N1-C1'-O4', 170.2(2)°, corresponds to the plus

antiperiplanar conformation. The anti conformation is found in similar structures but with different χ values as in 3'-5'-di-O-acetylthymidine[8], -115.3(3)° and -136.3(3)° for molecules A and B respectively, and -138.3(1.1)° in 3'-5'-di-O-2'-deoxy-5-iodouridine[11]. However a syn conformation about the glycosidic bond is observed in 2'-3'-5'-tri- O-acetyluridine with χ=74.2(6)° The furanose ring puckering is the commonly observed ^{3}E(C3' endo), the pseudorotation angle[12,13] P=17.7° and degree of pucker Ψ_m=40.8° in contrast to the 3-deazauridine[7] where ring puckering shows C2'-endo. An exception to this is again found in 2'-3'-5'-tri-O-acetyl uridine[10] which exhibits a $^{3}T_4$[C(3')-endo/C(4')-exo] conformation.

C5'-O5' is *trans* to C3'-C4' and *gauche* to O4'-C4' with dihedral angles P_{oc}(C3'-C4'-C5'-O5')=174.6° and P_{oo}(O4'-C4'-C5'-O5') =70.7°. The C4'-C5' conformation in this case is a gauche minus in contrast to 2'-3'-5'-tri-O-acetyluridine[10] which exhibit a normal[14] gauche plus conformation.

The crystal packing is illustrated in Fig.2 is governed, because of the absence of H-bond donors, by C-H--O type close contacts(Table 4). Molecules are packed in the crystalline space with segregation of hydrophobic and hydrophilic zones(Fig.3). Bases related by two fold screw axes with translation along b axis form the hydrophobic zones whereas the sugar moieties related by screw axes with translation along b axis form a hydrophilic zones.

REFERENCES

(1) Mcpartland,R.P.,Wang,M.C>,Bloch,A.annd W einfeld,H. Cancer Res. 1974,34,3107.

(2) Main, P.,Hull,S.E.,Lessinger,L.,Germain,G.,Declercq, J.P.and Woolfson,M.M. MULTAN78 University of York,England, and University Louvain,Belgium,1978

(3) Sheldrick,G.M. SHELX 76 Programs for Crystal Structure Analysis, Cambridge, England,1976.

(4) Cromer.D.T. and Waber,J.T. Acta Crystallogr.1965, 18,104.

(5) Steward, R. F., Davidson, E. R., and Simpson, W. T. J .Chem.Phys. 1965,42.,3175.

(6) Egert, E., Lindner, H.J., Hillen,W.and Gassen,H.G. Acta Crystallogr. 1977,B33,3704.

(7) Schwalbe,C.H.and Saenger,W. Acta Crystallogr.1973,B29,61.

(8) Wilson,C.C.,Low,J.N.,Tollin,P. and Wilson,H.R. Acta Crystallogr. 1984,C40,1712.

(9) Sundaralingam,M. Ann.N.Y..Acad.Sci.1975,225,3.

(10) Low,J.N. and Wilson,C.C. Acta Crystallogr.1984, C40,1030.

(11)Wilson,C.C.,Low,J.N., and Young,D.W. Acta Crystallogr. 1983,C39, 1103.

(12)Altona,C.,Geise,H.J.,Romers,C. Tetrahedron 1968,24, 13.

(13)Altona,C.and Sundaralingam,M. J.Am.Chem.Soc. 1972,94,8205.

(14)Sundaralingam,M. J.Am.Chem.Soc.1965,87.599.