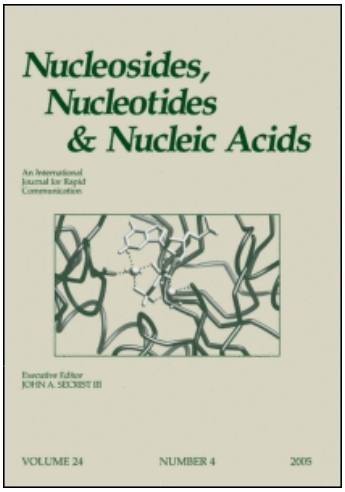

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Crystal and Molecular Structures of the Antiviral Acyclonucleoside 9-[4-Hydroxy-3-(hydroxymethyl)butyl]guanine (BRL 39123, Penciclovir) and its Prodrug 9-[4-Acetoxy-3-(acetoxymethyl)butyl]-2-aminopurine (BRL 42810, Famciclovir)

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CRYSTAL AND MOLECULAR STRUCTURES OF THE ANTIVIRAL ACYCLONUCLEOSIDE 9-[4-HYDROXY-3-(HYDROXYMETHYL)BUTYL]GUANINE (BRL 39123, PENCICLOVIR) AND ITS PRODRUG 9-[4-ACETOXY-3-(ACETOXYMETHYL)BUTYL]-2-AMINOPURINE (BRL 42810, FAMCICLOVIR)

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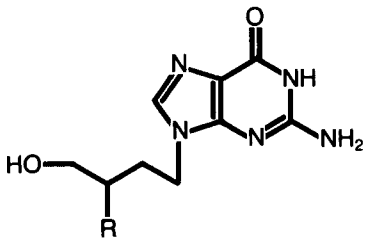
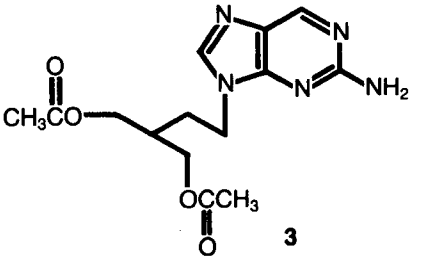
ABSTRACT. The crystal and molecular structures of two closely related antiviral purine derivatives are reported. In 9-[4-hydroxy-3-(hydroxymethyl)butyl]guanine **(2)** the plane of the acyclic N9 substituent is orthogonal to the purine ring. In crystals of **2** there is an extensive network of intermolecular hydrogen bonds. In 9-[4-acetoxy-3-(acetoxymethyl)butyl]-2-aminopurine **(3)** characteristic changes in the geometry of the pyrimidine ring in comparison with **2** are observed. In crystals of the 2-aminopurine derivative **3** there is an absence of major hydrogen bonding interactions and there are π-π interactions between parallel overlapping pyrimidine moieties.

We have reported previously the synthesis [1,2] of the acyclonucleoside 9-[4-hydroxy-3-(hydroxymethyl)butyl]guanine (2, BRL 39123, penciclovir) and its potent and selective activity against viruses of the herpes family, both in cell culture [2,3] and in animal infection models[4].



1 R = H
2 R = CH_2OH



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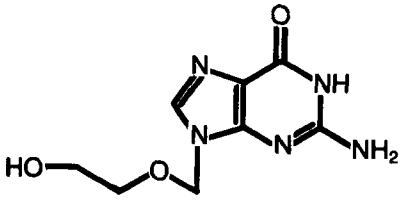

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The mechanism of action of 2, like that of acyclovir (4), involves selective phosphorylation by a herpesvirus-specified thymidine kinase and inhibition of the viral DNA polymerase by its triphosphate[5,6]. High concentrations of the triphosphate of 2 are, however, formed more rapidly in virus-infected cells than is the case with acyclovir triphosphate and, once formed, the triphosphate of 2 has a longer half-life[6,7]. Consequently, 2 has more persistent antiviral properties in cell culture[3] and in some animal models has been shown to be efficacious using less frequent dosing schedules than are required for demonstration of activity with acyclovir[4]. Intravenous and topical formulations of 2 are being progressed to clinical trials. Like acyclovir and other 9-substituted guanines the gastrointestinal absorption of 2 is, however, rather poor. The 6-deoxy congener of 2 and a series of its ester and other derivatives[8,9] were therefore synthesized for evaluation as orally active prodrugs of the antiviral acyclonucleoside. Many of these compounds are well absorbed after oral administration to rodents and are readily converted by esterases and xanthine oxidase to 2 in vivo. From results obtained in these studies and in infected animals, 9-[4-acetoxy-3-(acetoxymethyl)butyl]-2-aminopurine (3, BRL 42810, famciclovir) was selected for progression to clinical studies evaluating its potential as an orally active anti-herpesvirus agent. In this publication the crystal and molecular structures of 2 and 3 are described.

EXPERIMENTAL

The purine derivatives 2 and 3 were synthesized via the common intermediate 9-[4-acetoxy-3-(acetoxymethyl)butyl]-2-amino-6-

chloropurine, obtained by alkylation of 2-amino-6-chloropurine with 4-acetoxy-3-(acetoxymethyl)-1-bromobutane[10]. Subsequent hydrolysis gave the guanine derivative **2**, which was dissolved in aqueous ammonia and the ammonia allowed to evaporate at room temperature to afford crystals of its monohydrate, m.p. 277°C[11]: $C_{10}H_{15}N_5O_3.H_2O$, M = 271.3, orthorhombic, a = 8.204(1), b = 11.016(1), c = 13.888(2)Å, V = 1255Å^3, space group $Pn2_1a$, Z = 4, Dc = 1.44gcm^{-3}, Cu radiation, λ = 1.54178Å, μ(Cu-Kα) = 9cm^{-1}, $F(000)$ = 576.

The 2-aminopurine derivative **3** was obtained by hydrogenation of the above mentioned 9-alkylated 2-amino-6-chloropurine[8,12] and was recrystallised from water to provide crystals of its monohydrate, m.p. 87-95°C: $C_{14}H_{19}N_5O_4.H_2O$, M = 339.4, triclinic, a = 9.579(3), b = 10.102(4), c = 17.562(5)Å, α = 84.19(3), β = 75.76(3), γ = 85.31(3)°, V = 1636Å^3, space group $P\bar{1}$, Z = 4 (2 crystallographically independent molecules), Dc = 1.38gcm^{-3}, Cu radiation, λ = 1.54178A, μ(Cu-Kα) = 9cm^{-1}, $F(000)$ = 720. Data for a crystal of dimensions 0.12 x 0.22 x 0.22 mm for **2**, and of dimensions 0.20 x 0.27 x 0.40 mm for **3**, were measured on a Nicolet R3m diffractometer with Cu-Kα radiation (graphite monochromator) using ω-scans. For **2** 895 ($2\theta \leq 116°$) and for **3** 4108 ($2\theta \leq 110°$) independent reflections were measured, of which 879 and 3401, respectively, had $|F_o| > 3\sigma(|F_o|)$, and were considered to be observed. The data were corrected for Lorentz and polarisation factors; no absorption corrections were applied. The structures were solved by direct methods. The non-hydrogen atoms were refined anisotropically. For **2** a ΔF map revealed the presence of a molecule of water of crystallisation. The protons on O(13), O(14) and O(15) were located from a ΔF map and refined isotropically. The positions of the remaining hydrogen atoms were idealised, C-H = 0.96Å, assigned isotropic thermal parameters, U(H) = 1.2 U_{eq}(C), and allowed to ride on their parent carbon or nitrogen atoms. The polarity of the structure could not be determined unambiguously.

For **3** a ΔF map revealed the presence of two water molecules, one associated with each independent molecule. Both the water protons on O(40), and one on O(20), were located from a ΔF map and refined

TABLE 1. Atom coordinates ($x10^4$) and temperature factors ($Å^2 \times 10^3$) for **2** with estimated standard deviations in parentheses.

Atom	x	y	z	U_{eq}*
N(1)	-49(2)	2653	602(1)	35(1)
C(2)	-399(3)	2380(2)	1543(2)	34(1)
N(2)	-639(3)	1210(2)	1739(2)	48(1)
N(3)	-497(2)	3203(2)	2240(1)	36(1)
C(4)	-245(3)	4344(2)	1904(2)	31(1)
C(5)	132(3)	4701(2)	971(2)	34(1)
C(6)	273(3)	3809(2)	254(2)	32(1)
O(6)	601(2)	3956(2)	-612(1)	39(1)
N(7)	249(2)	5942(2)	910(1)	35(1)
C(8)	-24(3)	6323(3)	1789(2)	37(1)
N(9)	-333(2)	5399(2)	2423(1)	35(1)
C(10)	-738(3)	5530(2)	3446(2)	39(1)
C(11)	707(3)	5358(3)	4099(2)	39(1)
C(12)	187(3)	5257(3)	5154(2)	38(1)
C(13)	-366(3)	6444(3)	5599(2)	51(1)
O(13)	947(3)	7275(2)	5711(2)	77(1)
C(14)	1551(3)	4678(3)	5729(2)	42(1)
O(14)	1132(2)	4476(2)	6717(1)	48(1)
O(15)	3172(2)	3414(2)	8080(1)	51(1)

* Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor

isotropically. The positions of the remaining hydrogen atoms were idealised, C-H = 0.96Å, assigned isotropic thermal parameters, U(H) = 1.2 U_{eq}(C), and allowed to ride on their parent carbon or nitrogen atoms. The methyl groups were refined as rigid bodies. Refinement was by block-cascade full-matrix least-squares to give for **2** $\underline{R}$ = 0.030, $\underline{Rw}$ = 0.033 [$w^{-1} = \sigma^2(\underline{F}) + 0.00085\underline{F}^2$] and for **3** $\underline{R}$ = 0.096, $\underline{Rw}$ = 0.097 [$w^{-1} = \sigma^2(\underline{F}) + 0.00050\underline{F}^2$]. The maximum and residual electron densities in the final $\Delta\underline{F}$ maps were 0.15 and -0.20eÅ^{-3} for **2** and 0.46 and -0.44eÅ^{-3} for **3**, respectively. The mean and maximum shift/error in the final refinement were 0.033 and 0.334 for **2** and 0.056 and 0.176 for **3**, respectively. Computations were carried out on an Eclipse S140 computer using the SHELXTL program system[13]. The high final value of $\underline{R}$ for **3** is probably due to the tendency of the available crystals to be crazed. Relatively poor quality crystals and resulting high $\underline{R}$ values are not uncommon in nucleoside work.

TABLE 2. Bond lengths (Å) for **2** with e.s.d.'s in parentheses.

N(1)-C(2)	1.371(3)	N(1)-C(6)	1.387(3)
C(2)-N(2)	1.332(4)	C(2)-N(3)	1.329(3)
N(3)-C(4)	1.356(3)	C(4)-C(5)	1.389(3)
C(4)-N(9)	1.370(3)	C(5)-C(6)	1.404(3)
C(5)-N(7)	1.373(3)	C(6)-O(6)	1.244(3)
N(7)-C(8)	1.310(3)	C(8)-N(9)	1.369(3)
N(9)-C(10)	1.466(3)	C(10)-C(11)	1.505(3)
C(11)-C(12)	1.529(3)	C(12)-C(13)	1.515(4)
C(12)-C(14)	1.516(3)	C(13)-O(13)	1.422(4)
C(14)-O(14)	1.431(3)		

TABLE 3. Bond angles (°) for **2** with e.s.d.'s in parentheses.

C(2)-N(1)-C(6)	125.0(2)	N(1)-C(2)-N(2)	116.0(2)
N(1)-C(2)-N(3)	123.8(2)	N(2)-C(2)-N(3)	120.1(2)
C(2)-N(3)-C(4)	111.9(2)	N(3)-C(4)-C(5)	128.1(2)
N(3)-C(4)-N(9)	126.7(2)	C(5)-C(4)-N(9)	105.1(2)
C(4)-C(5)-C(6)	118.8(2)	C(4)-C(5)-N(7)	110.9(2)
C(6)-C(5)-N(7)	130.3(2)	N(1)-C(6)-C(5)	112.3(2)
N(1)-C(6)-O(6)	119.9(2)	C(5)-C(6)-O(6)	127.8(2)
C(5)-N(7)-C(8)	104.4(2)	N(7)-C(8)-N(9)	113.2(2)
C(4)-N(9)-C(8)	106.5(2)	C(4)-N(9)-C(10)	127.2(2)
C(8)-N(9)-C(10)	126.3(2)	N(9)-C(10)-C(11)	113.2(2)
C(10)-C(11)-C(12)	111.5(2)	C(11)-C(12)-C(13)	114.3(2)
C(11)-C(12)-C(14)	109.2(2)	C(13)-C(12)-C(14)	111.7(2)
C(12)-C(13)-O(13)	111.9(2)	C(12)-C(14)-O(14)	113.2(2)

RESULTS AND DISCUSSION

Fractional coordinates of the non-hydrogen atoms for **2** are given in TABLE 1[14]. TABLES 2 and 3 list the bond lengths and valence angles. FIG. 1 shows a perspective view of the molecule, and the included water molecule. The atoms of the sidechain N(9) ... O(14) are planar to within 0.26Å and this plane is almost perpendicular to the mean plane of the purine. The C(4)N(9)C(10)C(11) and C(8)N(9)C(10)C(11) torsion angles are 84.6(3) and - 97.9(3)° respectively. The purine unit exhibits characteristic departures from planarity, with the maximum deviation of 0.029Å for N(1). N(2) lies 0.049Å from this plane. This non-planarity is due to a small dihedral angle (2.5°) between the pyrimidine and imidazole rings, the imidazole ring being planar to

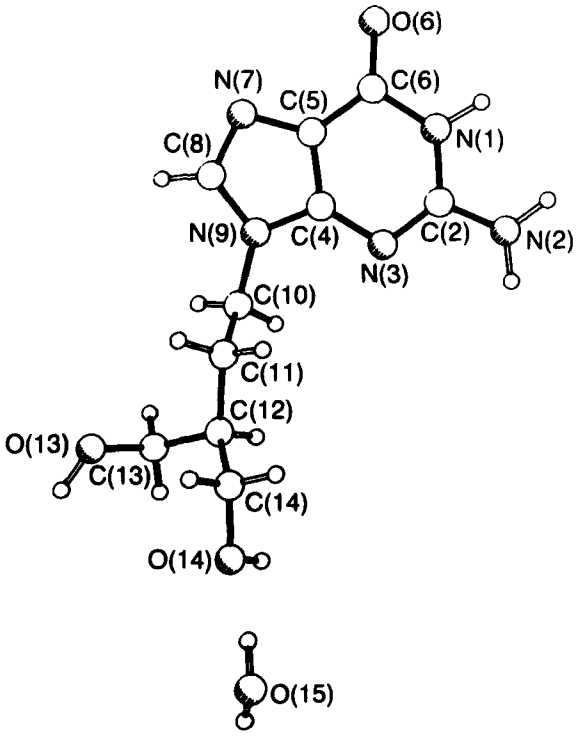

FIG. 1 : The molecular structure of 2.H_2O giving atom numbering.

within 0.005Å. The bond lengths and angles within the purine nucleus are identical within statistical significance to those reported for the closely related 9-(4-hydroxybutyl)guanine (1) [15] and in accord with the published "standard values"[16]. There are noticeable but small departures from the fully extended conformation in the N(9) to O(14) part of the side chain, with a maximum deviation from anti-geometry of 9° about the C(11) - C(12) bond. This is almost certainly due to the branching CH_2OH group on C(12) (the C(10)C(11)C(12)C(13) torsion angle being 72.9(3)°) and the associated hydrogen bonding interactions of the O(13) hydroxyl as well as that associated with O(14). In 9-(4-hydroxybutyl)guanine this side chain does not deviate by more than 2° from perfect all anti-geometry.

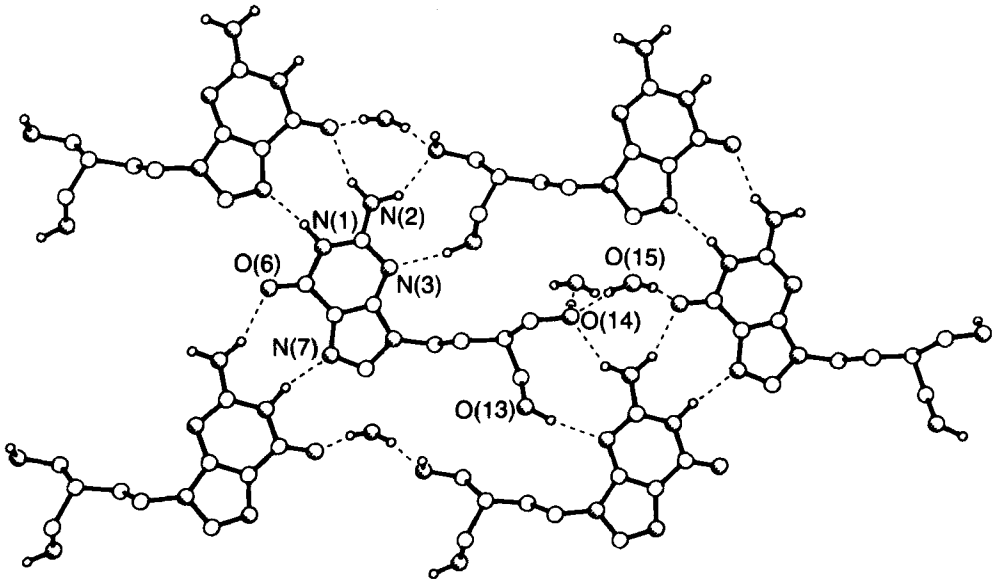

FIG. 2 : Part of one of the continous sheets of hydrogen bonded molecules in the structure of **2**.H_2O.

TABLE 4. Hydrogen bonding geometries X-H....Y for 2.

X	H	Y	X..Y (Å)	H..Y (Å)	$\hat{H}$ (°)
N(1)	H(1)	N(7)	2.83	1.88	167
N(2)	H(2a)	O(6)	2.93	2.02	158
N(2)	H(2b)	O(14)	2.90	2.07	144
O(13)	H(13)	N(3)	3.05	2.09	166
O(14)	H(14)	O(15)	2.71	1.73	175
O(15)	H(15a)	O(14)	2.78	1.81	172
O(15)	H(15b)	O(6)	2.85	1.89	166

TABLE 5. Atom coordinates ($x10^4$) and temperature factors ($Å^2 \times 10^3$) for 3 with estimated standard deviations in parentheses.

Atom	x	y	z	U_{eq}*
N(1)	614(5)	-6871(4)	4532(2)	44(2)
C(2)	981(5)	-6131(5)	3833(3)	38(2)
N(3)	1837(4)	-5090(4)	3664(2)	39(2)
C(4)	2298(5)	-4820(5)	4276(3)	35(2)
C(5)	2015(6)	-5489(5)	5022(3)	42(2)
C(6)	1100(6)	-6549(5)	5129(3)	44(2)
N(7)	2690(5)	-4951(5)	5523(3)	53(2)
C(8)	3375(6)	-3970(6)	5067(4)	53(2)
N(9)	3185(5)	-3842(4)	4319(3)	43(2)
C(10)	3833(6)	-2861(5)	3670(3)	47(2)
C(11)	2732(6)	-1829(5)	3450(3)	42(2)
C(12)	1944(6)	-921(5)	4085(3)	39(2)
C(13)	838(6)	29(5)	3796(3)	48(2)
O(13)	-287(4)	-738(3)	3662(2)	47(1)
C(14)	-1443(6)	-32(6)	3508(3)	49(2)
O(14)	-1573(5)	1154(4)	3473(3)	76(2)
C(15)	-2558(6)	-936(6)	3426(4)	57(2)
C(16)	2907(6)	-129(5)	4406(3)	42(2)
O(16)	3686(4)	762(3)	3761(2)	45(1)
C(17)	4405(5)	1661(5)	3985(3)	42(2)
O(17)	4484(4)	1744(4)	4642(2)	56(2)
C(18)	5123(7)	2589(6)	3299(4)	58(2)
N(19)	469(5)	-6504(5)	3240(3)	54(2)
O(20)	2333(6)	-5592(5)	7197(3)	87(2)
N(21)	182(5)	3077(4)	498(3)	47(2)
C(22)	-179(6)	3631(5)	1205(3)	44(2)
N(23)	435(5)	4607(4)	1426(3)	42(2)
C(24)	1564(6)	5056(5)	860(3)	39(2)
C(25)	2037(6)	4587(5)	113(3)	42(2)
C(26)	1304(6)	3578(5)	-36(3)	49(2)
N(27)	3227(5)	5274(5)	-316(3)	53(2)
C(28)	3412(6)	6093(6)	161(4)	56(2)
N(29)	2438(5)	6031(4)	893(3)	44(2)
C(30)	2394(6)	6823(5)	1541(3)	46(2)
C(31)	1111(6)	7849(5)	1667(3)	41(2)
C(32)	997(5)	8830(5)	964(3)	38(2)
C(33)	-347(5)	9752(5)	1165(3)	43(2)
O(33)	-1592(4)	8961(4)	1293(2)	47(1)
C(34)	-2889(6)	9618(6)	1466(3)	43(2)
O(34)	-3030(4)	10798(4)	1516(3)	70(2)
C(35)	-4071(6)	8719(7)	1565(4)	62(3)
C(36)	2295(5)	9660(5)	639(3)	42(2)
O(36)	2478(4)	10430(4)	1244(2)	45(1)
C(37)	3429(6)	11401(5)	1010(3)	46(2)
O(37)	4107(4)	11570(4)	335(3)	64(2)
C(38)	3512(7)	12170(6)	1659(4)	60(3)
N(39)	-1335(5)	3101(5)	1733(3)	60(2)
O(40)	4579(6)	4664(6)	-1934(3)	88(2)

* Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor

TABLE 6. Bond lengths (Å) for **3** with e.s.d.'s in parentheses.

N(1)-C(2)	1.355(6)	N(1)-C(6)	1.324(8)
C(2)-N(3)	1.350(7)	C(2)-N(19)	1.352(8)
N(3)-C(4)	1.319(7)	C(4)-C(5)	1.386(7)
C(4)-N(9)	1.373(7)	C(5)-C(6)	1.408(8)
C(5)-N(7)	1.386(8)	N(7)-C(8)	1.320(7)
C(8)-N(9)	1.363(8)	N(9)-C(10)	1.480(6)
C(10)-C(11)	1.513(8)	C(11)-C(12)	1.528(7)
C(12)-C(13)	1.517(8)	C(12)-C(16)	1.509(8)
C(13)-O(13)	1.454(7)	O(13)-C(14)	1.337(7)
C(14)-O(14)	1.191(7)	C(14)-C(15)	1.502(9)
C(16)-O(16)	1.462(6)	O(16)-C(17)	1.328(7)
C(17)-O(17)	1.186(7)	C(17)-C(18)	1.507(7)
N(21)-C(22)	1.368(7)	N(21)-C(26)	1.338(7)
C(22)-N(23)	1.324(8)	C(22)-N(39)	1.365(7)
N(23)-C(24)	1.350(6)	C(24)-C(25)	1.397(7)
C(24)-N(29)	1.358(7)	C(25)-C(26)	1.365(8)
C(25)-N(27)	1.396(7)	N(27)-C(28)	1.285(9)
C(28)-N(29)	1.389(7)	N(29)-C(30)	1.447(8)
C(30)-C(31)	1.529(7)	C(31)-C(32)	1.522(7)
C(32)-C(33)	1.515(7)	C(32)-C(36)	1.516(7)
C(33)-O(33)	1.449(6)	O(33)-C(34)	1.340(6)
C(34)-O(34)	1.198(7)	C(34)-C(35)	1.476(9)
C(36)-O(36)	1.431(7)	O(36)-C(37)	1.357(7)
C(37)-O(37)	1.205(7)	C(37)-C(38)	1.464(9)

There is an extensive network of hydrogen bonding between symmetry related and lattice translated molecules (FIG. 2). All potential donor and accceptor sites within the molecule, also the water molecule, are involved in inter-molecular hydrogen bonding interactions (TABLE 4). This results in continuous parallel hydrogen-bonded sheets of molecules, the water molecule serving to cross-link between adjacent sheets. These intermolecular hydrogen bonds, with the exception of those to the water molecule, involve the same pattern of donor acceptor atoms as observed for **1**. However, in contrast with 9-(4-hydroxybutyl)guanine, there is an absence of any base pair stacking.

Fractional atomic coordinates for **3** are given in TABLE 5. TABLES 6 and 7 list the bond lengths and valence angles. FIG. 3 shows a perspective view of one of the pair of crystallographically independent molecules in the crystal. As can been seen from the least-squares fit of the purine rings of the two molecules (FIG. 4), both have virtually

TABLE 7. Bond angles (°) for **3** with e.s.d.'s in parentheses.

C(2)-N(1)-C(6)	118.4(5)	N(1)-C(2)-N(3)	126.7(5)
N(1)-C(2)-N(19)	116.2(5)	N(3)-C(2)-N(19)	117.0(4)
C(2)-N(3)-C(4)	112.3(4)	N(3)-C(4)-C(5)	127.3(5)
N(3)-C(4)-N(9)	128.3(4)	C(5)-C(4)-N(9)	104.4(5)
C(4)-C(5)-C(6)	115.2(5)	C(4)-C(5)-N(7)	112.1(5)
C(6)-C(5)-N(7)	132.7(5)	N(1)-C(6)-C(5)	120.1(5)
C(5)-N(7)-C(8)	102.6(5)	N(7)-C(8)-N(9)	114.1(6)
C(4)-N(9)-C(8)	106.8(4)	C(4)-N(9)-C(10)	126.4(5)
C(8)-N(9)-C(10)	126.8(5)	N(9)-C(10)-C(11)	112.7(4)
C(10)-C(11)-C(12)	116.8(5)	C(11)-C(12)-C(13)	111.2(5)
C(11)-C(12)-C(16)	115.1(4)	C(13)-C(12)-C(16)	108.9(4)
C(12)-C(13)-O(13)	108.9(4)	C(13)-O(13)-C(14)	116.0(4)
O(13)-C(14)-O(14)	123.6(6)	O(13)-C(14)-C(15)	110.9(5)
O(14)-C(14)-C(15)	125.5(6)	C(12)-C(16)-O(16)	108.3(4)
C(16)-O(16)-C(17)	114.5(4)	O(16)-C(17)-O(17)	125.0(5)
O(16)-C(17)-C(18)	111.9(5)	O(17)-C(17)-C(18)	123.1(5)
C(22)-N(21)-C(26)	115.9(5)	N(21)-C(22)-N(23)	128.3(5)
N(21)-C(22)-N(39)	114.2(5)	N(23)-C(22)-N(39)	117.5(5)
C(22)-N(23)-C(24)	112.5(4)	N(23)-C(24)-C(25)	125.0(5)
N(23)-C(24)-N(29)	128.0(5)	C(25)-C(24)-N(29)	107.0(4)
C(24)-C(25)-C(26)	116.2(5)	C(24)-C(25)-N(27)	109.5(5)
C(26)-C(25)-N(27)	134.3(5)	N(21)-C(26)-C(25)	122.0(5)
C(25)-N(27)-C(28)	103.9(4)	N(27)-C(28)-N(29)	115.2(5)
C(24)-N(29)-C(28)	104.4(5)	C(24)-N(29)-C(30)	128.4(4)
C(28)-N(29)-C(30)	127.2(5)	N(29)-C(30)-C(31)	112.3(5)
C(30)-C(31)-C(32)	116.6(4)	C(31)-C(32)-C(33)	110.8(4)
C(31)-C(32)-C(36)	114.8(5)	C(33)-C(32)-C(36)	109.1(4)
C(32)-C(33)-O(33)	108.1(4)	C(33)-O(33)-C(34)	116.6(4)
O(33)-C(34)-O(34)	122.5(5)	O(33)-C(34)-C(35)	111.8(5)
O(34)-C(34)-C(35)	125.7(5)	C(32)-C(36)-O(36)	108.8(4)
C(36)-O(36)-C(37)	116.0(4)	O(36)-C(37)-O(37)	121.5(6)
O(36)-C(37)-C(38)	112.4(5)	O(37)-C(37)-C(38)	126.0(5)

identical conformations, the only differences being slight changes in the orientation of the side chains beyond C(11) due to a 6° difference in the torsion angles about the C(10) - C(11) bond, 62.8(6)° as compared with 56.9(6)°. Within the purine nucleus the maximum deviation from the least-squares fit of the two molecules is 0.027Å. As in **2** the plane of the N(9)...C(11) portion of the side chain is approximately orthogonal to the purine moiety. The C(4)N(9)C(10)C(11) and C(8)N(9)C(10)C(11) torsion angles for the two molecules are 70.5(6) and 111.0(6)°, and 72.4(6) and 108.6(6)°, respectively. However, whereas there is an anti-geometry about the C(10) - C(11) bond in **2**, here the geometry is gauche

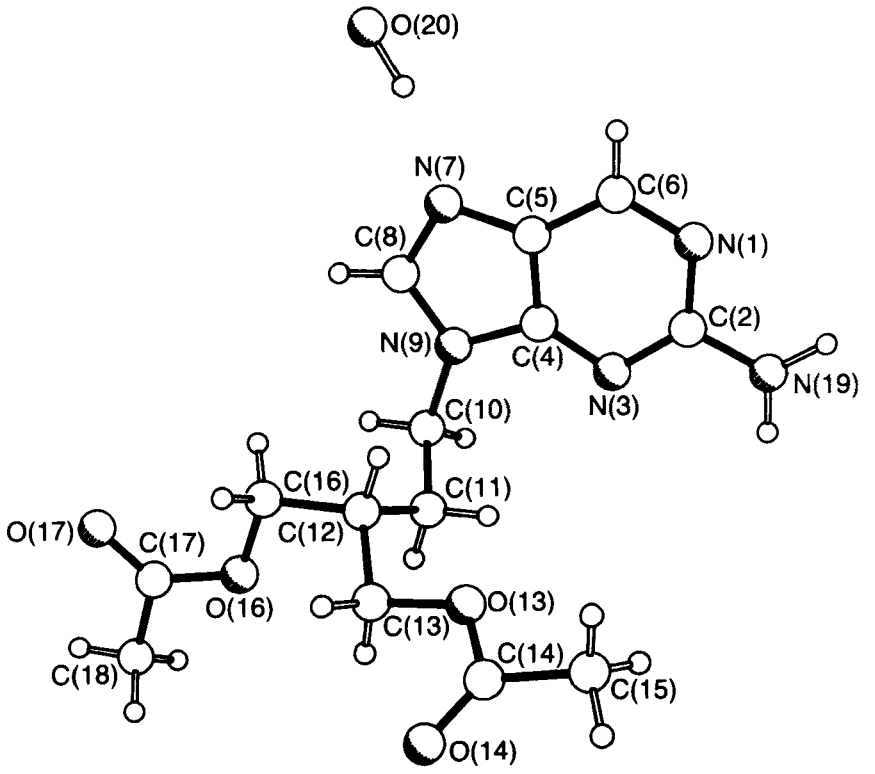

FIG. 3 : Perspective view of one of the pair of crystallographically independent molecules of **3**.H_2O giving atom numbering. (The numbers of the atoms in the second molecule are as in the first + 20).

(vide infra). A gauche geometry was also observed for this portion of the side chain in two of the three conformers in the crystal structure of acyclovir[17].

The purine units in both molecules are noticeably closer to planar (maximum deviations from planarity of 0.013Å in both molecules) than in **2**. This is due to an absence of any significant folding of the pyrimidine/imidazole rings in **3** . The bond lengths (TABLE 6) in **3** emphasise the presence of a double bond between N(1) and C(6) and there is the expected shortening of the N(7)-C(8) bond as compared with C(8) -

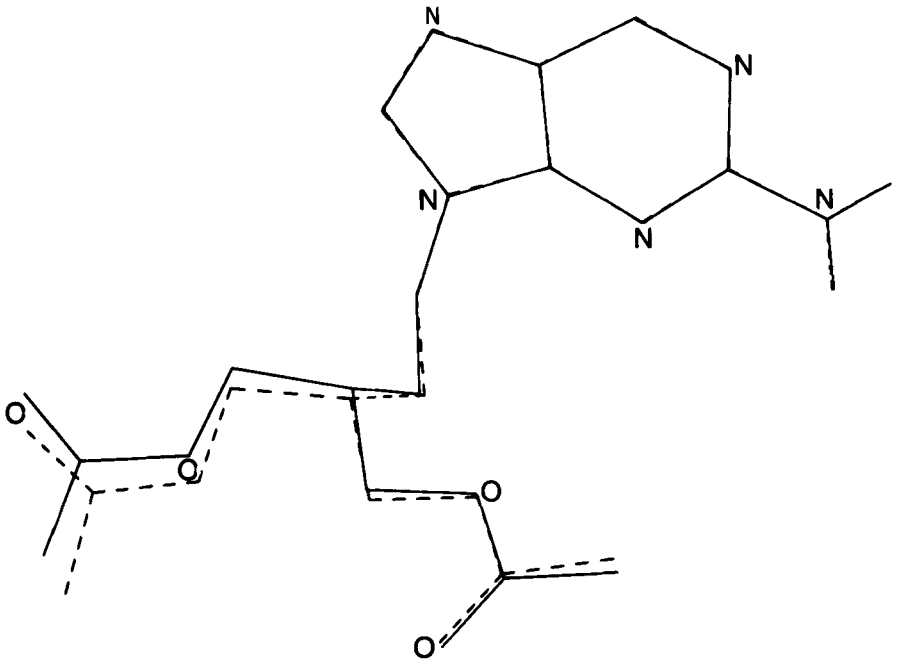

FIG. 4 : Least-squares fit of the purine components of the two independent molecules of **3**.

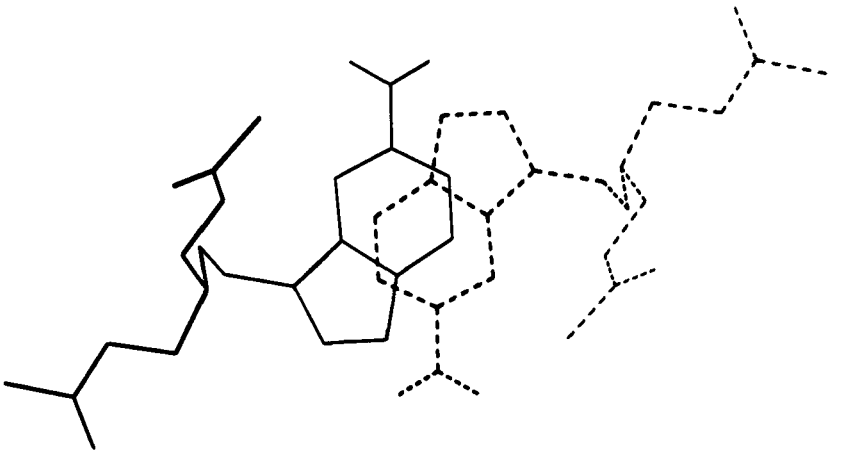

FIG. 5 : Parallel overlap of symmetry related pairs of molecules of **3**.

N(9). The presence of the N(1) - C(6) double bond and the absence of a C(6) carbonyl substituent results in appreciable changes in the angles within the pyrimidine ring. As expected, these differences occur at N(1) and C(6) with an 8° reduction in the angle at N(1) and a corresponding 9° increase at C(6) as compared with the values in 2. The remaining angles within the ring are essentially unchanged. Identical angles are observed in the structure of a 5-fluoro-1-methyluracil: 2-amino-9-ethylpurine complex.[18]

Because of the absence of strong hydrogen bonding donors in **3** there is not the extensive network of intermolecular interactions observed in either **1** [15] or **2** . Weak hydrogen bonds in each molecule (3.12 and 3.05Å) exist linking one of the amine protons and the ester carbonyl oxygen atoms, O(14) of 'like' molecules; i.e. bonds between identical conformers only. The included water molecules each form a single hydrogen bond to the imidazole nitrogen atom, N(7).

As in **2** there is no base pair stacking, though centrosymmetrically related pairs of molecules do exhibit π-π overlap (FIG. 5), possibly reflecting enhanced aromaticity of the purine in **3**. The interplanar separation between the purine planes is 3.30Å.

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