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N-[1-Phenyl-2(*R*)-propyl]-2-chloro-adenosine. An Activating Agent of the Adenosine A2 Receptor

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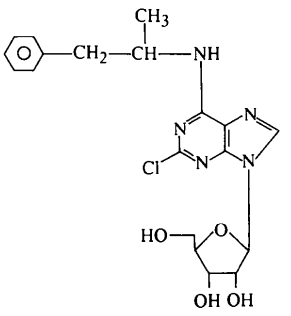
Abstract

In the title compound, 2-chloro-*N*-[1-phenyl-2(*R*)-propyl]-9-β-D-ribofuranosyl-9*H*-purin-6-amine, $C_{19}H_{22}ClN_5O_4$, the sugar moiety is *syn* relative to the adenosine base. The sugar pucker is C2′-*endo* and the C4′—C5′ conformation is *+sc*. The structure is stabilized in the crystal by N—H···O and O—H···O intermolecular hydrogen bonds.

Comment

Compounds containing 2-chloro and *N*-substituted adenosines are interesting because of their biological activity at A1 and A2 adenosine receptors (Daly, Padgett, Thompson, Kusachi, Bugni & Olsson, 1986). A1 receptors are coupled to the inhibition of adenylate cyclase through G_i protein and have also been shown to couple to other second-messenger systems, while A2 receptors are those at which adenosine agonists activate adenylate cyclase (Jacobson, van Galen & William, 1992; Stiles, 1992). The title compound, (I), synthesized by Thompson, Secunda, Daly & Olsson (1991), acts as an agonist at the adenosine A2 receptor.



(I)

The bond distances and angles in the title structure are similar to those in adenosine (Lai & Marsh, 1972). The C1′—O4′ bond is significantly shorter than the C4′—O4′ bond due to the anomeric effect and is in good agreement with the observations of Bugg, Thomas, Sundaralingam & Rao (1971). The dihedral angle between the phenyl and purine rings is 122.1 (8)°. The phenyl ring points away from the imidazole group.

The relative orientation of the base with respect to the sugar ring is given by the N-glycosidic torsion angle, χ (C4—N9—C1′—O4′), which is 49.5 (4)° (*syn*). The sugar pucker, similar to that found in adenosine, is ^2E (C2′-*endo*), with P = 161 (1)° and φ_m = 35 (1)°. The C4′—C5′ conformation, with γ = 52.8 (4)°, is *+sc* (*gauche–gauche*). The conformational parameters used follow the guidelines of the IUPAC-IUB Joint Commission on Biochemical Nomenclature (1983).

The intramolecular hydrogen bond O5′—H···N3 stabilizes the *+sc* conformation, with the base in a *syn* orientation. There are three intermolecular hydrogen bonds present in the structure: N6—H···O2′ ($-x+\frac{1}{2}$, $-y+1$, $z-\frac{1}{2}$) 3.074 (4), O2′—H···O5′ ($x-\frac{1}{2}$, $-y+\frac{1}{2}$, $-z+1$) 2.702 (4) and O3′—H···N7 ($-x+\frac{1}{2}$, $-y+1$, $z+\frac{1}{2}$) 2.856 (4) Å.

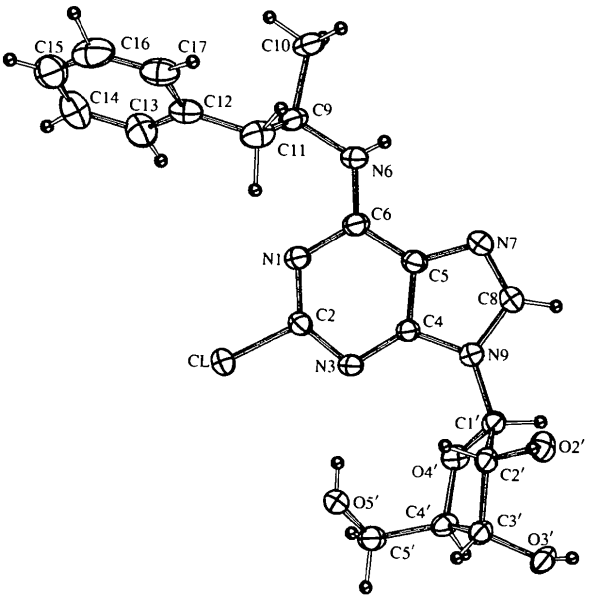


Fig. 1. *ORTEP* (Johnson, 1965) view of the title molecule showing the labelling of the non-H atoms. Displacement ellipsoids are shown at the 50% probability level and H atoms are drawn as small circles of arbitrary radii.

Experimental

Crystals of the title compound were obtained by slow evaporation of an aqueous methanol solution.

Crystal data

$C_{19}H_{22}ClN_5O_4$	Mo $K\alpha$ radiation
M_r = 419.87	λ = 0.71069 Å
Orthorhombic	Cell parameters from 25 reflections
$P2_12_12_1$	θ = 11–14°
a = 11.346 (2) Å	μ = 0.223 mm^{-1}
b = 12.305 (1) Å	T = 295 K
c = 14.327 (1) Å	Plate
V = 2000.2 (4) Å^3	0.43 × 0.38 × 0.24 mm
Z = 4	Transparent
D_x = 1.39 Mg m^{-3}	

Data collection

Enraf–Nonius CAD-4 diffractometer	θ_{max} = 28°
$\omega/2\theta$ scans	$h = 0 \rightarrow 15$
Absorption correction: none	$k = 0 \rightarrow 16$
2712 measured reflections	$l = 0 \rightarrow 18$
2712 independent reflections	3 standard reflections
2073 observed reflections [$F > 6\sigma(F)$]	frequency: 120 min
	intensity decay: <0.1%

Refinement

Refinement on F	$w = 1/[\sigma^2(F) + 0.011F^2]$
R = 0.0366	$(\Delta/\sigma)_{max}$ = 0.0007
wR = 0.0452	$\Delta\rho_{max}$ = 0.18 e Å^{-3}
S = 0.57	$\Delta\rho_{min}$ = −0.22 e Å^{-3}
2073 reflections	Atomic scattering factors from *SHELX*76 (Sheldrick, 1976)
350 parameters	
H atoms refined isotropically	

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2)

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	U_{eq}
Cl	0.7791 (1)	0.3367 (1)	0.2705 (1)	0.0532 (3)
N1	0.6138 (2)	0.4323 (3)	0.1784 (2)	0.044 (1)
C2	0.6460 (3)	0.4064 (3)	0.2641 (2)	0.039 (1)
N3	0.5949 (2)	0.4240 (2)	0.3456 (2)	0.038 (1)
C4	0.4968 (3)	0.4850 (3)	0.3338 (2)	0.035 (1)
C5	0.4522 (3)	0.5215 (3)	0.2498 (2)	0.041 (1)
C6	0.5114 (3)	0.4883 (3)	0.1683 (2)	0.043 (1)
N7	0.3523 (3)	0.5835 (3)	0.2636 (2)	0.051 (1)
C8	0.3394 (3)	0.5843 (3)	0.3538 (2)	0.048 (1)
N9	0.4221 (2)	0.5255 (2)	0.4012 (2)	0.039 (1)
C1′	0.4225 (3)	0.5043 (2)	0.5015 (2)	0.036 (1)
C2′	0.3864 (2)	0.3891 (3)	0.5277 (2)	0.034 (1)
C3′	0.4486 (3)	0.3753 (3)	0.6218 (2)	0.037 (1)
C4′	0.5610 (3)	0.4425 (3)	0.6092 (2)	0.041 (1)
O4′	0.5377 (2)	0.5193 (2)	0.5350 (2)	0.041 (1)
C5′	0.6715 (3)	0.3803 (4)	0.5857 (3)	0.053 (1)
O5′	0.6578 (3)	0.3104 (2)	0.5071 (2)	0.056 (1)
O3′	0.3840 (2)	0.4232 (2)	0.6951 (2)	0.050 (1)
O2′	0.2625 (2)	0.3816 (2)	0.5318 (2)	0.047 (1)
N6	0.4722 (3)	0.5082 (3)	0.0821 (2)	0.053 (1)
C9	0.5331 (3)	0.4724 (3)	−0.0021 (2)	0.046 (1)
C10	0.4821 (4)	0.5327 (4)	−0.0855 (3)	0.061 (1)
C11	0.5258 (4)	0.3493 (4)	−0.0138 (3)	0.059 (1)
C12	0.6125 (4)	0.3041 (3)	−0.0839 (3)	0.051 (1)
C13	0.7330 (4)	0.3265 (4)	−0.0760 (3)	0.066 (1)
C14	0.8129 (5)	0.2833 (5)	−0.1397 (5)	0.082 (2)
C15	0.7733 (8)	0.2142 (5)	−0.2081 (4)	0.090 (3)
C16	0.6563 (8)	0.1900 (4)	−0.2151 (3)	0.087 (2)
C17	0.5773 (5)	0.2348 (3)	−0.1545 (3)	0.066 (2)

Table 2. *Selected geometric parameters* (Å, °)

Cl—C2	1.739 (4)	C2′—O2′	1.410 (3)
C3′—O3′	1.410 (4)	C4′—O4′	1.447 (4)
C5′—O5′	1.426 (5)	N6—C9	1.458 (4)
C6—N6	1.335 (4)	N9—C1′	1.461 (4)
C1′—O4′	1.405 (4)		
C1′—O4′—C4′	109.6 (2)	C6—N6—C9	123.5 (3)
N1—C6—C5	117.8 (3)	C1′—C2′—O2′	109.8 (3)
C4—N9—C1′—O4′	49.5 (4)	C3′—C4′—O4′—C1′	−0.3 (3)
C2′—C1′—O4′—C4′	−21.9 (3)	C3′—C4′—C5′—O5′	52.8 (4)
O4′—C1′—C2′—C3′	34.7 (3)	C6—N6—C9—C10	−165.7 (3)
C1′—C2′—C3′—C4′	−33.3 (3)	N6—C9—C11—C12	−164.7 (3)
C2′—C3′—C4′—O4′	21.9 (3)		

The structure was solved using *SHELXS*86 (Sheldrick, 1985) and refined with *SHELX*76 (Sheldrick, 1976). The known handedness was chosen for the absolute structure. Anomalous-dispersion effects were included in F_c (Ibers & Hamilton, 1964). *PARST* (Nardelli, 1983) was used to calculate the molecular parameters. The figure was drawn using *ORTEP* (Johnson, 1965). Refinement was by full-matrix least squares and all calculations were performed on an ND570 computer.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: VJ1015). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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