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2,6-Diamino-9-(carboxymethyl)purine Ethyl Ester†

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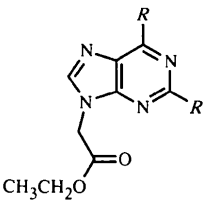
Abstract

In the crystal structure of the title compound (as its hemihydrate, $C_9H_{12}N_6O_2.0.5H_2O$), a potential intermediate for the synthesis of peptidic nucleic acids containing 2,6-diaminopurine, the asymmetric unit contains two molecules, one ordered and the other with twofold positional disorder about a pivot point near the 6-amino group, together with one water molecule. The side chain emerges at N9 with C8—N9—C10—C11 torsion angles of 93.0 (2) and 50.8 (6)/−97.0 (6)°, respectively.

Comment

Peptidic nucleic acids (PNA's) are DNA mimetics in which *N*-(2-aminoethyl)glycine units replace the conventional sugar–phosphate backbone (Hyrup & Nielsen, 1996; Egholm, Buchardt, Coull, Nielsen & Berg, 1992) and in which the DNA bases adenine (A), thymine (T), cytosine (C), guanine (G) (Egholm, Christensen *et al.*, 1993) and pseudoisocytosine (Egholm *et al.*, 1995) are attached to the peptidic backbone through methylene carbonyl linkers. PNA's bind with high affinity and specificity (Egholm, Buchardt *et al.*, 1993) to DNA targets and thus offer the possibility of inhibiting gene expression in a controlled manner (Thuong & Hélène, 1993). Our interest in modulating the affinity of PNA's for target nucleic acid sequences has prompted an investigation of PNA's containing 2,6-diaminopurine (D), which can make a three hydrogen-bond Watson–Crick base pair with T, compared with the two hydrogen-bond base pair made by A. The title compound, (1), is a potential intermediate in the synthesis of PNA's containing D.



(1) $R=NH_2$
(2) $R=Cl$
(3) $R=N_3$

We have successfully prepared (1) by two alternative routes, the first involving alkylation of 2,6-dichloropurine using ethyl bromoacetate (Chan, Schwalbe, Sood & Fraser, 1995) to give (2), followed by treatment with sodium azide at elevated temperature, resulting in substitution of both chloro groups to give (3) (Sood, Schwalbe & Fraser, 1997). Hydrogenolysis (10% Pd/C) of (3) under H_2 at room temperature for 4 d gave (1), in crystalline form, but with a very modest overall yield. The second and more direct method (Dueholm *et al.*, 1994) involved alkylation of diaminopurine using ethyl bromoacetate and sodium hydride. The reaction was regioselective, giving (1) in 79% yield with only a small amount of the corresponding N7 regioisomer. The structure determination shows that the ethyl carboxymethylene side chain is indeed attached at N9 and here we compare the crystal structure of (1) with those of other analogues.

Many geometric features of (1) (Table 1) resemble those previously found in its adenine (Flensburg & Egholm, 1994), 2,6-dichloropurine, (2) (Chan, Schwalbe, Sood & Fraser, 1995), and 2,6-diazidopurine, (3) (Sood, Schwalbe & Fraser, 1997), analogues. Two molecules of (1), along with a molecule of water, are present in the asymmetric unit: a well ordered molecule (1*A*) with an accompanying disordered molecule, either (1*B*) or (1*C*). The hydrogen-bonded 6-amino group is almost invariant in molecules (1*B*) and (1*C*) (Fig. 1). In (1*A*), atoms of the heterocycle are coplanar within 0.008 Å and the side chain emerges almost orthogonally from the heterocycle, where the torsion angle C8*A*—N9*A*—C10*A*—C11*A* is 93.0 (2)°, with the six atoms of the side chain coplanar within an r.m.s. deviation of 0.092 Å. Similarly, the side-chain atoms of (1*B*) and (1*C*) are reasonably coplanar, but with C8*B*—N9*B*—C10*B*—C11*B* and C8*C*—N9*C*—C10*C*—C11 torsion angles of 50.8 (6) and −97.0 (6)°, respectively. Compared with its adenine analogue, the N1*A*—C6*A*—C5*A* bond angle is expanded by 0.64 (15)° and the N3*A*—C2*A*—N1*A* bond angle is compressed by

† Alternative name: ethyl 2,6-diaminopurine-9-acetate.

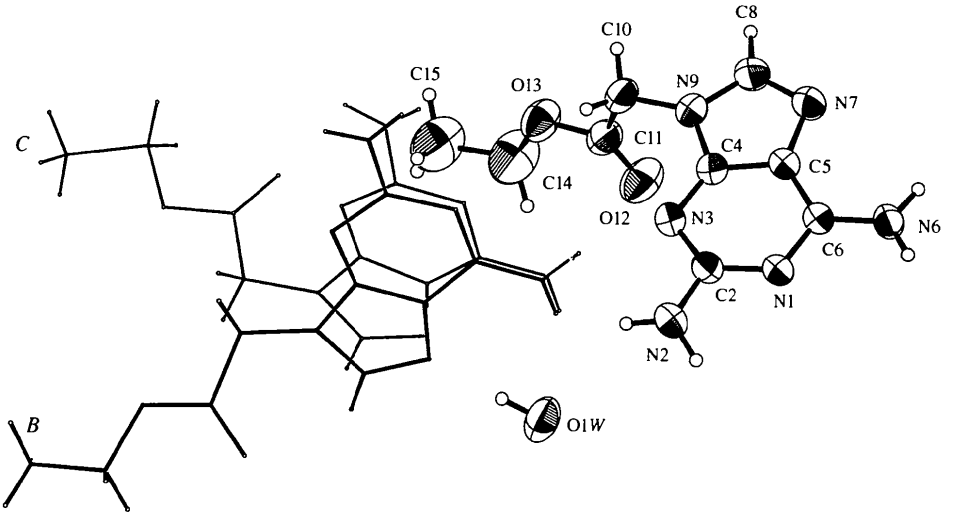


Fig. 1. An *ORTEP*II (Johnson, 1976) view of the independent molecules of the title compound. For molecule *A*, the displacement ellipsoids are shown at the 50% probability level and the atom-numbering scheme is indicated. The disordered alternative *B* and *C* sites are joined by heavier and lighter lines, respectively.

−1.65 (16)°. There are strong intermolecular hydrogen bonds between amino groups and heterocyclic N atoms, with an additional close contact to the water molecule and a weaker interaction (Table 2). The water molecule donates hydrogen bonds to N3 and N7 of molecule (1*B*/*C*).

Experimental

Two alternative methods were used to prepare crystals of the title compound. In method (i), the diazide (3) (4.04 g, 14.01 mmol) was suspended in anhydrous EtOH (50 ml) with 10% palladium on charcoal (300 mg) and hydrogenolized at room temperature under H_2 for 4 d. The product mixture was filtered through Celite and the solvent evaporated under vacuum. The title compound, (1), was isolated by flash column chromatography eluting with CH_2Cl_2–MeOH (8:1) and recrystallized from EtOAc (538 mg, 39%, m.p. 446–447 K). TLC (CH_2Cl_2–MeOH, 8:1): R_f 0.23. IR (KBr disc): ν_{max} 3388, 3306, 3168, 2981, 1747, 1603, 1589, 1429, 1348, 1259, 1024, 802, 749 cm^{-1}. ^1H NMR [250.1 MHz; $(CD_3)_2SO$]: δ 1.20 (*t*, 3H, *J* = 7.10 Hz, CH_3), 4.12 (*q*, 2H, *J* = 7.10 Hz, OCH_2), 4.84 (*s*, 2H, CH_2), 5.85 (*s*, 2H, NH_2, D_2O exchangeable), 6.73 (*s*, 2H, NH_2, D_2O exchangeable), 7.67 p.p.m. (*s*, 1H, H-8). ^{13}C NMR [62.1 MHz; $(CD_3)_2SO$]: δ 14.2 (CH_3), 43.6 (CH_2), 61.4 (OCH_2), 112.8 (C-5), 138.0 (CH-8), 156.3, 160.6, 162.2 (C-2, C-4, C-6), 168.5 p.p.m. (CO). MS (EI): *m*/*z* (%I_r) 236 (*M* + H, 50), 163 (100), 146 (30), 94 (20), 67 (22), 43 (65). Analysis calculated for $C_9H_{12}N_6O_2.0.5H_2O$: C 44.1, H 5.3, N 34.3%; elemental analysis found: C 43.9, H 5.0, N 34.0%. In method (ii), 2,6-diaminopurine (2.21 g, 14.7 mmol) was suspended in anhydrous DMF (35 ml) and NaH (0.77 g, 19.3 mmol, 60% dispersion in mineral oil) was added in portions with stirring under Ar. The reaction mixture was stirred for a further 4 h at room temperature and ethyl bromoacetate (2.22 ml, 20.0 mmol) was added over 4 h. After stirring overnight, the solvent was evaporated and the residual orange oil was shaken with water (30 ml), causing (1) to precipitate. Compound (1) was recrystallized from EtOAc (2.39 g, 79%, m.p. 446–447 K). All analytical data were identical to those given above.

Crystal data

$C_9H_{12}N_6O_2.0.5H_2O$
M_r = 245.25
Triclinic
$P\bar{1}$
a = 8.612 (2) Å
b = 11.658 (3) Å
c = 11.914 (2) Å
α = 79.72 (2)°
β = 85.97 (2)°
γ = 76.73 (2)°
V = 1145.0 (4) Å^3
Z = 4
D_x = 1.423 Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
λ = 1.54178 Å
Cell parameters from 25 reflections
θ = 22.8–29.1°
μ = 0.914 mm^{-1}
T = 293 (2) K
Hexagonal prism
0.60 × 0.35 × 0.35 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
4966 measured reflections
4126 independent reflections
3921 reflections with $I > 2\sigma(I)$

R_{int} = 0.028
θ_{max} = 68°
h = −1 → 10
k = −13 → 13
l = −14 → 14
3 standard reflections
frequency: 120 min
intensity decay: 2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.043
$wR(F^2)$ = 0.143
S = 1.096
4122 reflections
520 parameters
H atoms: see below

$\Delta\rho_{max}$ = 0.173 e Å^{-3}
$\Delta\rho_{min}$ = −0.208 e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.0054 (7)

$w = 1/[\sigma^2(F_o^2) + (0.0645P)^2 + 0.2193P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = -0.028$

Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

C2A—N2A	1.361 (2)	N9B—C10B	1.453 (4)
C6A—N6A	1.331 (2)	C2C—N2C	1.350 (11)
N9A—C10A	1.450 (2)	C6C—N6C	1.346 (11)
C2B—N2B	1.365 (12)	N9C—C10C	1.465 (4)
C6B—N6B	1.336 (11)		
N3A—C2A—N1A	127.55 (12)	N1B—C6B—C5B	119.8 (9)
N1A—C6A—C5A	118.13 (12)	N3C—C2C—N1C	128.0 (10)
N3B—C2B—N1B	128.2 (10)	N1C—C6C—C5C	118.1 (9)
C8A—N9A—C10A—C11A	93.0 (2)		
C8B—N9B—C10B—C11B	50.8 (6)		
C8C—N9C—C10C—C11C	−97.0 (6)		

Table 2. *Hydrogen-bonding geometry (Å, °)*

D—H···*A*	H···*A*	*D*···*A*	*D*—H···*A*
N2A—H2A···N1A^{i}	2.10 (2)	3.012 (2)	172 (2)
N6A—H4A···N7A^{ii}	2.10 (2)	2.973 (2)	162 (2)
N6A—H3A···O1W^{i}	2.08 (2)	2.932 (2)	162 (1)
N2A—H1A···O1W	2.47 (2)	3.180 (2)	137 (2)

Symmetry codes: (i) $1-x, 1-y, 2-z$; (ii) $1-x, 2-y, 2-z$.

Direct methods revealed molecule *A*, but only ambiguous indications of the other molecule. Successive electron density maps gave a consensus position for most of the other heterocycle atoms, with clear indications of disorder in the side chain, N9 and C8. Molecules *B* and *C* were constructed and refined subject to 50% occupancy and the *SAME* restraint in *SHELXL*93 (Sheldrick, 1993), which restrained bond and 1,3 distances to similar values to those in molecule *A*.

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989). Cell refinement: *CAD*-4 *Software*. Data reduction: *DATREDXL* (Brookhaven National Laboratory & University of Birmingham, 1986). Program(s) used to solve structure: *MULTAN*11/84 (Main, Germain & Woolfson, 1984). Program(s) used to refine structure: *SHELXL*93. Molecular graphics: *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *SHELXL*93.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: CF1160). Services for accessing these data are described at the back of the journal.

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6-Nitrophthalide

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Abstract

In the title compound, $C_8H_5NO_4$, the heterocycle is planar within 0.02 Å, and the nitro group plane makes an angle of 10.0 (1)° to it. Dipolar interactions and possible weak C—H···O hydrogen bonding feature in the crystal packing. In a series of phthalides, bond lengths in the lactone ring can be related to substituent effects; in the title compound, the nitro group exerts less influence than it does in the homologous 3-nitromethylenephthalide.