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2,6-Diazido-9-(carboxymethyl)purine Methyl Ester

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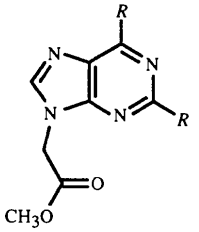
Abstract

The title compound (methyl 2,6-diazidopurine-9-acetate, $C_8H_6N_{10}O_2$) is a potential intermediate for the synthesis of peptidic nucleic acids containing diaminopurine. Its two azido groups are approximately parallel and at their attachment points, the internal ring angles are 1.4 (3)° smaller than in the dichloro homologue.

Comment

The use of peptidic nucleic acids (PNA's; Hyrup & Nielsen, 1996) containing the DNA bases (Dueholm *et al.*, 1994), in addition to pseudoisocytosine (Egholm *et al.*, 1995), offers the possibility of inhibiting gene expression in a controlled manner through triplex formation (Thuong & Hélène, 1993) with target nucleic acid sequences. Our interest in the development of PNA's containing other purine bases, including 2,6-diaminopurine, has prompted the synthesis of 2,6-diazido-9-(carboxymethyl)purine methyl ester, (1), as an intermediate for the synthesis of PNA's. Alkylation of 2,6-dichloropurine (Chan, Sood, Schwalbe & Fraser, 1995) using methyl bromoacetate gave 2,6-dichloro-9-(carboxymethyl)purine methyl ester, (2), which, on treatment with sodium azide at elevated temperature, resulted in substitution of both of the chloro groups giving the title compound, (1).



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

Many geometrical features of (1) (Table 1) resemble those previously found in the ethyl ester homologue of (2) (Chan, Sood, Schwalbe & Fraser, 1995). The atoms of the heterocycle are coplanar within ±0.013 (2) Å and the side chain avoids steric interference with the heterocycle by means of a large twist about the N9—C10 bond. The 2,6-diazido-substituted compound (1), however, exhibits increased external N1—C2—N21 and N1—C6—N61 angles [by 3.1 (4) and 3.9 (4)°, respectively] and decreased internal N1—C2—N3 and N1—C6—C5 angles [both by 1.4 (4)°] compared with the ethyl ester homologue of (2). Although most bond distances are similar to within 3σ, C5—C6 is longer in (1) by 0.025 (6) Å and N9—C10 shorter by 0.017 (5) Å.

Torsion angles near 0° for both N1—C2—N21—N22 and N1—C6—N61—N62 indicate that the two azido groups are almost parallel, resembling a pair of jaws. A similar disposition of azido groups was found in the crystal structure of 2,4-diazido-6-diazoacetylpyrimidine (Kartsev, Aliev, Voronina & Atovmyan, 1990), while one of the azido groups is rotated by *ca* 180° about the C—N bond in 2,4-diazido-5-iodopyrimidine (Allen, Buckland & Nowell, 1976).

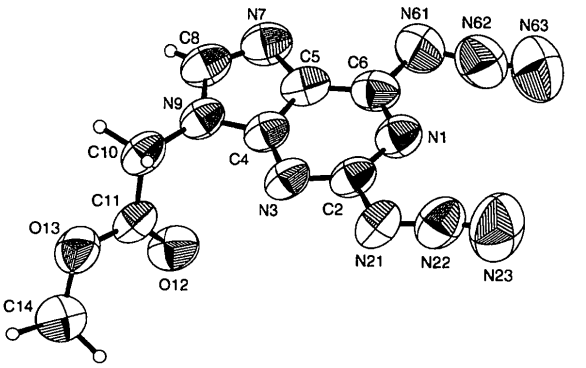


Fig. 1. *ORTEP*II view (Johnson, 1976) of the title molecule. Displacement ellipsoids are shown at the 50% probability level. H atoms are shown as small spheres with arbitrary radii.

Experimental

Preparation of 2,6-dichloro-9-(carboxymethyl)purine methyl ester, (2): to a solution of 2,6-dichloropurine (1.00 g, 5.31 mmol) in dry MeCN (20 ml) was added K_2CO_3 (0.88 g, 6.38 mmol) and methyl bromoacetate (1.00 g, 6.38 mmol). After stirring at room temperature for 48 h under argon, the product solution was filtered and the solvent evaporated under vacuum. The residue was subjected to flash column chromatography on silica and the product eluted with EtOAc. Recrystallization from MeOH gave the title compound (2) (538 mg, 39%; m.p. 424–426 K) as colourless crystals. TLC (EtOAc): R_f 0.25. IR (KBr disc): ν_{max} 3108, 2998, 2958, 1739, 1596, 1556, 1379, 1340, 1234, 1157, 951, 879 cm^{-1}. ^1H NMR [250.1 MHz; $(CD_3)_2SO$]: δ 3.73 (*s*, 3H, CH_3), 5.26 (*s*, 2H, CH_2), 8.70 (*s*, 1H, H-8). ^{13}C NMR [62.1 MHz; $(CD_3)_2SO$]: δ 45.9 (CH_2), 54.0 (CH_3), 130.3 (C-5), 150.1 (C-8), 150.3 (C-2), 151.5 (C-4 and C-6), 162.2 (CO). MS (EI): *m/z* (I_r) 264 (M^+, 6%), 262 (M^+, 30%), 260 (M^+, 45%), 204 (13%), 203 (23%), 201 (33%), 77 (40%), 59 (100%). Analysis calculated for $C_8H_6Cl_2N_4O_2$: C 36.8, H 2.3, Cl 27.1, N 21.4%; found: C 36.8, H 2.3, Cl 27.2, N 21.1%.

Preparation of 2,6-diazido-9-(carboxymethyl)purine methyl ester, (1): a mixture of (2) (351 mg, 1.34 mmol), sodium azide (95 mg, 6.15 mmol), Me_2CO (15 ml) and MeOH (55 ml) was refluxed for 96 h at 353 K. The solvent was evaporated and the residue then subjected to flash chromatography, eluting with EtOAc. Recrystallization from MeOH gave the title compound (1) (74 mg, 20%; m.p. 399–401 K) as pale yellow–brown crystals. TLC (EtOAc): R_f 0.34. IR (KBr disc): ν_{max} 3109, 2949, 2131, 1737, 1616, 1577, 1348, 1234, 995, 788, 626 cm^{-1}. ^1H NMR [250.1 MHz; $(CD_3)_2SO$]: δ 3.71 (*s*, 3H, CH_3), 5.16 (*s*, 2H, CH_2), 8.41 (*s*, 1H, H-8). ^{13}C NMR [62.1 MHz; $(CD_3)_2SO$]: δ 40.7 (CH_2), 52.9 (CH_3), 120.8 (C-5), 146.2 (C-8), 152.9, 154.3, 155.1 (C-2, C-4 and C-6), 168.2 (CO). MS (electrospray): *m/z* (I_r): 274 (M + H 28%), 246 (18%), 160 (44%), 107 (28%), 95 (46%), 80 (74%), 59 (100%). Accurate mass for $C_8H_6N_{10}O_2$: calculated 274.068; found 274.068.

Crystal data

$C_8H_6N_{10}O_2$
M_r = 274.23
Monoclinic
$P2_1/c$
a = 12.761 (2) Å
b = 12.1276 (13) Å
c = 7.9969 (9) Å
β = 102.907 (10)°
V = 1206.3 (3) Å^3
Z = 4
D_x = 1.510 Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
λ = 1.54178 Å
Cell parameters from 25 reflections
θ = 22.2–44.3°
μ = 1.015 mm^{-1}
T = 293 (2) K
Lath
0.50 × 0.15 × 0.05 mm
Pale yellow–brown

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
4316 measured reflections
2173 independent reflections
1384 reflections with $I > 2\sigma(I)$

R_{int} = 0.0580
θ_{max} = 67.7°
$h = -15 \rightarrow 15$
$k = 0 \rightarrow 14$
$l = -9 \rightarrow 9$
3 standard reflections
frequency: 120 min
intensity decay: 19%

Refinement

Refinement on F^2
$R(F)$ = 0.0629
$wR(F^2)$ = 0.1961
S = 1.036
2172 reflections
205 parameters
All H atoms refined
$w = 1/[\sigma^2(F_o^2) + (0.0999P)^2 + 0.0504P]$
where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max}$ = 0.004
$\Delta\rho_{max}$ = 0.27 e Å^{-3}
$\Delta\rho_{min}$ = −0.24 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

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

N1—C6	1.324 (4)	C8—N9	1.371 (4)
N1—C2	1.345 (4)	N9—C10	1.436 (4)
C2—N3	1.313 (4)	C10—C11	1.490 (4)
C2—N21	1.402 (4)	C11—O12	1.203 (3)
N3—C4	1.331 (3)	C11—O13	1.319 (4)
C4—N9	1.367 (4)	O13—C14	1.444 (5)
C4—C5	1.379 (4)	N21—N22	1.219 (5)
C5—N7	1.379 (4)	N22—N23	1.127 (5)
C5—C6	1.400 (5)	N61—N62	1.250 (5)
C6—N61	1.389 (4)	N62—N63	1.121 (6)
N7—C8	1.304 (5)		
N3—C2—N1	128.4 (3)	N1—C6—N61	120.8 (3)
N3—C2—N21	114.1 (3)	N1—C6—C5	120.1 (3)
N1—C2—N21	117.5 (3)	N61—C6—C5	119.1 (3)
C4—N9—C10—C11	−76.8 (3)	N1—C2—N21—N22	−0.1 (4)
C8—N9—C10—C11	103.6 (3)	N1—C6—N61—N62	2.8 (5)

Structure determination by direct methods revealed all non-H atoms. Full-matrix least-squares refinement converged normally to reasonable geometry, including independent refinement of positions and isotropic displacement parameters for all H atoms. The azido groups show a monotonic increase in equivalent isotropic displacement parameters from the N atom attached to the free end indicating considerable atomic motion there.

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*84 (Main, Germain & Woolfson, 1984). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *SHELXL*93.

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Lists of atomic coordinates, displacement parameters, structure factors and complete geometry have been deposited with the IUCr (Reference: BM1122). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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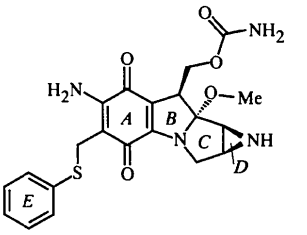

(I)

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Structural Studies of Mitomycins. IX. 6-Demethyl-6-(phenylthiomethyl)-mitomycin C

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Abstract

The title compound, (1a*S*)-6-amino-8-{[(aminocarbonyl)-oxy]methyl}-1,1a,2,8,8a,8b-hexahydro-8a-methoxy-5-(phenylthiomethyl)azirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione, $C_{21}H_{22}N_4O_5S$, is a C6-substituted methyl mitomycin C which possesses potent antitumor activities. The N4 atom is more pyramidal than the corresponding atom in both mitomycin C anhydride and mitomycin C dihydrate.

Comment

Mitomycins are potent antitumor antibiotics produced by various *Streptomyces* cultures. Among these compounds, mitomycin C has been extensively used in cancer chemotherapy against a variety of solid tumors. Its use, however, is limited due to detrimental side effects. Many derivatives of mitomycins have been screened from nature and synthesized to obtain less toxic and more potent compounds. A series of C6-substituted methyl mitomycins was synthesized and evaluated for anticellular and antitumor activities (Arai *et al.*, 1994). The results suggested that C6-substituted methyl mitomycins would have a different biological character from that of mitomycin C. We are undertaking the structural analysis of a series of C6-substituted methyl mitomycins in order to understand the structure–activity relationships and present here the structure of the title compound, (I).

An *ORTEP*II (Johnson, 1976) drawing of (I), together with the atomic numbering scheme is shown in Fig. 1. The absolute configuration of the molecule was suggested by referring to that of 1-*N*-(*p*-bromobenzoyl)-mitomycin C (Shirahata & Hirayama, 1983). Most of the bond lengths are in the range observed in other mitomycins. The N1a—C1, N1a—C2 and C1—C2 bonds are significantly shorter than the corresponding bonds in both mitomycin C anhydride (MMCA) (Arora, 1979) and mitomycin C dihydrate (MMCD) (Ogawa, Nomura, Fujiwara & Tomita, 1979). The sum of the bond angles around N4 is 343.9 (6)°, significantly smaller than those around N4 in MMCA and MMCD, and N4 is more pyramidal than the corresponding atoms in MMCA and MMCD. The exocyclic bond angles around atoms C5, C6, C7 and C8 are highly asymmetric. The asymmetry around C6 is greatly increased in the title compound due to the large phenylthiomethyl substituent.

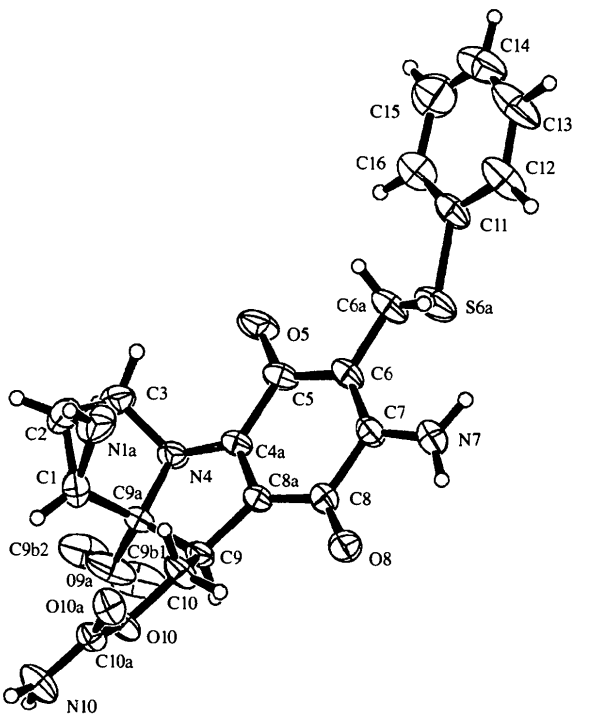

Fig. 1. *ORTEP*II (Johnson, 1976) drawing of the title compound showing the atomic numbering. Displacement ellipsoids are shown at the 30% probability level for non-H atoms and the H atoms are shown as small spheres of arbitrary size.