Experimental

Recrystallization from ether gave the title compound as colourless crystals. A parallelepipedic crystal [(100)(010)(001)] was chosen for X-ray analysis.

Crystal data

$C_{19}H_{32}O_5S$
M_r = 372.51
Orthorhombic
$P2_12_12_1$
a = 7.150 (2) Å
b = 10.284 (2) Å
c = 27.726 (2) Å
V = 2038.8 (7) Å^3
Z = 4
D_x = 1.214 Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
λ = 0.71069 Å
Cell parameters from 32 reflections
θ = 30–32°
μ = 0.183 mm^{-1}
T = 293 (2) K
Prism
0.68 × 0.47 × 0.32 mm
Colourless

Data collection

Stoe Siemens AED-2 diffractometer
ω–θ/2 scans
Absorption correction: none
3093 measured reflections
2706 independent reflections
2038 reflections with $I > 2\sigma(I)$
R_{int} = 0.017
θ_{max} = 27.51°
$h = -1 \rightarrow 9$
$k = -13 \rightarrow 13$
$l = 0 \rightarrow 36$
3 standard reflections
frequency: 60 min
intensity decay: 10.1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.039
$wR(F^2)$ = 0.117
S = 1.042
2706 reflections
279 parameters
H atoms constrained
$w = 1/[\sigma^2(F_o^2) + (0.1P)^2 + 2.0P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = -0.011$
$\Delta\rho_{max}$ = 0.158 e Å^{-3}
$\Delta\rho_{min}$ = −0.162 e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.0004 (12)
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute structure: Flack (1983)
Flack parameter = 0.13 (13)

Table 1. *Selected bond lengths (Å)*

S—O2	1.513 (2)	C5—C6	1.327 (4)
S—C20	1.793 (3)	C6—C7	1.518 (4)
S—C8	1.869 (3)	C7—C16	1.536 (4)
O1—C2	1.379 (4)	C7—C8	1.570 (4)
O1—C17	1.422 (4)	C8—C9	1.541 (4)
O3—C3	1.403 (4)	C8—C10	1.549 (4)
O3—C17	1.427 (4)	C10—C11	1.525 (4)
O4—C10	1.438 (3)	C11—C12	1.528 (4)
O5—C5	1.381 (3)	C12—C13	1.510 (5)
O5—C2	1.442 (4)	C13—C14	1.519 (5)
C2—C3	1.539 (4)	C14—C15	1.483 (7)
C3—C4	1.544 (4)	C17—C19	1.479 (5)
C4—C5	1.494 (4)	C17—C18	1.489 (6)
C4—C9	1.520 (4)		

An ω–θ/2 step-scan mode in N steps of 0.035° was used, with N_{min} = 37, time per step t_{min} = 1.0 s and t_{max} = 4.0 s, aperture D = 4.0 mm, and standard reflections 228, $\bar{2}28$ and $22\bar{8}$. A solution with all non-H atoms was found with the multi-solution tangent direct methods of *SHELXS*86 (Sheldrick, 1990). Successive refinements and difference Fourier maps allowed the S, O and C atoms to be distinguished (R = 0.160). H atoms were refined as rigid groups associated with their neighbours (R = 0.039) and their displacement parameters were restrained to be equal in order to decrease the number of refined parameters.

Data collection: *DIF*4 (Stoe & Cie, 1987). Cell refinement: *DIF*4. Data reduction: *REDU*4 (Stoe & Cie, 1985). Program(s) used to solve structure: *SHELXS*86. Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP* (Johnson, 1965).

The authors are indebted to Dr R. Retoux for his help in the X-ray data collection.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: OS1011). Services for accessing these data are described at the back of the journal.

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Acta Cryst. (1998). C**54**, 1987–1990

N^4,5-Dimethyl-2′-deoxycytidine

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(Received 16 March 1998; accepted 8 June 1998)

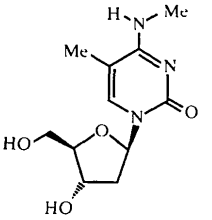
Abstract

In the title molecule ($C_{11}H_{17}N_3O_4$) the pyrimidine ring adopts the anticlinal ($-ac$) conformation [χ = 245.10 (18)°]. The deoxyribose sugar ring has the C2′-*endo* (^2E) envelope conformation. The pseudorotational parameters of the deoxyribose sugar ring are P = 168.92 (2)° and τ_m = 33.86 (2)°. The exocyclic side chain at C5′ has the g^+ conformation [γ = 55.0 (2)°].

Comment

Deoxycytidine analogues with selectivity and resistance to mammalian deaminases are of therapeutic interest. The rationale for deoxycytidines as superior therapeutic agents for the treatment of herpes simplex virus (HSV) infection has been discussed previously (Gupta *et al.*, 1991, 1993). Our findings that 5-methoxymethyl-2′-deoxycytidine (MMdCyd) and (*E*)-5-(2-bromovinyl)-2′-deoxycytidine (BrVdCyd) are potent and selective inhibitors of HSV type 1 (HSV-1) replication when co-administered with deaminase inhibitors, are consistent with the hypothesis that in HSV-infected cells, these analogues are metabolized primarily by the virus-induced deoxycytidine kinase–deoxycytidylate kinase pathway (Aduma, Gupta, Stuart & Tourigny, 1990; Aduma, Gupta & De Clercq, 1990, 1991; Gupta *et al.*, 1991, 1993).

Systematic investigations to develop antiherpes compounds resistant to ubiquitously present deaminases in blood and mammalian cells by modification of the cytosine moiety (N^4-amino group) have been undertaken (Jia *et al.*, 1990*a*; Zoghaib, 1996; Audette *et al.*, 1997). As part of this research program, 5-methoxymethyl-N^4-methyl-2′-deoxycytidine (N^4-methyl-MMdCyd) and (*E*)-5-(2-bromovinyl)-N^4-methyl-2′-deoxycytidine (N^4-methyl-BrVdCyd) were synthesised. N^4-Methyl-MMdCyd was devoid of antiviral activity, and the loss of bioactivity was found to be due to the conformation of the molecule (Jia *et al.*, 1990*b*; Gupta *et al.*, 1992). Interestingly, N^4-methyl-BrVdCyd is a potent inhibitor of HSV-1 replication (Gupta, unpublished results). The title compound, N^4-methyl-5-methyl-2′-deoxycytidine (N^4-methyl-5-Me-dCyd), (I), was prepared and shown to be devoid of anti-HSV activity. These investigations are part of our program of research aimed at elucidating the relationship of alkyl substitution on the cytosine moiety, the steric conformation of the furanose ring, and conformation of the 5′-CH_2OH side chain. In this report, we present the structure of N^4-methyl-5-Me-dCyd, (I).



(I)

Selected bond distances and angles of N^4-methyl-5-Me-dCyd (Fig. 1) are presented in Table 1. Bond lengths and angles are similar in range to those reported for other 2′-deoxycytidine analogues (Young & Wilson, 1975; Sato, 1988; Jia *et al.*, 1990*a*,*b*). Intermolecular hydrogen bonds occurring between symmetry-related molecules in the crystal are summarized in Table 2.

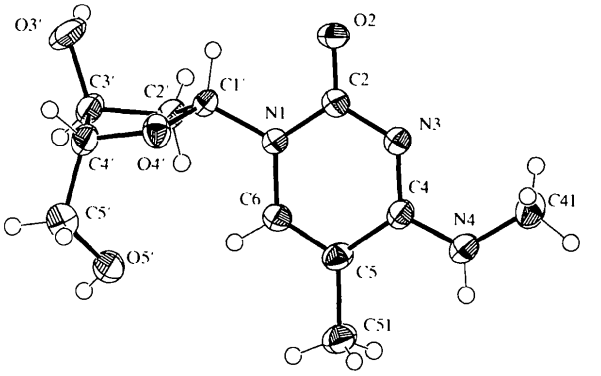


Fig. 1. A perspective *ORTEP*II (Johnson, 1976) plot of N^4-methyl-5-Me-dCyd. All non-H-atom ellipsoids are drawn at the 50% probability level and H atoms are shown as spheres of small arbitrary size.

In the title molecule, the pyrimidine ring adopts the anticlinal (−*ac*) conformation, with χ = 245.10 (18)°. In contrast, 5-methyl-dCyd differs from N^4-methyl-5-Me-dCyd by adopting the synclinal (+*sc*) conformation, with χ = 46.3 (3)° (Sato, 1988). The conformation of the glycosidic bond in dCyd, MMdCyd and N^4-methyl-dCyd is similar to that in the title molecule (Young & Wilson, 1975; Jia *et al.*, 1990*a*,*b*). However, the value of the torsion angle in N^4-methyl-MMdCyd [χ = 193.8 (2)°] is smaller than in N^4-methyl-5-Me-dCyd [χ = 245.10 (18)°].

The exocyclic 5′-CH_2OH side chain of N^4-methyl-5-Me-dCyd adopts the g^+ conformation [γ = 55.0 (2)°]. The g^+ conformation has been reported for both molecules of MMdCyd (Jia *et al.*, 1990*b*). Similarly, the g^+ conformation is also the most common conformation found in cytidine and deoxycytidine compounds (Young & Wilson, 1975). However, N^4-methyl-MMdCyd and 5-methyl-dCyd display the *t* conformation for the exocyclic side chain (Sato, 1988; Jia *et al.*, 1990*a*).

The deoxyribose sugar ring of N^4-methyl-5-Me-dCyd adopts the C2′-*endo* (^2E) envelope conformation, with pseudorotational parameters of P = 168.92 (2)° and τ_m = 33.86 (2)° (Altona & Sundaralingam, 1972). This conformation of the deoxyribose ring is most commonly found in deoxycytidine compounds (Young & Wilson, 1975; Sato, 1988; Jia *et al.*, 1990*b*). In contrast, the sugar ring in N^4-methyl-MMdCyd has been reported to have the C1′-*exo* ($_1E$) envelope conformation.

The N^4-methyl group of N^4-methyl-5-Me-dCyd has a *cis* orientation with respect to N3, with an N3—C4—N4—C41 torsion angle of −0.4 (3)°. The *cis* relationship between the N^4 substituent and N3 has been reported for N^4-aminocytidine, a potent mutagen (Takahashi *et al.*, 1988), N^4-methyl-MMdCyd (Jia *et al.*, 1990*a*) and 3,4-etheno-MMdCyd (Audette *et al.*, 1997). In 3,4-etheno-MMdCyd, the N^4 substituent is forced to adopt the *cis* conformation with respect to N3 by a covalent bond.

Crystallographic and NMR spectroscopic studies indicate that the conformation of the 5′-exocyclic side chain (O5′—C5′—C4′—C3′ torsion angle γ) is important in determining the activation of 5-substituted pyrimidine-2′-deoxyribonucleosides by the HSV-induced dThd/-dCyd kinase (HSV-TK). The g^+ conformer ($\gamma \simeq 55°$) appears to be the preferred orientation required by HSV-TK, whereas the t conformer ($\gamma \simeq 175°$) appears to be an unfavourable orientation (Gupta *et al.*, 1987, 1992; Jia *et al.*, 1990*a*,*b*; Stuart *et al.*, 1997). The C5′-hydroxy groups of 5-methyl-dCyd and N^4-methyl-MMdCyd have the t conformation. Thus, one rational explanation for the lack of anti-HSV activity of 5-methyl-dCyd and N^4-methyl-MMdCyd is that phosphorylation (activation) by the HSV-TK does not occur due to the t conformation of the 5′-CH_2OH group of the furanose ring. Therefore, physiologically significant levels of the triphosphate (active form of the drug) are not formed in the HSV-infected cells.

Experimental

The title compound was prepared from N^4-methyl-3′,5′-diacetyl-2′-deoxythymidine using the triazolization procedure (Jia *et al.*, 1990*b*). Single crystals were obtained at 293 K using the vapour-diffusion method with methanol as the solvent and diethyl ether as the precipitant.

Crystal data

$C_{11}H_{17}N_3O_4$
M_r = 255.27
Orthorhombic
$P2_12_12_1$
a = 7.436 (2) Å
b = 8.438 (2) Å
c = 19.607 (3) Å
V = 1230.1 (5) Å^3
Z = 4
D_x = 1.378 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.7107 Å
Cell parameters from 25 reflections
θ = 8.30–26.32°
μ = 0.106 mm^{-1}
T = 287 (2) K
Rod-like
0.53 × 0.38 × 0.30 mm
Colourless

Data collection

Nonius CAD-4 diffractometer
ω scan
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.836, T_{max} = 0.974
2920 measured reflections
2487 independent reflections

1942 reflections with $I > 2\sigma(I)$
R_{int} = 0.020
θ_{max} = 26.21°
$h = -9 \rightarrow 9$
$k = -10 \rightarrow 10$
$l = -24 \rightarrow 24$
3 standard reflections
frequency: 100 min
intensity decay: none

Refinement

Refinement on F^2
$R(F)$ = 0.036
$wR(F^2)$ = 0.106
S = 1.058
2487 reflections
167 parameters
H atoms riding
$w = 1/[\sigma^2(F_o^2) + (0.071P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.163 e Å^{-3}
$\Delta\rho_{min}$ = −0.242 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

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

C2—O2	1.235 (2)	N4—C41	1.448 (3)
C4—N4	1.330 (2)	C5—C51	1.506 (2)
O2—C2—N3	121.70 (16)	C4—C5—C51	122.28 (16)
C4—N4—C41	123.64 (18)		
N3—C4—N4—C41	−0.4 (3)	C2′—C3′—C4′—O4′	23.97 (19)
C2—N1—C1′—O4′	−114.90 (18)	C2′—C1′—O4′—C4′	−17.09 (18)
O4′—C1′—C2′—C3′	31.40 (19)	C3′—C4′—O4′—C1′	−4.49 (19)
C1′—C2′—C3′—C4′	−33.23 (19)	C3′—C4′—C5′—O5′	55.0 (2)

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

D—H···A	D—H	H···A	D···A	D—H···A
N4—H4···O3′^{i}	0.86	2.16	2.986 (2)	161
O3′—H3′1···O2^{ii}	0.82	1.90	2.717 (2)	172
O5′—H5′···N3^{iii}	0.82	2.13	2.943 (2)	173

Symmetry codes: (i) $\frac{3}{2} - x, 1 - y, z - \frac{1}{2}$; (ii) $1 - x, y - \frac{1}{2}, \frac{3}{2} - z$; (iii) $x, y - 1, z$.

With the absence of suitable anomalous scatterers within the molecule, determination of the absolute configuration of (I) was not possible from our present X-ray analysis. However, the knowledge gained from our previous chemical and crystallographic studies (Jia *et al.*, 1990*a*,*b*; Zoghaib, 1996; Audette *et al.*, 1997), as well as the configuration of the parent molecule (N^4-methyl-3′,5′-diacetyl-2′-deoxythymidine), indicates that the proposed conformation is correct.

Data collection: *CAD-4 EXPRESS* (Enraf–Nonius, 1992). Cell refinement: *CAD-4 EXPRESS*. Data reduction: *Xtal*3.4 (Hall *et al.*, 1995) and *NRCVAX* (Gabe *et al.*, 1989). Program(s) used to solve structure: *Xtal*3.4. Program(s) used to refine structure: *NRCVAX* and *SHELXL*97 (Sheldrick, 1997). Molecular graphics: *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *NRCVAX*.

This research was funded by grants from the Medical Research Council of Canada to SVG (MT-10254), and from the Natural Science and Engineering Research Council of Canada to JWQ.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1466). Services for accessing these data are described at the back of the journal.

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Acta Cryst. (1998). C**54**, 1990–1992

Epiclusianone: a New Natural Product Derivative of Bicyclo[3.3.1]nonane-2,4,9-trione

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(*Received 21 October 1997; accepted 5 May 1998*)

Abstract

Epiclusianone [3-benzoyl-4-hydroxy-6,6-dimethyl-1,5,7-tris(3-methyl-2-butenyl)bicyclo[3.3.1]non-3-ene-2,9-dione] is a new isomeric form of the $C_{33}H_{42}O_4$ compound identified by X-ray diffraction analysis. Structure comparison with the known clusianone evidences a case of epimerism in one of the chiral C atoms. A comparison of the melting point and the optical activity of the two isomers shows them to have different values.

Comment

The title compound, (I), was isolated from *Rheedia gardneriana*. NMR, UV, IR and MS characterization indicated a formula of $C_{33}H_{42}O_4$ for the compound, which is consistent with clusianone [(II); McCandlish *et al.*, 1976; Delle Monache *et al.*, 1991; Oliveira *et al.*, 1996]. The values obtained for the melting point and optical rotation of (I) (m.p. 365–366 K and $[\alpha]_D^{25}$ +77°, respectively) were inconsistent with those previously determined for clusianone, (II). In addition, the NMR spectra

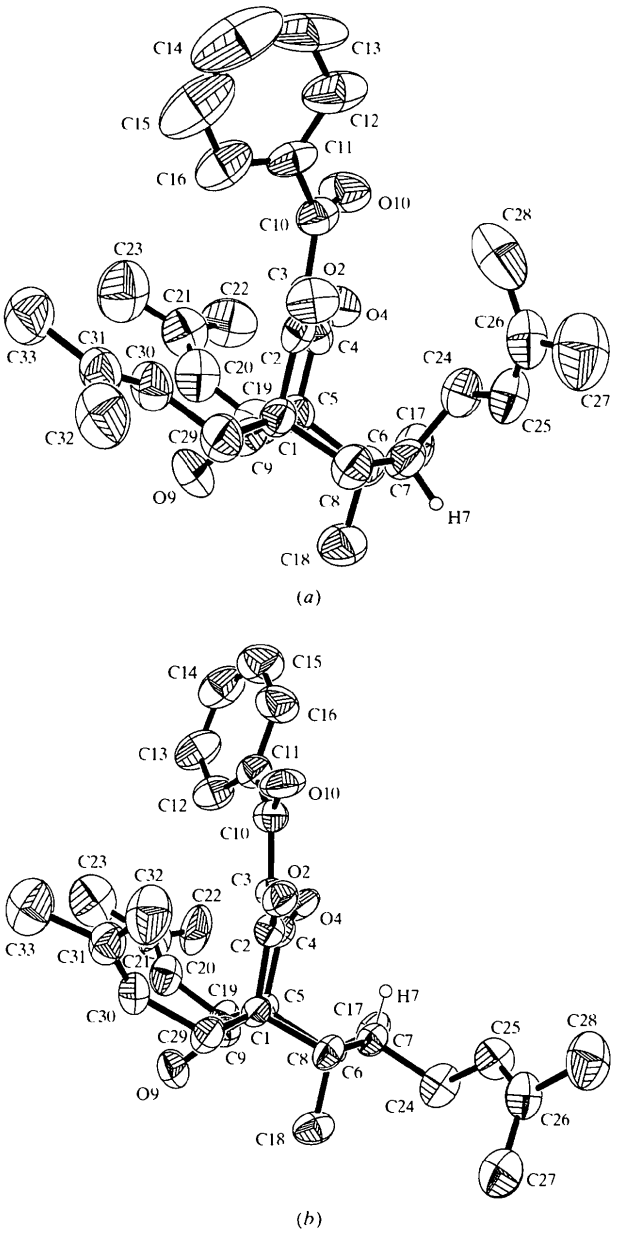

Fig. 1. A view of the molecular structures of (*a*) (I) and (*b*) (II) with 50% probability ellipsoids. The different configurations of the isopentenyl group and the H atom bound to C7 can be seen clearly.