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Benzyl 5-{2-[2-(diethoxyphosphinoyl)acetyl]-3-oxo-7-thia-2,4-diazabicyclo[3.3.0]oct-6-yl}pentanoate, a novel biotin derivative

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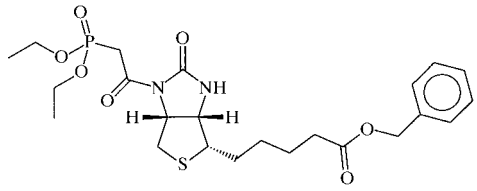
The title compound, $C_{23}H_{33}N_2O_7PS$, has its phosphonoacetate carbonyl group rotated slightly out of the plane of the ureido ring, with a C—N—C—O torsion angle of −6.9 (4)°. The sulfur-containing ring has an envelope conformation, while the ureido ring is nearly planar.

Comment

Biotin, or vitamin H, is found in all animals, plants and bacteria, and functions as a cofactor for a group of enzymes that catalyze carboxylation, transcarboxylation and decarboxylation reactions (Wagner & Folkers, 1964; Wood & Barden, 1977). The reactions catalyzed by biotin-dependent enzymes are involved in diverse but essential metabolic pathways such as gluconeogenesis, fatty acid synthesis and amino acid catabolism (Wood & Barden, 1977). The first step in all biotin-dependent carboxylases involves the carboxylation of biotin at the 1′-N position (Guchhait *et al.*, 1974). This is accomplished by the ATP-dependent phosphorylation of bicarbonate, the source of CO_2, forming a reactive carboxyphosphate intermediate. The carboxyl group is then transferred to biotin to form carboxybiotin. Recently, a novel reaction intermediate analogue of biotin-dependent carboxylases that incorporates the carboxyphosphate intermediate and biotin has been synthesized and found to inhibit biotin carboxylase from *Eschericia coli* (Knowles, 1989).

We reported recently (Amspacher *et al.*, 1999) the structure of the title compound, (I), at room temperature. It was obtained as a reaction intermediate to the inhibitor, and was obtained *via* an Arbuzov reaction with triethyl phosphite and biotin acylated with chloroacetyl chloride (Knowles, 1989). The 299 K data were sufficient to establish the connectivity and relative configuration of the molecule, but little else. We report herein a refinement of the structure with high-resolution low-temperature data.



(I)

The carbonyl group of the phosphonoacetate moiety of (I) is rotated slightly out of the plane of the ureido ring, with a C3—N2—C18—O4 torsion angle of −6.9 (4)°. This contrasts with 1′-*N*-methoxycarbonylbiotin methyl ester (Stallings *et al.*, 1980), in which the methoxycarbonyl group and the ureido ring are nearly coplanar, with torson angles in two independent molecules of −1.1 and −2.9°. Since the title compound is a reaction intermediate analogue of the carboxylation of biotin, this is consistent with computational studies and host–guest experiments which suggest that the carboxyl group of carboxybiotin is rotated out of the plane of the ureido ring when biotin is carboxylated and decarboxylated (Gregory *et al.*, 1986).

The five atoms of the ureido ring are nearly coplanar, with a maximum deviation of 0.029 (2) Å for N2. The sulfur-containing ring has the envelope conformation with the S atom at the flap position, lying 0.850 (4) Å from the best plane of the four C atoms. These two planes form a dihedral angle of 60.94 (13)°.

Experimental

The title compound was synthesized according to the method of Amspacher *et al.* (1999). Crystals were obtained from ethyl acetate by evaporation.

Crystal data

$C_{23}H_{33}N_2O_7PS$
M_r = 512.57
Monoclinic, $P2_1$
a = 10.455 (2) Å
b = 12.410 (2) Å
c = 10.592 (2) Å
β = 115.077 (10)°
V = 1244.7 (4) Å^3
Z = 2
D_x = 1.368 Mg m^{-3}
Mo–Kα radiation
Cell parameters from 25 reflections
θ = 8.9–18.2°
μ = 0.24 mm^{-1}
T = 100 K
Prism, colourless
0.50 × 0.33 × 0.18 mm

Data collection

Enraf–Nonius CAD-4 diffractometer (with an Oxford Cryostreams Cryostream cooler)
$\theta/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.920, T_{max} = 0.959
5600 measured reflections
5297 independent reflections
4521 reflections with $I > 2\sigma(I)$
R_{int} = 0.033
θ_{max} = 30°
$h = 0 \rightarrow 14$
$k = -13 \rightarrow 17$
$l = -14 \rightarrow 13$
3 standard reflections
frequency: 60 min
intensity decay: 2.9%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0378P)^2 + 0.6507P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.040$	$(\Delta/\sigma)_{max} = 0.002$
$wR(F^2) = 0.101$	$\Delta\rho_{max} = 0.44$ e Å^{-3}
$S = 1.12$	$\Delta\rho_{min} = -0.43$ e Å^{-3}
5297 reflections	Absolute structure: Flack (1983)
309 parameters	Flack parameter = −0.07 (8); 1521 Friedel pairs
H-atom parameters constrained	

Table 1
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1N···O5^{i}	0.88	2.02	2.881 (3)	167

Symmetry code: (i) $1-x, \frac{1}{2}+y, 2-z$.

H atoms were placed in calculated positions with C—H = 0.95–1.00 Å, N—H = 0.88 Å, and $U_{iso} = 1.2U_{eq}$ for the bonded atom (1.5 for methyl), and treated as riding. A torsional parameter was refined for the methyl groups.

Data collection: *CAD*-4 *EXPRESS* (Enraf–Nonius, 1994); cell refinement: *CAD*-4 *EXPRESS*; data reduction: *PROCESS* in *MolEN* (Fair, 1990); program(s) used to solve structure: direct methods using *SIR* (Burla *et al.*, 1989); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); software used to prepare material for publication: *CIFTAB* in *SHELXL*97.

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