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Diethyl 3,3′-(*cis*-[4a]-*cisoid*-[4a,4b]-*cis*-[4b]-9,11-dimethyl-2,4,6,8-tetraoxoperhydrocyclobuta[1,2-*d*:3,4-*d*]dipyrimidine-1,5-diyl)dipropionate

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.003 Å
Disorder in main residue
R factor = 0.046
wR factor = 0.118
Data-to-parameter ratio = 15.2

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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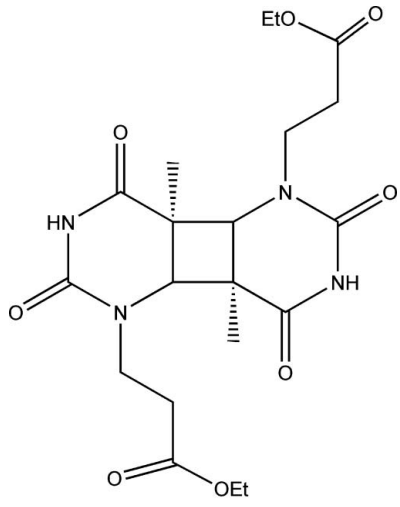
In the title compound, $C_{20}H_{28}N_4O_8$, the two methyl groups attached to the cyclobutane ring are *cis* oriented. The crystal structure is stabilized by intermolecular N—H···O hydrogen bonds.

Comment

DNA repair has attracted considerable attention in recent years, as ozone depletion threatens to significantly increase DNA damage by UV radiation (Friedberg *et al.*, 1995). Cyclobutane pyrimidine dimers (CPDs) are the major photoproducts formed in DNA by this radiation and have, therefore, been well investigated. In double-stranded DNA, the major alteration is the formation of *cis–syn* CPDs, while in single-stranded DNA, a small amount of *trans–syn* species are formed (Heelis *et al.*, 1995). In organisms such as *E. coli*, *D. melanogaster* and *X. laevis*, this damage is repaired, in the presence of light, by the CPD photolyases (Sancar, 2003).



(I)

Much of the detailed mechanistic information on the monomerization of the pyrimidine photodimer has come from model studies on the fragmentation of the CPDs. These model systems can be readily synthesized by the dimers linked to the chromophores. There are only four isomers of CPDs with significant yields and they are the *cis–syn*, *cis–anti*, *trans–syn* and *trans–anti* configurations. The investigation of the cleavage reaction with *cis–syn*, *trans–syn* and *trans–anti* CPD model compounds revealed an enhanced vulnerability for the *cis–syn* isomer; the *trans–syn* dimer was ten times more stable (Epple *et al.*, 1997). The *cis–syn* thymine dimer attached to a tryptophan residue can also be efficiently split (Song *et al.*, 2005). To compare the splitting efficiency of the *cis–anti* dimer with that

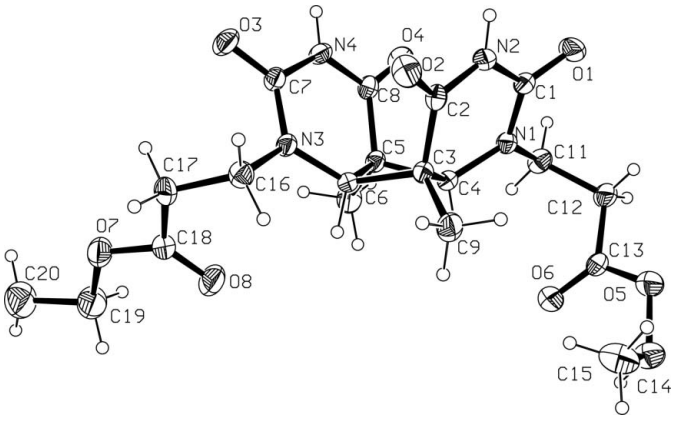


Figure 1
Drawing of the title compound, with the atomic numbering scheme and displacement ellipsoids drawn at the 30% probability level.

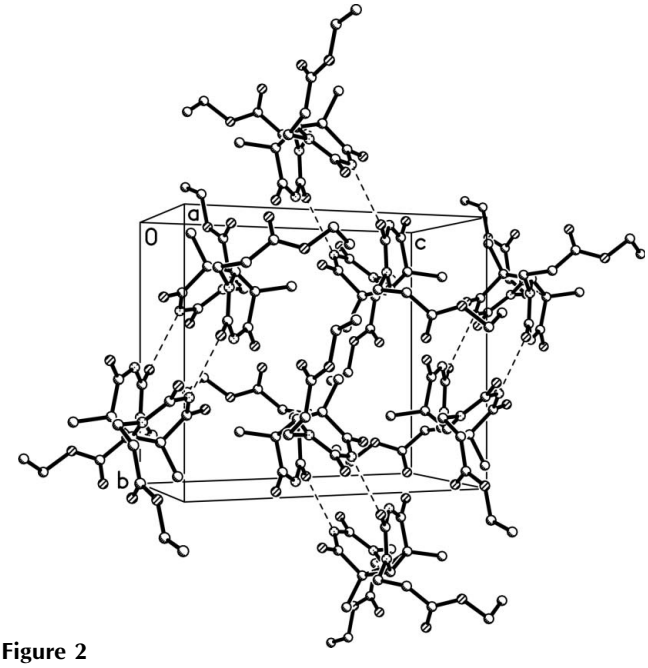


Figure 2
The network-like structure of the title compound, with hydrogen bonds shown as dashed lines. H atoms have been omitted

of the *cis–syn* dimer, we have prepared the *cis–anti* thymine dimer covalently linked to a tryptophan residue. Under identical conditions to those for the *cis–syn* compound (Song *et al.*, 2005), however, no splitting was detected for the *cis–anti* compound.

With the above background, the title compound, (I), has been synthesized and its crystal structure is presented here. In the cyclobutane ring, the torsion angle C3—C4—C5—C6 is −21.25 (13)°, and the two methyl groups are on the same side of the ring. The structure is similar to *cis–syn* cyclobutane thymine dimer diethyl esters (Song *et al.*, 2005) with respect to the bond lengths and torsion angles of the cyclobutane ring. It would appear, therefore, that crystal structure analysis cannot help us to understand the observed difference in splitting efficiencies.

In the packing of the title compound, the molecules are linked into networks (Fig. 2) by intermolecular N—H···O hydrogen bonds (Table 1). No significant π–π interactions are observed in the crystal structure.

Experimental

The title compound was prepared by dissolving ethyl thymine-1-propionate (2.00 g, 8.8 mmol) in acetone/MeCN (200 ml, 1:4) and the solution placed in a photochemical apparatus (Pyrex), purged with nitrogen, degassed for 15 min, and irradiated with a 300 W Hg high-pressure lamp for 20 h. The reaction mixture was filtered and evaporated to dryness *in vacuo*. The residual solid material was dissolved in EtOAc (20 ml) and subjected to column chromatography (silica gel-H, petroleum ether/EtOAc/MeOH 3:2:0.1) to yield the *cis–syn* and *cis–anti* isomers. The purified isomer was crystallized by dissolving in EtOAc (20 ml) and adding cyclohexane (10 ml) to the solution. Upon standing at room temperature, single crystals appeared, which were separated from the solvent by decantation. Analysis calculated for $C_{20}H_{28}N_4O_8$: C 53.09, H 6.24, N 12.38%; found: C 52.97, H 6.27, N 12.20%.

Crystal data

$C_{20}H_{28}N_4O_8$
M_r = 452.46
Monoclinic, $P2_1/c$
a = 12.918 (6) Å
b = 12.090 (6) Å
c = 15.488 (8) Å
β = 110.993 (8)°
V = 2258 (2) Å^3
Z = 4
D_x = 1.331 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.10 mm^{-1}
T = 293 (2) K
Block, colorless
0.38 × 0.36 × 0.34 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.903, T_{max} = 1.000
12464 measured reflections
4613 independent reflections
2990 reflections with $I > 2\sigma(I)$
R_{int} = 0.031
θ_{max} = 26.4°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.046
$wR(F^2)$ = 0.118
S = 1.01
4613 reflections
304 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0517P)^2 + 0.5195P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.18 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2A···O4^{i}	0.86	2.32	3.148 (3)	163
N4—H4A···O1^{i}	0.86	2.01	2.795 (3)	151

Symmetry code: (i) $-x, -y+1, -z$.

All H atoms were included in the riding-model approximation, with C—H = 0.96–0.98 Å and N—H = 0.86 Å, and with U_{iso}(H) = 1.2U_{eq}(C,N) and 1.5U_{eq}(methyl C). One ethyl group (C14—C15 and the attached H atoms), was found to be disordered over two sites; the occupancy factors refined to 0.535 (5) and 0.465 (5). They were refined with C—C distances restrained to 1.54 (1) Å.

Data collection: *SMART* (Bruker, 1998); cell refinement: *SAINT* (Bruker, 1999); data reduction: *SAINT*; program(s) used to solve

structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 1999); software used to prepare material for publication: *SHELXTL*.

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