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Succinyl Oleanolic Acid

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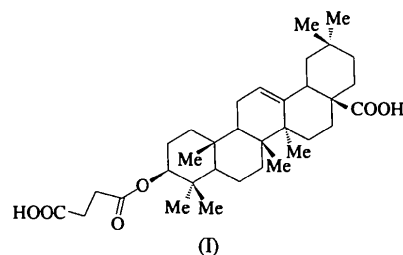
Abstract

The title compound, 3-[(2-carboxyethyl)carboxyloxy]olean-12-en-28-oic acid, C₃₄H₅₂O₆, was synthesized as a derivative of oleanolic acid in order to improve its solubility and bioavailability. It has been used as an anti-inflammatory and antihepatitis drug in east Asia. The present study reveals that the succinyl moiety is equatorial with respect to the six-membered ring to which it is attached. The molecules are packed in layers in the crystal.

Comment

Oleanolic acid can be extracted from various plant sources, including the seeds of *Luffa cylindrica* and *Glechoma hederaceae* L. (Ohigashi, Takamura, Koshimizu, Tokuda & Ito, 1986). It displays dose-related anti-inflammatory activity in a variety of test models (Singh, Singh, Bani, Gupta & Banerjee, 1991). A study by Dai, Hang, Li & Tan (1989) also shows it to inhibit

the type I allergic reaction. Oleanolic acid, however, is virtually insoluble in either water or non-polar solvents. Various derivatives have been synthesized in attempts to improve its solubility and hence bioavailability. One of these derivatives is succinyl oleanolic acid, (I), which was synthesized by reacting oleanolic acid with succinic acid (Jia, 1996). The present crystal structure determination will not only help us understand the detailed three-dimensional arrangement of the compound, which could be useful for designing new derivatives, but will also contribute to the structural database in which there are very few structures containing the oleanolic acid moiety. The only entry in the Cambridge Structural Database (Allen *et al.*, 1987) is oleanolic acid diacetate bromolactone (van Schalkwyk & Kruger, 1974), which lacks the characteristic double bond in the oleanolic acid framework.



The crystal structure of the title compound reveals that the succinyl moiety is equatorial at position C3 in the C1–C6 ring. Three of the five six-membered rings in the molecule [C1–C6 (A); C1, C6–C10 (B); C17–C22 (E)] are in chair conformations. The other two rings [C7, C11–C14, C8 (C); C13–C18 (D)] exhibit twisted-chair conformations due to flattening of the C12=C13 double bond. The carboxyl group at C17 is equatorial with respect to ring E and axial with respect to the ring D. The molecules are packed in layers along the *ac* plane in the crystal, as shown in the packing diagram (Fig. 2). The packing is stabilized by intermolecular hydrogen bonds approximately along one diagonal direction in the

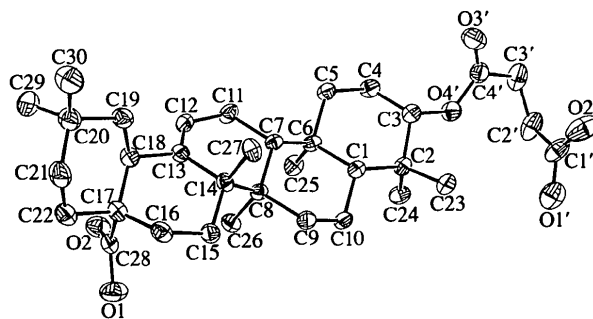


Fig. 1. View of succinyl oleanolic acid with the non-H-atom displacement ellipsoids drawn at the 50% probability level. H atoms have been omitted for clarity.

ab plane and van der Waals interactions along both the *a* and *b* directions. The intermolecular hydrogen bonds are formed between the carboxyl group at C17 and the carboxyl group in the succinyl moiety of the symmetry-related molecule at $(1-x, y-\frac{1}{2}, -z)$, and between the carboxyl group in the succinyl moiety and the carboxyl group at C17 of the symmetry-related molecule at $(1-x, \frac{1}{2}+y, -z)$. These hydrogen bonds are summarized in Table 2.

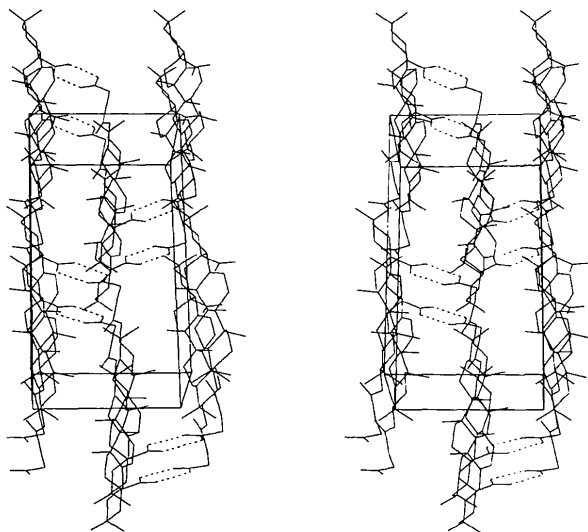


Fig. 2. Stereoscopic packing diagram of the title compound. Axes *a*, *b* and *c* are in the directions of the approximate perpendicular to the page, the horizontal and the vertical, respectively. H atoms have been omitted for clarity.

Experimental

The title compound was synthesized by reacting oleanolic acid with succinic acid (Jia, 1996). Crystals were obtained by vapor diffusion.

Crystal data

C₃₄H₅₂O₆

M_r = 556.77

Monoclinic

*P*2₁

a = 7.3710 (7) Å

b = 11.1271 (16) Å

c = 19.1910 (16) Å

β = 99.725 (8)°

V = 1551.4 (3) Å³

Z = 2

D_x = 1.192 Mg m⁻³

D_m = 1.216 Mg m⁻³

D_m measured by flotation

Data collection

Enraf–Nonius CAD-4
diffractometer

Mo K α radiation

λ = 0.7093 Å

Cell parameters from 25
reflections

θ = 15–20°

μ = 0.07 mm⁻¹

T = 287 K

Prism

0.35 × 0.20 × 0.20 mm

Colorless

$\omega/2\theta$ scans

Absorption correction: none

3147 measured reflections

2874 independent reflections

2502 reflections with

$I_{\text{net}} > \sigma(I_{\text{net}})$

Refinement

Refinement on *F*

R = 0.047

wR = 0.050

S = 1.71

2501 reflections

360 parameters

H atoms: see below

$w = 1/[\sigma^2(F) + 0.0003F^2]$

h = -8 → 8

k = 0 → 13

l = 0 → 22

3 standard reflections

frequency: 120 min

intensity decay: 2%

$(\Delta/\sigma)_{\text{max}} < 0.001$

$\Delta\rho_{\text{max}} = 0.20 \text{ e \AA}^{-3}$

$\Delta\rho_{\text{min}} = -0.16 \text{ e \AA}^{-3}$

Extinction correction: none

Scattering factors from *International Tables for X-ray*

Crystallography (Vol. IV)

Table 1. Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)

$$U_{\text{eq}} = (1/3)\sum_i \sum_j U^{ij} a_i^* a_j^* a_i \cdot a_j$$

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U_{eq}</i>
O1	0.8309 (4)	0.33568	0.35341 (17)	0.080 (2)
O2	0.5802 (4)	0.2233 (3)	0.34518 (16)	0.0687 (18)
C1	0.2524 (4)	0.4516 (4)	-0.01628 (16)	0.0371 (17)
C2	0.2066 (4)	0.4418 (4)	-0.09834 (16)	0.0406 (17)
C3	-0.0046 (4)	0.4423 (4)	-0.11766 (17)	0.0431 (17)
C4	-0.1031 (4)	0.3513 (4)	-0.07965 (18)	0.0503 (19)
C5	-0.0521 (4)	0.3681 (4)	0.00063 (18)	0.0460 (19)
C6	0.1577 (4)	0.3611 (4)	0.02729 (17)	0.0391 (17)
C7	0.1931 (4)	0.4072 (4)	0.10545 (16)	0.0370 (16)
C8	0.3961 (4)	0.4298 (4)	0.14026 (17)	0.0388 (17)
C9	0.4896 (4)	0.5074 (4)	0.08920 (17)	0.0465 (18)
C10	0.4565 (4)	0.4605 (4)	0.01293 (17)	0.0444 (18)
C11	0.0925 (4)	0.3307 (4)	0.15479 (18)	0.051 (2)
C12	0.1635 (4)	0.3469 (4)	0.23133 (17)	0.0458 (19)
C13	0.2995 (4)	0.4170 (4)	0.26000 (17)	0.0414 (17)
C14	0.3978 (4)	0.4965 (4)	0.21339 (17)	0.0404 (17)
C15	0.5987 (4)	0.5249 (4)	0.24833 (17)	0.0488 (19)
C16	0.6255 (5)	0.5438 (4)	0.32844 (19)	0.053 (2)
C17	0.5547 (4)	0.4367 (4)	0.36649 (18)	0.050 (2)
C18	0.3473 (4)	0.4219 (4)	0.34046 (17)	0.0460 (18)
C19	0.2336 (4)	0.5166 (5)	0.37218 (17)	0.053 (2)
C20	0.2730 (5)	0.5253 (5)	0.45283 (19)	0.062 (2)
C21	0.4801 (6)	0.5469 (5)	0.47582 (18)	0.069 (3)
C22	0.5984 (5)	0.4523 (5)	0.4481 (2)	0.064 (2)
C23	0.2772 (5)	0.5540 (4)	-0.13095 (19)	0.054 (2)
C24	0.2902 (5)	0.3314 (4)	-0.12920 (19)	0.055 (2)
C25	0.2203 (5)	0.2300 (4)	0.01920 (19)	0.051 (2)
C26	0.5029 (4)	0.3112 (4)	0.15382 (18)	0.050 (2)
C27	0.2956 (5)	0.6188 (4)	0.20444 (19)	0.050 (2)
C28	0.6549 (5)	0.3220 (5)	0.35245 (18)	0.053 (2)
C29	0.2125 (6)	0.4121 (5)	0.4870 (2)	0.075 (3)
C30	0.1662 (7)	0.6320 (5)	0.4759 (2)	0.082 (3)
O1'	0.2375 (5)	0.5145 (4)	-0.32953 (16)	0.087 (2)
O2'	-0.0092 (5)	0.6317 (4)	-0.3415 (2)	0.105 (3)
O3'	-0.3111 (4)	0.5260 (4)	-0.20181 (16)	0.087 (2)
O4'	-0.0497 (3)	0.4218 (3)	-0.19437 (12)	0.0538 (15)
C1'	0.0618 (7)	0.5322 (6)	-0.3349 (2)	0.070 (3)
C2'	-0.0522 (7)	0.4207 (5)	-0.3365 (2)	0.077 (3)
C3'	-0.2296 (6)	0.4423 (5)	-0.3070 (2)	0.074 (3)
C4'	-0.2055 (5)	0.4700 (5)	-0.2290 (2)	0.056 (2)

Table 2. Selected geometric parameters (Å, °)

O1—C28	1.303 (5)	O2'—C1'	1.222 (8)
O2—C28	1.225 (6)	O3'—C4'	1.184 (6)
C2—C23	1.527 (6)	O4'—C4'	1.338 (5)
C2—C24	1.538 (6)	C1'—C2'	1.496 (7)
C3—O4'	1.471 (4)	C2'—C3'	1.529 (7)
C6—C25	1.545 (6)	C3'—C4'	1.510 (6)
C8—C26	1.537 (6)	O1...O2'	2.65 (1)

C17—C28	1.521 (7)	O2...O1 ⁱ	2.73 (1)
C20—C29	1.521 (8)	O1'...O2 ⁱⁱ	2.73 (1)
C20—C30	1.532 (7)	O2'...O1 ⁱⁱ	2.65 (1)
O1'—C1'	1.297 (6)		
C1—C2—C23	109.1 (3)	C18—C17—C28	109.8 (4)
C1—C2—C24	114.4 (3)	C22—C17—C28	104.4 (3)
C3—C2—C23	107.4 (3)	C19—C20—C29	111.4 (4)
C3—C2—C24	111.4 (3)	C19—C20—C30	108.8 (4)
C23—C2—C24	108.0 (3)	C21—C20—C29	110.8 (4)
C2—C3—O4'	106.8 (2)	C21—C20—C30	109.3 (4)
C4—C3—O4'	109.5 (3)	C29—C20—C30	108.4 (4)
C1—C6—C25	113.0 (3)	O1—C28—O2	122.3 (4)
C5—C6—C7	107.2 (3)	O1—C28—C17	114.3 (4)
C5—C6—C25	108.3 (3)	O2—C28—C17	123.3 (3)
C7—C6—C25	113.7 (3)	C3—O4'—C4'	117.6 (3)
C7—C8—C26	111.3 (3)	O1'—C1'—O2'	123.4 (5)
C9—C8—C26	108.4 (3)	O1'—C1'—C2'	115.2 (5)
C14—C8—C26	109.0 (3)	O2'—C1'—C2'	121.3 (5)
C8—C14—C27	112.4 (3)	C1'—C2'—C3'	112.0 (4)
C13—C14—C27	107.7 (3)	C2'—C3'—C4'	115.8 (3)
C15—C14—C27	106.2 (3)	O3'—C4'—O4'	124.5 (4)
C16—C17—C28	110.7 (3)	O3'—C4'—C3'	124.6 (4)

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

All H atoms were placed in calculated positions on their corresponding O (O—H 0.85 Å) and C atoms (C—H 1.00 Å). These H atoms were not refined. The U_{iso} value of each H atom was assigned to be equal to the U_{eq} value of the parent atom plus 0.01. Selected geometric parameters for those atoms that are not part of the oleonic acid five-ring framework are listed. The omitted bond lengths have e.s.d.'s of 0.005 Å and the omitted bond angles have e.s.d.'s of 0.3°. The ω -scan width was $(0.90 + 0.35 \tan \theta)^\circ$, with a θ -scan rate of 0.75–2.75° min⁻¹. The scan angle was extended by 25% on each side of each peak for background measurement. Refinement was by full-matrix least-squares methods.

Data collection: *CAD-4 Manual* (Enraf–Nonius, 1988). Cell refinement: *CAD-4 Manual*. Data reduction: *NRCVAX DAT-RD2* (Gabe, Le Page, Charland, Lee & White, 1989). Program(s) used to solve structure: *NRCVAX SOLVER*. Program(s) used to refine structure: *NRCVAX LSTSQ*. Molecular graphics: *ORTEPII* (Johnson, 1976) in *NRCVAX*. Software used to prepare material for publication: *NRCVAX TABLES* (Version of January 1994).

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: BK1288). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CHI 2HU, England.

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Inclusion Complex of (S)-1,3-Butanediol with (S,S)-(+)-trans-2,3-Bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.4]nonane

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Abstract

(S)-1,3-Butanediol (guest), C₄H₁₀O₂, was found to be resolved from the racemate by inclusion crystallization with (S,S)-(+)-trans-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.4]nonane (host), C₃₃H₃₂O₄. The unit cell of the crystal contains two pairs of host and guest molecules. There are four crystallographically independent hydrogen bonds, which form a belt-like structure along the *b* axis of the unit cell. The inclusion complex appears to be stabilized by hydrogen bonds and van der Waals interactions.

Comment

An optically active host having a 4,5-bis(hydroxydiphenylmethyl)-1,3-dioxolane framework is one of the most useful hosts, because it is derived simply from optically active tartaric acid (Seebach, Beck, Imwinkelried, Roggo & Wonnacott, 1987) and furthermore, it is capable of efficiently resolving many racemates (Toda & Tanaka, 1988). A prediction of optimum host–guest pairs, however, is very difficult since the optical resolution capability is often changed dramatically by a slight difference in the chemical structure in a host (Toda, Sato, Nassimbeni & Niven, 1991; Toda, Tanaka, Leung, Meetsma & Feringa, 1994; Toda, Matsuda & Tanaka, 1991). To enable the prediction of optimal host–guest