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3α,4α-Epoxy-5α-androstan-17-one

J. A. PAIXÃO,[a] M. RAMOS SILVA,[a] M. J. DE ALMEIDA,[a] E. J. TAVARES DA SILVA,[b] M. L. SÁ E MELO[c] AND A. S. CAMPOS NEVES[b]

[a]*Departamento de Física, Fac. Ciências e Tecnologia, Universidade de Coimbra, P-3000 Coimbra, Portugal,* [b]*Lab. Química Farmacêutica, Faculdade de Farmácia, Universidade de Coimbra, P-3000 Coimbra, Portugal, and* [c]*Centro de Estudos Farmacêuticos, Lab. Química Farmacêutica, Fac. de Farmácia, Universidade de Coimbra, P-3000 Coimbra, Portugal. E-mail: jap@pollux.fis.uc.pt*

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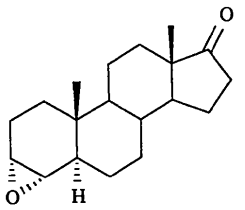
Abstract

The structure of the title compound, 3α,4α-epoxy-5α-androstan-17-one, $C_{19}H_{28}O_2$, shows evidence of the strain caused by the presence of an epoxy O atom bonded to C3 and C4 in the molecule. Ring *A* has a sizeable distortion and assumes a conformation intermediate between 10-β-sofa and 1,10-half chair. Ring *D* has a 14-α-envelope conformation. Cohesion of the crystal is due only to van der Waals interactions and weak intermolecular C—H···O interactions.

Comment

The title compound, (I), was prepared during work on the synthesis of formestane, an irreversible aromatase inhibitor which has been shown to be very effective in the treatment of estrogen-dependent breast cancer (Tavares da Silva, Sá e Melo & Campos Neves, 1996). The X-ray analysis unequivocally establishes the molecular structure as an α configuration [bowing angle 3.8 (2)°] and the stereochemistry of the epoxy O atom as 3α,4α.



(I)

An *ORTEP*II (Johnson, 1976) drawing of the molecule with the atomic numbering scheme is shown in Fig. 1. The distance between the terminal O atoms, O3 and O17, is 9.797 (4) Å. Bond lengths and angles of the non-H atoms are within the range of expected values (*International Tables for Crystallography*, 1992, Vol. C). Due to the epoxy O3 atom, ring *A* is highly distorted from its normal chair conformation. Hence, the short C3—C4 bond length and the larger than average C2—C3—C4 and C3—C4—C5 bond angles can clearly be attributed to the epoxy formation. Another short distance is C2—C3; this has also been observed in other related steroidal crystal structures with unsaturated cyclohexane rings (Ramos Silva *et al.*, 1996).

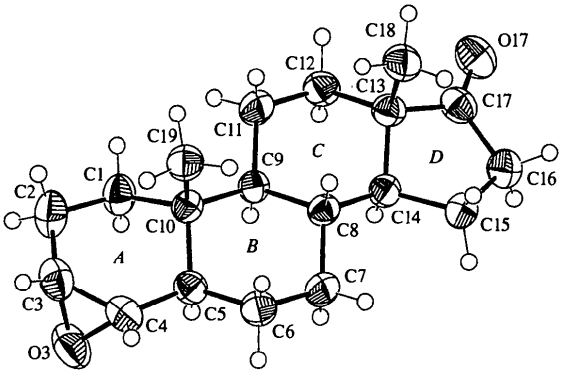


Fig. 1. *ORTEP*II (Johnson, 1976) plot of the title compound. Displacement ellipsoids are drawn at the 50% probability level, except for H atoms, which were given arbitrary radii.

The conformational features of the molecule are better described in terms of torsion angles and asymmetry parameters (Duax & Norton, 1975). The values $\Delta C_s(3) = 9.4\,(3)$, $\Delta C_2(3,4) = 16.8\,(4)$ and $\Delta C_2(1,2) = 53.3\,(4)°$ show that the conformation of ring *A* is intermediate between 10-β-sofa and 1,10-half chair, similar to that found in other steroids with extra rings connected to atoms C3 and C4 (Lisgarten, Palmer, Maes, Lisgarten & Wyns, 1995). Rings *B* and *C* have normal slightly flattened chair conformations, as shown by the smaller than 60° mean values of their torsion angles [56 (2) and 56 (5)° for rings *B* and *C*, respectively]. The five-membered *D* ring conformation is very similar to those found for similar steroids having a carbon C17 with an sp^2 hybridization (Weeks, Cooper, Norton, Hauptman & Fisher, 1971; Ramos Silva *et al.*, 1996). Ring *D* assumes a 14-α-envelope conformation [$\Delta C_s(14) = 2.3\,(3)$, $\varphi_m = 42.8\,(3)$ and $\Delta = -41.0\,(6)°$ (Altona, Geise & Romers, 1968)]. The mean value of 1.516 (1) Å obtained for the C13—C17 and C16—C17 distances is close to the expected value for a C_{sp^2}—C_{sp^3} bond (*International Tables for Crystallography*, 1992, Vol. C). The four atoms C13, C16, C17 and O17 are coplanar within experimental error, as can be seen from the sum of the valence angles about the C17 atom of 360 (1)°. The other valence angles on the *D* ring are all less than the tetrahedral angle of 109.5°.

The strain inherent in the *C*/*D* ring junction is responsible for the high values of the valence angles C12—C13—C17 and C8—C14—C15 (Geise, Altona & Romers, 1967), which are greater than those normally observed for quaternary- (109.5°) and tertiary-substituted C atoms (100.5°). The pseudo-torsion angle

C19—C10—C13—C18, which measures the twist along the molecule, is 2.97 (2)°.

Cohesion of the crystal is mainly the result of van der Waals interactions. There are no strong hydrogen bonds as the only possible donors are C atoms. There is a short contact between atoms C(3) and O(3) of neighbouring molecules which is less than the sum of the van der Waals radii, with a C(3)—H(3)···O(3) angle that could possibly qualify the interaction as a weak hydrogen bond [C(3)···O(3^i) 3.206 (4) Å and C(3)—H(3)···O(3^i) 132.4 (9)°; symmetry code: (i) $-x+2, y-\frac{1}{2}, -z+2$].

It should be noted that the absolute configuration known from chemical studies could not be reliably determined from our data because none of the atoms is a strong enough anomalous scatterer at the Mo $K\alpha$ wavelength.

Experimental

Oxidation of 5α-androstan-3-en-17-one, easily prepared from the available androstan-4-ene-3,17-dione in the presence of Zn/AcOH under ultrasonic irradiation (Salvador, Sá e Melo & Campos Neves, 1993), was carried out in dichloromethane with performic acid generated *in situ*. The main product of this reaction has been isolated and identified by IR, MS, ^{1}H and ^{13}C NMR spectroscopy as the title compound 3α,4α-epoxy-5α-androstan-17-one (Tavares da Silva, Sá e Melo & Campos Neves, 1996). Crystals suitable for X-ray experiments were obtained by slow evaporation of a solution of the steroid in diethyl ether (m.p. 431–432 K).

Crystal data

$C_{19}H_{28}O_2$
M_r = 288.41
Monoclinic
$P2_1$
a = 9.269 (2) Å
b = 6.459 (2) Å
c = 13.989 (2) Å
β = 106.43 (2)°
V = 803.3 (3) Å^3
Z = 2
D_x = 1.192 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.7093 Å
Cell parameters from 25 reflections
θ = 11.43–20.07°
μ = 0.075 mm^{-1}
T = 293 (2) K
Rectangular plate
0.49 × 0.49 × 0.12 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
Profile data from ω–2θ scans
Absorption correction: none
3044 measured reflections
1528 independent reflections
1204 reflections with $I > 2\sigma(I)$

R_{int} = 0.027
θ_{max} = 25°
$h = -11 \rightarrow 11$
$k = 0 \rightarrow 7$
$l = -16 \rightarrow 16$
3 standard reflections
frequency: 120 min
intensity decay: 2.5%

Refinement

Refinement on F^2
$R(F)$ = 0.0348
$wR(F^2)$ = 0.1036
S = 1.004
1528 reflections
192 parameters
$w = 1/[\sigma^2(F_o^2) + (0.0575P)^2 + 0.1427P]$
where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.137 e Å^{-3}
$\Delta\rho_{min}$ = −0.131 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

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

C5—C4	1.510 (4)	C4—O3	1.443 (4)
C5—C10	1.552 (3)	C4—C3	1.457 (4)
C10—C1	1.533 (4)	C3—O3	1.442 (4)
C14—C15	1.534 (4)	C3—C2	1.494 (4)
C14—C13	1.535 (3)	C17—O17	1.207 (3)
C13—C17	1.516 (4)	C17—C16	1.515 (4)
C1—C2	1.536 (4)	C15—C16	1.537 (4)
C8—C14—C15	120.8 (2)	O17—C17—C16	125.5 (3)
C17—C13—C12	117.6 (2)	O17—C17—C13	126.1 (3)
O3—C4—C3	59.7 (2)	C16—C17—C13	108.4 (2)
C3—C4—C5	121.5 (2)	C3—O3—C4	60.7 (2)
C4—C3—C2	120.2 (2)		
C4—C5—C10—C1	−54.8 (3)	C5—C4—C3—C2	−2.7 (5)
C5—C10—C1—C2	62.9 (3)	C4—C3—C2—C1	8.4 (5)
C10—C5—C4—C3	27.1 (4)	C10—C1—C2—C3	−40.1 (4)

The structure was solved by direct methods. The H atoms were placed at calculated positions and refined as riding using the *SHELXL*93 (Sheldrick, 1993) defaults O—H = 0.82, C—H = 0.93 Å and U(H) = 1.5U_{eq}(parent atom). Examination of the crystal structure with *PLATON* (Spek, 1995) showed that there were no solvent-accessible voids in the crystal lattice. All calculations were performed on a Pentium 150 MHz PC running LINUX.

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989). Cell refinement: *CAD-4 Software*. Data reduction: *SDP-Plus* (Frenz, 1985). Program(s) used to solve structure: *MULTAN*11/82 (Main *et al.*, 1982). 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: NA1273). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Succinyl Oleanolic Acid

JIAN YANG,[a] J. WILSON QUAIL[a] AND ZONGCHAO JIA[b]*

[a]*Department of Chemistry, University of Saskatchewan, Saskatoon, Saskatchewan, Canada S7N 5C9, and* [b]*Department of Biochemistry, Queen's University, Kingston, Ontario, Canada K7L 3N6. E-mail: jia@crystal.biochem.queensu.ca*

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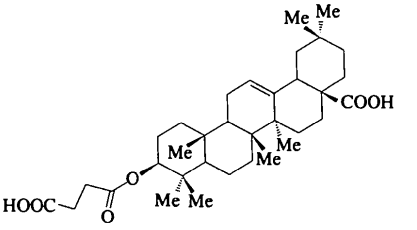
Abstract

The title compound, 3-[(2-carboxyethyl)carbonyloxy]-olean-12-en-28-oic acid, $C_{34}H_{52}O_6$, 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 bioavailabilty. 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.



(I)

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

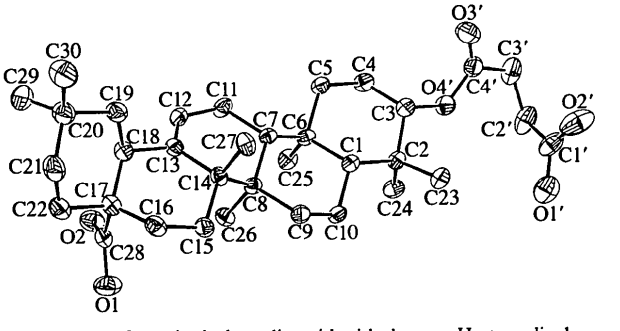


Fig. 1. View of succinyl oleanolic acid with the non-H-atom displacement ellipsoids drawn at the 50% probability level. H atoms have been omitted for clarity.