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3 α -Hydroxy-5 α -androstane-4,17-dione

L. C. R. ANDRADE,^a J. A. PAIXÃO,^a M. J. DE ALMEIDA,^a E. J. TAVARES DA SILVA,^b M. L. SÁ E MELO^b AND A. S. CAMPOS NEVES^b

^aDepartamento de Física, Faculdade de Ciências e Tecnologia, Universidade de Coimbra, P-3000 Coimbra, Portugal, and ^bCentro de Estudos Farmacêuticos, Laboratório de Química Farmacêutica, Faculdade de Farmácia, Universidade de Coimbra, P-3000 Coimbra, Portugal. E-mail: jap@pollux.fis.uc.pt

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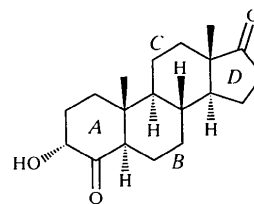
Abstract

The asymmetric unit of the title compound, C₁₉H₂₈O₃, contains two independent molecules with almost identical geometry. The molecules have a planar 5 α config-

uration as a result of a *trans*-A/B junction of the rings. The compound crystallizes in a triclinic cell, which is unusual for steroids. The molecules are linked head-to-tail *via* hydrogen bonds between the ring A hydroxyl group and the ketone group of ring D, forming two independent chains running along the *c* axis.

Comment

Our interest in preparing steroid aromatase inhibitors (Campos Neves *et al.*, 1999; Tavares da Silva *et al.*, 1996, 1997), clinically used as antitumor agents especially in the treatment of estrogen-positive breast cancers, led us to the title compound, 3 α -hydroxy-5 α -androstane-4,17-dione, (I). 3 $\alpha,4\beta$ -Dihydroxy-5 α -androstane-17-one, a key intermediate in the aforementioned synthesis, was selectively oxidized at C₄ with oxone, a mixed persulfate reagent, to give (I). The best conditions to perform this reaction (Tavares da Silva, 1997) use the oxidant in the presence of hydrated alumina (Hirano *et al.*, 1991) under ultrasonic irradiation. Furthermore, an efficient and environmentally friendly chemical process has been achieved for this particular transformation, using the combination of a solid supported reagent and sonochemistry.



(I)

The unit cell contains two crystallographically independent molecules (1 and 2) with almost identical geometry. An ORTEPII (Johnson, 1976) view of the two molecules with the atom-numbering scheme is shown in Fig. 1. The internal degree of isostructurality between the two molecules as defined by Kálman *et al.* (1991) is given by I_B^{25} (distances) = 99.5% and I_B^{23} (valency angles) = 99.5%. The *trans*-A/B ring junctions produce almost planar molecules [bowing angle 6.43 (10)° for molecule 1 and 7.8 (2)° for molecule 2], with an angle of 19.02 (6)° between the average least-squares planes of molecules 1 and 2. The distances between terminal O atoms were found to be 9.707 (6) and 9.657 (6) Å, and the values of the pseudo-torsion angles C19—C10—C13—C18 are 3.1 (2) and 1.7 (2)°, respectively, for molecules 1 and 2, indicating that molecule 1 is slightly more twisted than molecule 2. Rings A, B and C have slightly flattened chair conformations evidenced by the mean values of their torsion angles being less than 60% [57 (2), 56.0 (6) and 55 (5)° for molecule 1, and 57 (2), 56.0 (8) and 55 (5)° for molecule 2]. Ring D adopts a less common 13 β ,14 α -half-chair conformation distorted towards a 14 α -envelope, as can be seen from

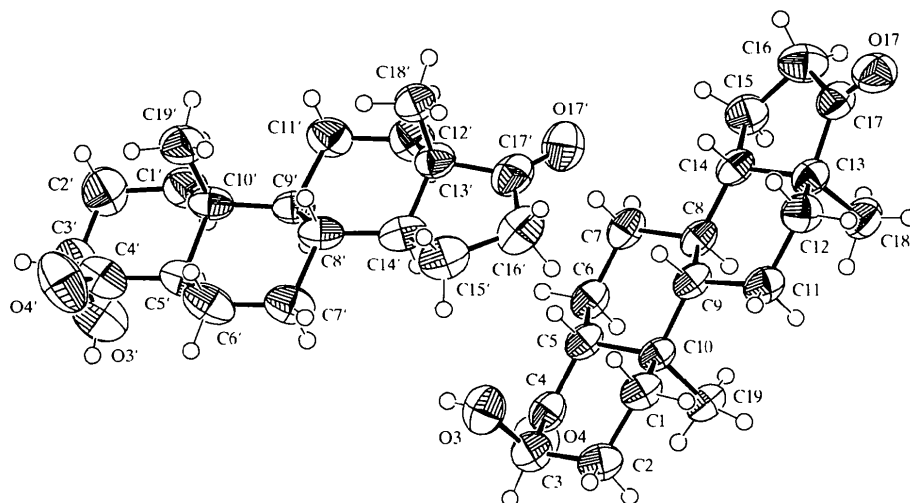


Fig. 1. ORTEP (Johnson, 1976) plot of the two symmetry independent molecules of the title compound. Displacement ellipsoids are drawn at the 50% probability level.

the asymmetry parameters ΔC_s (Duax & Norton, 1975) and pseudo-rotation parameters Δ and φ_m (Altona *et al.*, 1968): molecule 1, $\Delta C_s(14) = 10.6(3)^\circ$, $\Delta C_2(13,14) = 7.1(4)^\circ$, $\varphi_m = 42.4(3)^\circ$ and $\Delta = -12.2(6)^\circ$; molecule 2, $\Delta C_s(14) = 10.5(4)^\circ$, $\Delta C_2(13,14) = 6.8(4)^\circ$, $\varphi_m = 41.3(3)^\circ$ and $\Delta = -12.1(7)^\circ$.

The bond lengths and angles in (I) are within the normal ranges expected for this type of compound (Allen *et al.*, 1987). The molecules are linked head-to-tail *via* hydrogen bonds between the hydroxyl group of ring A and the ketone atom of ring D, forming chains running along the *c* axis. Each chain is built exclusively of molecules 1 or 2, and there are no strong hydrogen bonds between the two crystallographically independent molecules. The strength of the hydrogen bonds is similar in the two chains. Remarkably, the ketone O4 atoms are not involved in hydrogen bonding, except possibly for rather weak C—H \cdots O interactions. Interactions between the chains appear to be mainly of the van der Waals type.

It should be stated that because none of the atoms is a strong enough anomalous scatterer at the Mo *K* α wavelength, the absolute configuration was not determined from the X-ray data, and the assumed chirality of the molecule is that determined from the route of synthesis.

Experimental

To a solution of 3 α ,4 β -dihydroxy-5 α -androstan-17-one (50 mg, 0.16 mmol) in dichloromethane containing a small amount of methanol (1.7 ml), wet alumina (335 mg) and oxone (252 mg, 0.41 mmol) were added. The suspension, under an inert atmosphere, was sonicated in a cleaning bath ('Bandelin', 450 W, 35 kHz) at 295 K until the steroid was consumed

(30 min, thin-layer chromatography). After dilution with dichloromethane, the suspension was filtered, washed with aqueous NaHCO₃ and water, dried over magnesium sulfate and evaporated to dryness to give a crude material (43 mg, 87%) from which the title compound was isolated by crystallization. NMR: δ_H (500 MHz, CDCl₃, Me₄Si) 0.77 (3H, *s*, 19-H₃), 0.87 (3H, *s*, 18-H₃), 2.09 (1H, *ddd*, $J_{16\alpha,16\beta} = 19.0$, $J_{16\alpha,15\beta} = 9.5$, $J_{16\alpha,15\alpha} = 9.5$ Hz, 16 α -H), 2.14 (1H, *d*, $J_{3\alpha-OH,3\beta-H} = 3.5$ Hz, 3 α -OH; disappears with D₂O), 2.45 (1H, *dd*, $J_{16\beta,16\alpha} = 19.0$, $J_{16\beta,15\beta} = 9.0$ Hz, 16 β -H), 2.86 (1H, *dd*, $J_{5\alpha,6\beta} = 12.5$, $J_{5\alpha,6\alpha} = 3.0$ Hz, 5 α -H), 4.0 (1H, *ddd*, $J_{3\beta,2\beta} = 3.0$, $J_{3\beta,2\alpha} = 3.0$, $J_{3\beta-H,3\alpha-OH} = 3.5$ Hz, 3 β -H; collapses with D₂O to a *dd* of $J_{3\beta,2\beta} = 3.0$ and $J_{3\beta,2\alpha} = 3.0$ Hz); δ_C (50.3 MHz, CDCl₃, Me₄Si) 13.9 (CH₃, C19), 14.0 (CH₃, C18), 20.0 (CH₂), 21.1 (CH₂), 21.9 (CH₂), 29.4 (CH₂), 30.3 (CH₂), 31.7 (CH₂), 32.2 (CH₂), 34.8 (CH), 36.0 (CH₂), 43.2 (C_q), 47.9 (C_q), 51.4 (CH), 53.6 (CH), 54.6 (CH), 74.1 (CH, C3), 213.6 (C_q, C4), 221.3 (C_q, C17); *m/z* (EI): 304.2 (*M*⁺, 100%). Crystals of good quality suitable for X-ray analysis were grown from a mixture of ethyl acetate and hexane.

Crystal data

C₁₉H₂₈O₃
M_r = 304.43
 Triclinic
 P1
a = 7.869 (2) Å
b = 10.113 (3) Å
c = 10.771 (5) Å
 α = 76.21 (3) $^\circ$
 β = 85.78 (3) $^\circ$
 γ = 84.60 (3) $^\circ$
V = 827.6 (5) Å³
Z = 2

D_x = 1.222 Mg m⁻³
D_m not measured

Data collection

Enraf-Nonius CAD-4
 diffractometer

Mo *K* α radiation
 λ = 0.71073 Å
 Cell parameters from 25
 reflections
 θ = 8.92–12.43 $^\circ$
 μ = 0.081 mm⁻¹
T = 293 (2) K
 Prism
 0.51 × 0.24 × 0.12 mm
 Colourless

*R*_{int} = 0.016
 θ_{\max} = 27.41 $^\circ$

Profile data from ω - 2θ scans $h = -10 \rightarrow 10$
 Absorption correction: none $k = -13 \rightarrow 12$
 4431 measured reflections $l = -13 \rightarrow 13$
 4377 independent reflections 3 standard reflections
 2741 reflections with frequency: 180 min
 $I > 2\sigma(I)$ intensity decay: 1.3%

Refinement

Refinement on F^2 $(\Delta/\sigma)_{\max} = 0.001$
 $R[F^2 > 2\sigma(F^2)] = 0.039$ $\Delta\rho_{\max} = 0.196 \text{ e } \text{\AA}^{-3}$
 $wR(F^2) = 0.113$ $\Delta\rho_{\min} = -0.133 \text{ e } \text{\AA}^{-3}$
 $S = 1.005$ Extinction correction: none
 4377 reflections Scattering factors from
 403 parameters *International Tables for*
 H atoms constrained *Crystallography* (Vol. C)
 $w = 1/[\sigma^2(F_o^2) + (0.0577P)^2$
 $+ 0.0792P]$
 where $P = (F_o^2 + 2F_c^2)/3$

Table 1. Selected geometric parameters (\AA , $^\circ$)

C3—O3	1.429 (4)	C3'—O3'	1.415 (5)
C4—O4	1.213 (4)	C4'—O4'	1.209 (4)
C15—C16	1.540 (5)	C15'—C16'	1.532 (6)
C16—C17	1.509 (5)	C16'—C17'	1.501 (6)
C17—O17	1.214 (4)	C17'—O17'	1.218 (4)
C2—C3—C4	108.7 (3)	C4'—C3'—C2'	108.7 (3)
C5—C4—C3	114.6 (3)	C5'—C4'—C3'	114.5 (3)
C16—C17—C13	108.6 (3)	C16'—C17'—C13'	108.5 (3)

Table 2. Hydrogen-bonding geometry (\AA , $^\circ$)

$D-H \cdots A$	$D-H$	$H \cdots A$	$D \cdots A$	$D-H \cdots A$
O3—H28 \cdots O17'	0.82	2.04	2.813 (4)	158
O3'—H28' \cdots O17''	0.82	1.98	2.790 (4)	168

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

Examination of the structure with *PLATON* (Spek, 1998) showed that there were no solvent-accessible voids in the crystal lattice.

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989). Cell refinement: *CAD-4 Software*. Data reduction: *HELENA* (Spek, 1997). Program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997). Molecular graphics: *ORTEPII* (Johnson, 1976). Software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1300). Services for accessing these data are described at the back of the journal.

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Triterpenoide. XVII.† 3,28-Dimethoxy-3,11,28-trioxo-2,3-seco-18 β -olean-12-en-2,9 α -olid

ANDRZEJ GZELLA

Lehrstuhl für Organische Chemie der K. Marcinkowski Universität der Medizinischen Wissenschaften Poznań, ul. Grunwaldzka 6, 60-780 Poznań, Polen. E-mail: akgzella@eucalyptus.usoms.poznan.pl

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Abstract

The structure of the title compound, $C_{32}H_{46}O_7$, previously derived by spectroscopic methods, is confirmed. Steroidal ring *C* has a slightly distorted sofa form and all other six-membered rings have a chair conformation. Rings *B* and *C* are trans-fused, and rings *D* and *E* are cis-fused. The lactone ring has a conformation intermediate between envelope and half-chair.

† Teil XVI: Gzella (1999).