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17-Oxo-5α-androstane-3α,4β-diyl diacetate and 17-oxo-5β-androstane-3α,4β-diyl diacetate

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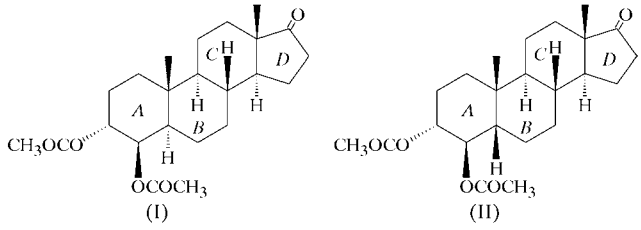
The title compounds, both $C_{23}H_{34}O_5$, are the 5α and 5β configurations of two diacetate epimers. The 5β-diacetate crystallizes in an hexagonal structure, unusual for steroid molecules. The unit cell has an accessible solvent volume of 358 Å^3, responsible for clathrate behaviour. The 5β-epimer also features some shorter than average bond lengths in the 3α,4β-acetoxy groups. The conformations of the molecules of both epimers are compared with those obtained through *ab initio* quantum chemistry calculations. Cohesion of the crystals can be attributed to van der Waals and weak molecular C—H···O interactions.

Comment

The title compounds, (I) and (II), are the diacetate forms of 3α,4β-dihydroxy-5α-androstan-17-one (Paixão, Andrade, de Almeida, Costa *et al.*, 1998) and 3α,4β-dihydroxy-5β-androstan-17-one (Andrade *et al.*, 2003), respectively. These diols have been prepared as new key intermediates in recently developed strategies for the syntheses of formestane (Tavares da Silva *et al.*, 1996, 2002), a potent aromatase inhibitor clinically used as an antitumour agent in the treatment of estrogen-dependent breast cancers, and of related ring *D* lactone derivates (Andrade *et al.*, 1999; Tavares da Silva *et al.*, 1997; Paixão, Andrade, de Almeida, Tavares da Silva *et al.*, 1998). Following our work on the determination of the molecular and crystal structures of potential aromatase inhibitors and intermediates of their syntheses, the present X-ray analysis aims to contribute to the elucidation of the different reactivities of the precursors of the above-mentioned intermediates (Tavares da Silva *et al.*, 2002).

ORTEPII (Johnson, 1976) drawings of the molecules of (I) and (II), with the corresponding atomic numbering schemes and ring labels, are shown in Figs. 1 and 2. The 5β-diacetate (II) crystallizes in a hexagonal structure, space group $P6_5$. During structure analysis it became evident that the hexagonal symmetry, most unusual for this type of compound, creates large accessible voids in the crystal structure that tend to host disordered solvent molecules. Crystals from two samples, *A* and *B*, prepared with different solvents, were used to collect crystal data, but both exhibited the same clathrate behaviour. This affects the diffraction pattern mostly at low scattering angles; this diffuse scattering effect was corrected with the *SQUEEZE* program (Spek, 2003). The reported X-ray results for this compound were obtained with a crystal from sample *A*, grown from diethyl ether/diisopropyl ether solution.



For both molecules under study, most bond lengths and angles are within the expected ranges (Allen *et al.*, 1987) [average values: Csp^3—Csp^3 = 1.532 (11) and 1.530 (14) Å, Csp^3—Csp^2 = 1.501 (15) and 1.502 (6) Å, C=O = 1.197 (6) and 1.195 (20) Å, Csp^3—O = 1.457 (1) and 1.451 (3) Å, and Csp^2—O = 1.349 (3) and 1.316 (2) Å, respectively, for the molecules of (I) and (II)]. The short C2—C3 bond lengths common to other related steroids were also found in this study (Tables 1 and 2). Compound (II) contains a very short C20=O20 bond, of 1.161 (5) Å, and a significantly shorter than average distance for both Csp^2—O bonds. This short C20=O20 bond distance is probably an artifact of the relatively large anisotropic displacement tensor of atom O20. The distances between the terminal atoms are 11.040 (5) and 10.95 (5) Å (O20···O17), and 10.684 (5) and 8.501 (5) Å (O22···C17) for the two molecules. The C19—C10—C13—C18 pseudo-torsion angles are 0.6 (3) and 0.6 (4)° for (I) and (II), showing that the steroid nuclei are essentially untwisted. Rings *A*, *B* and *C* have slightly flattened chair conformations, with average torsion angles of 52 (2), 56 (3) and 56 (2)°, respectively, for (I), and 56 (2), 54.5 (2) and 55 (2)° for (II);

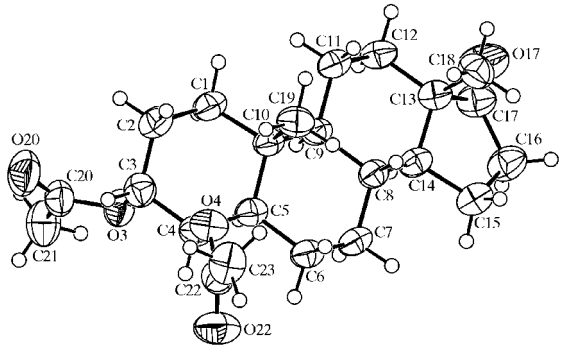


Figure 1
The molecular structure of (I), showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

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the presence of the acetoxy groups bonded to atoms C3 and C4 does not disturb the usual chair conformation of ring *A* of the steroid nucleus. The *A*/*B* ring junction is 5α,10β-quasi-*trans* [C1—C10—C5—C4 = −50.9 (4)° and C9—C10—C5—C6 = 59.4 (4)°] for (I) and 5β,10β-quasi-*cis* [C1—C10—C5—C4 = 49.6 (4)° and C9—C10—C5—C6 = 53.8 (3)°], with a bowing angle of 67.5 (1)°, for (II). Both five-membered *D* rings assume a conformation intermediate between a 14α-envelope and a 13β,14α-half-chair, being closer to the second in (I) and to the first in (II) [puckering parameters (Cremer & Pople, 1975; Boeyens, 1978), calculated using the atom sequence C13–C17: q_2 = 0.434 (4) and 0.421 (5) Å, φ_2 = 205.2 (5) and 208.0 (7)°; pseudorotation (Altona *et al.*, 1968) and asymmetry parameters: Δ = −13.8 (7) and −18.8 (7)°, φ_m = 44.5 (4) and 43.4 (3)°, ΔC_s(13) = 23.4 (4) and 24.5 (4)°, ΔC_s(14) = 10.4 (4) and 7.8 (4)°, and ΔC_2(13,14) = 8.3 (4) and 11.1 (4)°, respectively, for (I) and (II)]. The environment around atom C17 is planar [the sum of the valence angles is 360.0 (6)° in (I) and 360.0 (7)° in (II)]. For the 5α molecule (I), the 3α and 4β ring substituents are axial (Luger & Bulow, 1983), with angles of 4.9 (2) and 8.3 (2)°, respectively, while these substituents are equatorial, with angles of 68.4 (2) and 62.4 (2)°, respectively, for the 5β-epimer (II). The acetoxy groups attached to ring *A* are planar (the sums of the valence angles around atoms C20 and C22 are both equal to 360.0° within the s.u. values). For (I), the angles subtended by the C3/O3/C20/O20/C21 and C4/O4/C22/O22/C23 least-square planes to the C1–C17 reference plane are 89.44 (13) and 72.17 (12)°, respectively, and the angle between the C3/O3/C20/O20/C21 and C4/O4/C22/O22/C23 planes is 67.84 (12)°, showing a twist of the two groups; for (II), the angles between the acetoxy least-square planes and the plane of ring *A* are 82.10 (17) and 88.27 (13)°, and the angle between these acetoxy planes is 51.17 (18)°.

In order to infer whether the peculiarities of the 3α,4β-substituent bond lengths of (II) are intrinsic to the molecular configuration or solid-state effects, a quantum chemistry calculation of the optimized geometry of the isolated molecules of (I) and (II) was performed using the computer program *GAMESS* (Schmidt *et al.*, 1993). The Roothaan Hartree–Fock molecular orbital (MO) method was used for the *ab initio* calculations. An extended 6-31G(*d*,*p*) basis set was used with tight conditions for convergence of both the self-consistent field (SCF) cycles and the maximum energy and density gradients at the final optimized geometry (10^{-5} atomic units). The code was run in parallel on a cluster of 12 Compac XP1000 workstations (Alpha EV67 processors, 667 MHz) running Linux.

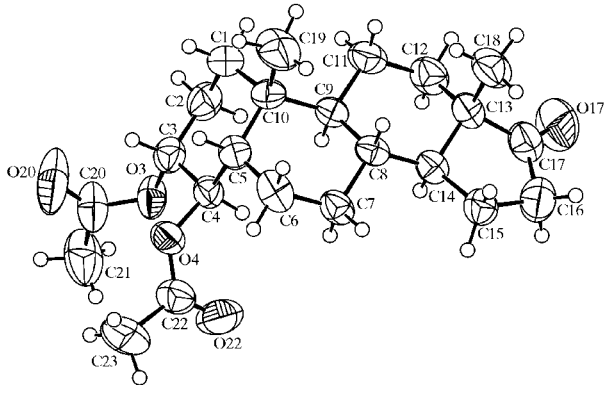

Figure 2
The molecular structure of (II), showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

The conformations of the steroid nuclei determined from the X-ray diffraction analysis are well reproduced by the *ab initio* MO calculations [for (II), C4—C5—C6—C7: calculated 72.06, observed 73.1 (4)°; O3—C3—C4—O4: calculated −65.1, observed −66.9°]. The bond angles and lengths are also well reproduced by the calculations; however, for both epimers, they predict Csp^2—O bond lengths that are closer to the values observed for the 5β-epimer [O3—C20: calculated for (I) = 1.329 Å and for (II) = 1.329 Å; O4—C22: calculated for (I) = 1.331 Å and for (II) = 1.328 Å]. The calculated values of the carbonyl C17═O17, C20═O20 and C22═O22 bonds are 1.19 Å for both epimers.

Owing to the absence of any strong donor group, cohesion of these structures is mainly achieved by van der Waals interactions and weak hydrogen bonds involving CH groups. In both compounds, a few short contacts with suitable geometry to be classified as potential weak hydrogen bonds can be identified between the methylene H atoms of the acetoxy groups and the carbonyl O atoms attached to either ring *D* or the acetoxy group of a neighbouring molecule.

Experimental

For the preparation of (II), 3α,4β-dihydroxy-5β-androstan-17-one (33.5 mg, 0.11 mmol) was dissolved in dry pyridine (1.5 ml) and acetic anhydride (0.3 ml) was added. After 120 h of stirring at room temperature, the solution was diluted with dichloromethane (100 ml) and the organic phase was washed with 10% aqueous hydrochloric acid (3 × 100 ml), 10% sodium hydrogen carbonate (2 × 100 ml) and water (2 × 100 ml), dried, and evaporated to dryness to give (II) (36.5 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si): δ 0.85 (3H, *s*, 19-H$_3$), 1.02 (3H, *s*, 18-H$_3$), 2.01 (3H, *s*, $COCH_3$), 2.04 (3H, *s*, $COCH_3$), 2.44 (1H, *dd*, *J*16β,16α = 19.0 Hz, *J*16β,15β = 8.0 Hz, 16β-H), 4.79 (1H, *ddd*, *J*3β,2α = 12.5 Hz, *J*3β,4α = 9.5 Hz, *J*3β,2α = 5.0 Hz, 3β-H), 5.38 (1H, *dd*, *J*4α,5β = 11.0 Hz, *J*4α,3β = 9.5 Hz, 4α-H); ^{13}C NMR (75.6 MHz, $CDCl_3$, Me_4Si): δ 13.8, 20.1, 20.9, 21.1, 21.2, 21.7, 23.3, 24.8, 25.0, 31.0, 31.6, 34.1, 35.0, 35.9, 37.0, 42.2, 46.9, 51.2, 71.4, 75.8, 170.6, 170.8, 221.1. Crystals of samples *A* and *B* suitable for X-ray analysis were obtained by slow evaporation of solutions of the steroid in diethyl ether/diisopropyl ether and acetone/*n*-hexane, respectively. The treatment of 3α,4β-dihydroxy-5α-androstan-17-one under the same conditions as described above gives an identical yield of (I). ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si): δ 0.86 (3H, *s*, 19-H$_3$), 1.02 (3H, *s*, 18-H$_3$), 2.07 (3H, *s*, $COCH_3$), 2.08 (3H, *s*, $COCH_3$), 2.45 (1H, *dd*, *J*16β,16α = 19.0 Hz, *J*16β,15β = 9.0 Hz, 16β-H), 4.84 (2H, *m*, 3-H, 4-H); ^{13}C NMR (75.6 MHz, $CDCl_3$, Me_4Si): δ 13.6, 13.8, 19.6, 21.1, 21.3, 21.7, 22.2, 24.4, 31.0, 31.4, 32.0, 34.8, 35.7, 35.8, 44.0, 47.7, 51.5, 55.0, 69.4, 73.2, 169.8, 169.9, 221.3. Crystals suitable for X-ray analysis were obtained by slow evaporation of a solution of the steroid in diethyl ether/diisopropyl ether.

Compound (I)

Crystal data

$C_{23}H_{34}O_5$	Mo $K\alpha$ radiation
M_r = 390.50	Cell parameters from 25 reflections
Orthorhombic, $P2_12_12_1$	θ = 4.8–9.3°
a = 6.742 (7) Å	μ = 0.08 mm^{-1}
b = 12.174 (4) Å	T = 293 (2) K
c = 25.893 (6) Å	Plate, colourless
V = 2125 (2) Å^3	0.50 × 0.45 × 0.10 mm
Z = 4	
D_x = 1.220 Mg m^{-3}	

Data collection

Enraf–Nonius CAD-4 diffractometer	θ_{max} = 27.6°
ω–2θ scans	$h = -8 \rightarrow 8$
5566 measured reflections	$k = -15 \rightarrow 15$
2812 independent reflections	$l = -33 \rightarrow 33$
1613 reflections with $I > 2\sigma(I)$	3 standard reflections
R_{int} = 0.035	frequency: 200 min
	intensity decay: 5.4%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0451P)^2 + 0.8677P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.041	$(\Delta/\sigma)_{max}$ = 0.047
$wR(F^2)$ = 0.127	$\Delta\rho_{max}$ = 0.20 e Å^{-3}
S = 1.00	$\Delta\rho_{min}$ = −0.20 e Å^{-3}
2812 reflections	
257 parameters	
H-atom parameters constrained	

Table 1
Selected geometric parameters (Å) for (I).

O3—C20	1.347 (4)	O20—C20	1.191 (5)
O4—C22	1.352 (4)	C2—C3	1.511 (5)

Compound (II)

Crystal data

$C_{23}H_{34}O_5$	Mo $K\alpha$ radiation
M_r = 390.50	Cell parameters from 25 reflections
Hexagonal, $P6_5$	θ = 8.8–18.5°
a = 22.885 (3) Å	μ = 0.08 mm^{-1}
c = 7.9582 (12) Å	T = 293 (2) K
V = 3609.4 (9) Å^3	Prism, colourless
Z = 6	0.37 × 0.24 × 0.24 mm
D_x = 1.078 Mg m^{-3}	

Data collection

Enraf–Nonius CAD-4 diffractometer	θ_{max} = 27.5°
ω–2θ scans	$h = -18 \rightarrow 25$
7826 measured reflections	$k = -16 \rightarrow 25$
2953 independent reflections	$l = -10 \rightarrow 10$
1369 reflections with $I > 2\sigma(I)$	3 standard reflections
R_{int} = 0.033	frequency: 150 min
	intensity decay: 6.5%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0825P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.046	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2)$ = 0.140	$\Delta\rho_{max}$ = 0.19 e Å^{-3}
S = 0.87	$\Delta\rho_{min}$ = −0.16 e Å^{-3}
2953 reflections	Extinction correction: *SHELXL97*
258 parameters	Extinction coefficient: 0.0041 (12)
H-atom parameters constrained	

Table 2
Selected geometric parameters (Å) for (II).

O3—C20	1.315 (4)	O20—C20	1.161 (5)
O4—C22	1.319 (5)	C2—C3	1.502 (5)

All H atoms were refined as riding on their parent atoms [C—H = 0.96–0.98 Å, and $U_{iso} = 1.5U_{eq}$(C) for methyl groups and $1.2U_{eq}$(C) for the other H atoms]. Owing to the absence of any significant anomalous scatterers, the absolute configurations of the molecules were not determined from the X-ray data but were known from the synthesis route and remained unchanged during the syntheses; Friedel pairs were therefore merged. A correction for diffuse effects due to the inclusion of disordered solvent molecules in the crystal structure was made for (I) using the SQUEEZE option of *PLATON* (van der Sluis & Spek, 1990; Spek, 2003). The total potential solvent volume per unit cell was calculated to be 358 Å^3 (9.9% of the cell volume). The main void is located around the origin (0.000, 0.000, −0.038), and has a volume of 356.3 Å^3 and a diffuse electron count of 8.9 electrons, as determined using SQUEEZE.

For both compounds, data collection: *CAD-4 Software* (Enraf–Nonius, 1989); cell refinement: *CAD-4 Software*; data reduction: *HELENA* (Spek, 1997); structure solution: *SHELXS97* (Sheldrick, 1997); structure refinement: *SHELXL97* (Sheldrick, 1997); molecular graphics: *HELENA* for (I) and *ORTEPII* (Johnson, 1976) for (II).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1786). Services for accessing these data are described at the back of the journal.

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