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17-Oxo-5β-hydroxyandrostan-3β-yl acetate

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Key indicators

Single-crystal X-ray study
T = 292 K
Mean σ(C–C) = 0.003 Å
R factor = 0.032
wR factor = 0.092
Data-to-parameter ratio = 8.1

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

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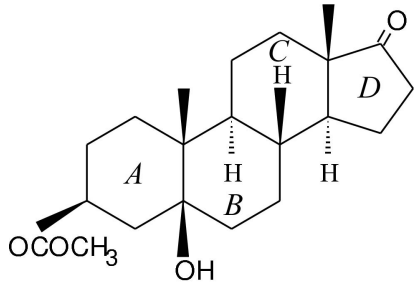
The title compound, $C_{21}H_{32}O_4$ crystallizes in a triclinic unit cell, which is very unusual for steroids. The asymmetric unit contains two independent molecules with almost identical geometry, although they are slighly twisted in opposite directions. These molecules form a dimer interconnected *via* hydrogen bonds. Both molecules have a *cis* *A*/*B* ring junction characteristic of a 5β-configuration, but differ in the orientation of their hydroxyl groups.

Comment

The title compound, (I), is the 3-acetate form of 3β,5β-dihydroxy-androstan-17-one, a by-product formed during a convergent synthesis recently developed for the preparation of the potent aromatase inhibitor formestane (Tavares da Silva *et al.* 2002), which is a steroid used clinically as an anti-tumour agent in the treatment of oestrogen-dependent breast cancer. Following our work on the elucidation of several androstane structures as potential aromatase inhibitors and intermediates of their syntheses, the present X-ray analysis aims to contribute to the elucidation of the observed different reactivities of the precursors of the above-mentioned intermediates (Tavares da Silva *et al.* 2002).



(I)

The unit cell of (I), which is the asymmetric unit, contains two crystallographically independent molecules, 1 and 2, with almost identical geometry. An *ORTEPII* (Johnson, 1976) drawing of both molecules, with the corresponding atomic numbering scheme, is shown in Fig. 1.

The internal degree of structural similarity between the two molecules (Kálmán *et al.*, 1991) can be inferred from the values $I_D^{(25)}$ (distances) = 99.6% and $I_D^{(23)}$ (valency angles) = 99.3%. Bond lengths and internal angles are within the expected ranges (Allen *et al.*, 1987), with mean values Csp^3—Csp^3 = 1.53 (1) and 1.53 (1) Å, Csp^3—Csp^2 = 1.51 (1) and 1.51 (2) Å, Csp^3—O = 1.45 (1) and 1.46 (1) Å, and Csp^2═O = 1.199 (7) and 1.194 (18) Å, for molecules 1 and 2, respectively.

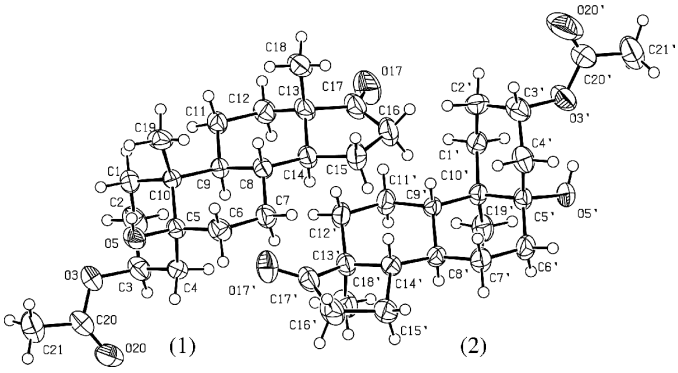


Figure 1
The two independent molecules of (I), showing the atomic numbering schemes. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

The higher standard deviation for this last mean value is due to a slightly shorter than average C20═O20 bond length of 1.178 (4) Å for molecule 2.

The *cis A*/*B* ring junctions characteristic of a 5β-configuration are evidenced by bowing angles between the least-squares plane of ring *A* and the C5–C17 plane of 70.10 (8) and 70.09 (8)°, for molecules 1 and 2, respectively. The corresponding distances between terminal O atoms were found to be 10.688 (3) and 10.762 (4) Å, respectively, and the values for the improper torsion angles C19—C10—C13—C18 are −1.3 (2) and 3.0 (2)°, respectively, indicating that the two molecules are only slightly twisted, although in opposite directions.

Rings *A*, *B* and *C* have slightly flattened chair conformations [mean values of the torsion angles are 53 (2), 55.0 (10) and 55 (2)°, respectively, for molecule 1, and 53.0 (10), 55.1 (5) and 56 (2)°, respectively, for molecule 2]. In both molecules, ring *D* adopts a 14α-envelope conformation distorted towards a 13β,14α-half-chair. Puckering parameters (Cremer & Pople, 1975), calculated using the atom sequence C13–C17, are q_2 = 0.413 (3) and 0.423 (3) Å and φ_2 = 206.0 (4) and 208.5 (4)°, and pseudo-rotation (Altona *et al.*, 1968) and asymmetry parameters (Duax & Norton, 1975) are Δ = −15.2 (4) and −20.5 (4)°, φ_m = 42.3 (2) and 43.2 (2)°, $\Delta C_s(14)$ = 9.1 (2) and 7.0 (2)° and $\Delta C_2(13,14)$ = 8.9 (2) and 12.2 (3)° for molecules 1 and 2, respectively. The 3β-acetoxy group, which does not disturb the usual chair conformation of ring *A*, is planar [the sums of the valency angles around C20 are 360.0 and 360.0° for molecules 1 and 2, respectively] and oriented axially in both molecules (Luger & Bulow, 1983), with α angles of 9.48 (14) and 7.53 (14)°, respectively, and corresponding angles between the 3β group and ring *A* of 82.09 (9) and 80.70 (12)°, respectively.

The two symmetry-independent molecules differ in the orientation of their hydroxyl groups. In molecule 1, the hydroxyl group establishes an intermolecular hydrogen bond towards the hydroxyl group of the other symmetry-independent molecule, while in molecule 2, the hydroxyl group establishes an intramolecular hydrogen bond with the O atom of the 3-acetoxy group bonded to the steroid nucleus (Fig. 2).

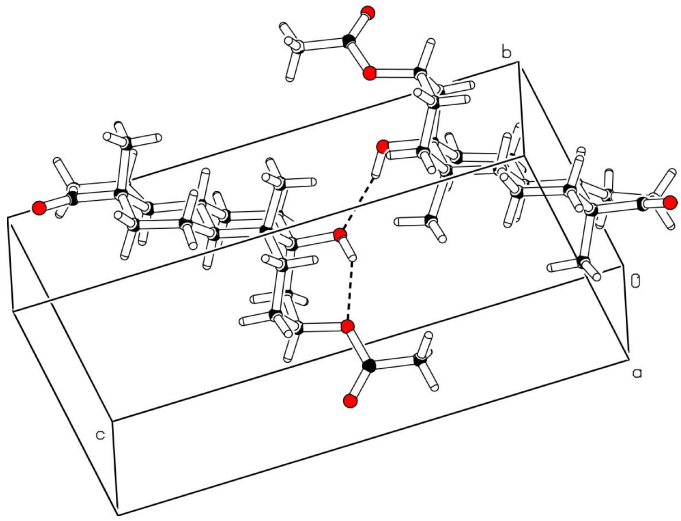


Figure 2
A view of the unit-cell contents of (I), showing the hydrogen-bonding scheme (dashed lines).

Experimental

3β,5β-Dihydroxyandrostan-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 washed with 10% aqueous hydrochloric acid (3 × 100 ml), 10% sodium hydrogencarbonate (2 × 100 ml) and water (2 × 100 ml), dried and evaporated to dryness to give (I) (yield 32.5 mg, 85%). Spectroscopic analysis: ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si, δ, p.p.m.): 0.86 (3H, *s*, 18-H3), 1.00 (3H, *s*, 19-H$_3$), 2.09 (3H, *s*, $COCH_3$), 2.28 (1H, *dd*, $J_{4\beta,4\alpha}$ = 15.5 Hz, $J_{4H,3\alpha}$ = 3.6 Hz, 4-H), 2.46 (1H, *dd*, $J_{16\beta,16\alpha}$ = 19.0 Hz, $J_{16\beta,15\beta}$ = 8.5 Hz, 16β-H), 5.25 (1H, *m*, 3α-H); ^{13}C NMR (75.6 MHz, $CDCl_3$, Me_4Si, δ, p.p.m.): 13.7, (CH_3, C18) 17.0, (CH_3, C19) 20.7, 21.5, 21.8, 24.4, 25.6, 27.4, 31.5, 34.1, 34.2, 35.4, 35.8, 40.6, 43.5, 47.7, 51.5, 71.3, 73.6, 169.4, (CO, C3), 220.9 (C17). Crystals suitable for X-ray experiments were obtained by slow evaporation of a solution of the steroid in methanol and checked by photographic methods prior to data collection.

Crystal data

$C_{21}H_{32}O_4$	Z = 2
M_r = 348.47	D_x = 1.214 Mg m^{-3}
Triclinic, *P*1	Cu $K\alpha$ radiation
a = 7.6386 (9) Å	Cell parameters from 25 reflections
b = 8.259 (2) Å	θ = 22.0–28.7°
c = 15.7610 (12) Å	μ = 0.66 mm^{-1}
α = 84.415 (12)°	T = 292 (2) K
β = 89.480 (8)°	Prism, colourless
γ = 74.529 (19)°	0.20 × 0.20 × 0.07 mm
V = 953.6 (3) Å^3	

Data collection

Enraf–Nonius MACH3 diffractometer	R_{int} = 0.016
Profile data from ω scans	θ_{max} = 71.8°
Absorption correction: ψ scan (North *et al.*, 1968)	h = −9 → 9
T_{min} = 0.869, T_{max} = 0.951	k = −10 → 10
7274 measured reflections	l = −19 → 19
3750 independent reflections	3 standard reflections
3510 reflections with $I > 2\sigma(I)$	frequency: 180 min
	intensity decay: 10.7%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0556P)^2 + 0.0858P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.032$	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2) = 0.092$	$\Delta\rho_{max} = 0.14$ e Å^{-3}
$S = 1.06$	$\Delta\rho_{min} = -0.16$ e Å^{-3}
3750 reflections	
463 parameters	
H atoms treated by a mixture of independent and constrained refinement	

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

D—H···A	D—H	H···A	D···A	D—H···A
O5—H5···O5′	0.90 (3)	2.11 (3)	2.983 (2)	165 (3)
O5′—H5′···O3′	0.84 (3)	2.07 (3)	2.798 (2)	144 (3)

For hydroxyl H atoms the coordinates were freely refined, with U_{iso}(H) = 1.2U_{eq}(O). All other H atoms were refined as riding on their parent atoms, with C—H distances in the range 0.96–0.98Å and with U_{iso}(H) = 1.2U_{eq}(C), or 1.5U_{eq}(C) for methyl groups. The absolute configuration was not determined from the X-ray data, as no strong anomalous scatterer was present, but was known from the synthesis route. Friedel pairs were merged before refinement. The rather large linear decay of the intensity with exposure time appears to be related to the crystal and not to the source and it suggests that the compound is radiation sensitive.

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, 1997); 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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