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17-Oxo-5α-androst-6-en-3β-yl acetate

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In the title compound, $C_{21}H_{30}O_3$, a potential inhibitor of aromatase, all rings are fused *trans*. Rings *A* and *C* have chair conformations which are slightly flattened, whereas the conformation of ring *B* is close to a half-chair. Ring *D* has a 14α-envelope conformation. The steroid nucleus has a small twist, as shown by the C19—C10···C13—C18 (steroid numbering) torsion angle of −6.9 (3)°. *Ab initio* calculations of the equilibrium geometry of the molecule reproduce this small twist, which appears to be due to the conformation of ring *B* rather than to packing effects.

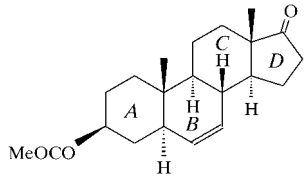
Comment

Aromatase (oestrogen synthetase) is a cytochrome P-450 enzyme complex which catalyzes the conversion of androgens, androstenedione and testosterone into oestrogens, oestrone and oestradiol (Thomson & Siiteri, 1974; Miller & Santem, 2001). Aromatization of androgens is thought to proceed with three sequential oxygenations at the C19 position. In the third step, the angular methyl group at C19 and the 1β,2β H atoms are eliminated, resulting in the aromatization of the *A* ring of the androgen to form the oestrogen.

Steroid analogues of androstenedione with substituents at C4, C6, C7, C14 and C19 are known to be potent inhibitors of aromatase (Brodie & Njar, 2000; Brodie & Long, 2001), and for this reason they may be of value in the treatment of oestrogen-dependent diseases. Indeed, some of these compounds, namely formestane (Lentaron) and examestane (Aromasin), have already been approved for breast cancer therapy (Brueggemeier, 2002; Buzdar, 2003).

The biological activity of these steroids and their ability to bind to the enzyme depends on whether the configuration at C5 is α or β, due to the shape of the two epimers (Laurence *et al.*, 1986). The 5α steroids are flat, whereas the 5β epimers are bent at the *A*/*B* ring junctions. Structure–activity relationships and recent aromatase modelling studies have revealed the existence of a hydrophobic binding pocket with a limited accessible volume in the region corresponding to the β side, rather than the α side, of the C4, C6 and C7 positions of the androstenedione substrate (Numazawa *et al.*, 2002).

The title compound, (I), is a key intermediate in the synthesis of new steroid inhibitors, possibly including inactivators of aromatase, and is particularly interesting due to the presence of a strategic double bond in the *B* ring which is easily functionalized. Furthermore, compound (I) itself is a potential aromatase inhibitor, as it combines the steric requirements with the presence of the C17 carbonyl group, which is crucial to the inhibition of the enzyme. The preliminary biological evaluation of (I) is currently in progress.



(I)

A view of the molecule of (I), with the corresponding atomic numbering scheme, is shown in Fig. 1. Bond lengths and angles are within the expected ranges (Allen *et al.*, 1987), with average distances Csp^3—Csp^3 = 1.53 (1), Csp^2=Csp^2 = 1.317 (4), Csp^3—Csp^2 = 1.503 (8), O—Csp^3 = 1.452 (4), O—Csp^2 = 1.322 (6) and O=Csp^2 = 1.200 (6) Å. All ring junctions are *trans*. Rings *A* and *C* have average torsion angles of 55.2 (13) and 57.5 (15)°, respectively, and slightly flattened chair conformations, as shown by the Cremer & Pople (1975) puckering parameters [ring *A* (C1–C5/C10): Q = 0.567 (4) Å, θ = 6.9 (4) and φ = 254 (3)°; ring *C* (C8/C9/C11–C14): Q = 0.590 (3) Å, θ = 5.7 (3) and φ = 279 (3)°]. The conformation of ring *B*, which contains a double bond between atoms C6 and C7, is close to a half-chair, with a weighted average torsion angle of 43 (9)° and a pseudo-binary axis running through the middle of the C6—C7 and C9—C10 bonds [asymmetry parameter (Duax & Norton, 1975): ΔC_2(C6—C7) = 5.0 (4)°; puckering parameters (C5–C10): Q = 0.529 (3) Å, θ = 46.4 (3)° and φ = 276.0 (5)°].

The five-membered *D* ring has a 14-envelope conformation with an average torsion angle of 30 (6)°. The puckering parameters calculated using the atom sequence C13–C17 are q_2 = 0.411 (4) Å and φ_2 = 210.2 (5)° [pseudorotation (Altona *et*

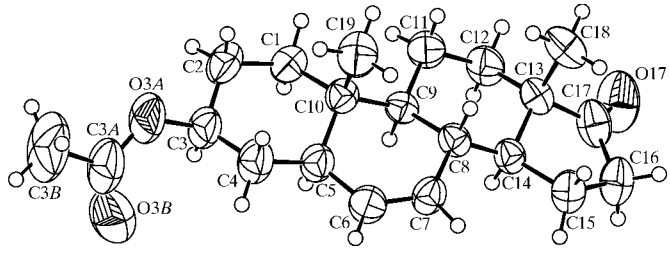


Figure 1
The molecular structure of (I), showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

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al., 1968) and asymmetry parameters: Δ = 23.7 (6), φ_m = 42.4 (2) and $\Delta C_s(14)$ = 5.4 (3)°].

The C3 substituent is equatorial to ring *A*. The acetyl group is planar, with an average deviation of the non-H atoms from the least-squares plane of 0.001 (5) Å. The angle between this plane and the least-squares plane of ring *A* is 58.34 (15)°. The distance between the terminal atoms, O17···C3*B*, is 13.156 (5) Å and the C19—C10···C13—C18 torsion angle is −6.9 (3)°, showing that the molecule is twisted. For *trans*-fused rings, this torsion angle rarely exceeds 4%, except when bulky sustituents, *e.g.* attached to ring *D* at C17, induce larger deviations due to steric effects (Andrade *et al.*, 2001). In the crystal structure of the closely related compound 3β-hydroxyandrosta-5,15-dien-17-one acetate (Khazheeva *et al.*, 1989), an even larger twist angle of 10° was observed.

In order to investigate whether this unusual twist would be present in the isolated molecule of (I), we have performed an *ab initio* molecular orbital Roothaan Hartree–Fock (MO–RHF) calculation of the equilibrium molecular geometry using the computer program *GAMESS* (Schmidt *et al.*, 1993). An extended 6-31G(*d*,*p*) basis set was used and tight conditions were applied for the self-consistent field convergence (SCF) cycles and location of the equilibrium geometry, the final electron-density variation at the end of the SCF cycles and the maximum energy gradient at the end of the geometry optimization being less than 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.

The conformation of the steroid nucleus as determined from the X-ray data is well reproduced by the MO–RHF calculations, the mean deviation of bond lengths and angles being 0.012 Å and 0.52°. The largest deviation between the two geometries is the torsion angle of the acetyl susbtituent, which has some rotational freedom around O3*A*—C3. The calculated value of the C3*A*—O3*A*—C3—C2 torsion angle for the isolated molecule is 154.2°, compared with the value measured in the crystal of 151.1 (4)°.

Interestingly, the equilibrium geometry of the isolated molecule also features a sizeable C19—C10···C13—C18 twist angle of −8.2°, compared with the experimental value of −6.9 (3)°. It can be concluded that the observed twist is not due to packing effects but probably arises from the unusual conformation of ring *B*, due to the C6═C7 double bond.

There are no strong hydrogen bonds in the structure of (I), due to the absence of standard donor groups, and thus cohesion of the crystal structure is maintained through weak intermolecular interactions. A short contact is present between one of the H atoms attached to atom C1 and atom O17, and this can be classified as one of the weak interactions. Another short contact exists between the H atom bound to atom C3 and atom O3*B*, which may exert some influence in the orientation of the acetyl group.

Experimental

Oxidation of commercially available dehydroepiandrosterone acetate according to the procedures described by Salvador & Clark (2001) afforded the compound 7,17-dioxo-androst-5-en-3β-yl acetate, which in turn was reduced using zinc/acetic acid/ultrasound (Salvador *et al.*, 1993), to give a mixture of the two isomers of (I). Crystals of (I) were obtained by fractional crystallization from *n*-hexane [m.p.: 416.0 (5) K]. Spectroscopic analysis, IR: 1726, 1739, 2867, 2948, 3004 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 0.83 (*s*, 18-H3), 0.91 (*s*, 18-H3), 2.04 (*s*, CH_3CO), 4.73 (*m*, 3α-H); ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ): 126.87, 131.25 (C6 and C7), 170.573 (CH_3CO), 220.47 (C17), 73.37 (C—O).

Crystal data

$C_{21}H_{30}O_3$
M_r = 330.45
Orthorhombic, $P2_12_12_1$
a = 12.6847 (17) Å
b = 9.2934 (17) Å
c = 16.266 (3) Å
V = 1917.5 (6) Å^3
Z = 4
D_x = 1.145 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 5.3–18.6°
μ = 0.08 mm^{-1}
T = 293 (2) K
Block, colourless
0.25 × 0.17 × 0.15 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
Profile data from $\omega/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.941, T_{max} = 0.988
4760 measured reflections
2485 independent reflections
1252 reflections with $I > 2\sigma(I)$
R_{int} = 0.047
θ_{max} = 27.5°
$h = -16 \rightarrow 16$
$k = -12 \rightarrow 0$
$l = -21 \rightarrow 0$
3 standard reflections
frequency: 180 min
intensity decay: 1.9%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.044
$wR(F^2)$ = 0.130
S = 1.01
2485 reflections
220 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0599P)^2 + 0.1192P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.12 e Å^{-3}
$\Delta\rho_{min}$ = −0.13 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

C6—C7	1.317 (4)		
C3*A*—O3*A*—C3—C2	151.2 (4)	C19—C10—C13—C18	−6.9 (3)

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C1—H1*B*···O17^{i}	0.97	2.49	3.263 (4)	137
C3—H3···O3*B*	0.98	2.38	2.683 (5)	97

Symmetry code: (i) $\frac{3}{2} - x, 1 - y, z - \frac{1}{2}$.

All H atoms were refined as riding on their parent atoms using *SHELXL*97 (Sheldrick, 1997) defaults [C—H = 0.93–0.98 Å and U_{iso}(H) = 1.5U_{eq}(C) for methyl H atoms and 1.2U_{eq}(C) for the other H atoms]. The absolute configuration was not determined from the X-ray data but was known from the synthesis route. Due to the lack of any significant anomalous scattering at the Mo $K\alpha$ wavelength, Friedel pairs were merged before refinement.

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: *HELENA* (Spek, 1997); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1627). Services for accessing these data are described at the back of the journal.

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