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3,17-Dioxoandrost-4-en-4-yl acetate

L. C. R. Andrade,[a] J. A. Paixão,[a] M. J. M. de Almeida,[a] F. M. Fernandes Roleira[b] and E. J. Tavares da Silva[b]*

[a]CEMDRX, Department of Physics, University of Coimbra, P-3004-516 Coimbra, Portugal, and [b]Centro de Estudos Farmacêuticos, Laboratório de Química Farmacêutica, Faculty of Pharmacy, University of Coimbra, P-3000-295 Coimbra, Portugal
Correspondence e-mail: jap@pollux.fis.uc.pt

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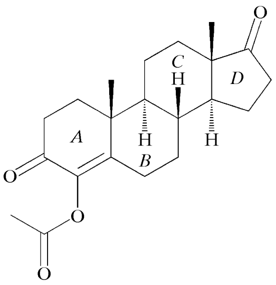
The title compound, $C_{21}H_{28}O_4$, has a 4-acetoxy substituent positioned on the steroid α face. The six-membered ring *A* assumes a conformation intermediate between 1α,2β-half chair and 1α-sofa. A long Csp^3—Csp^3 bond is observed in ring *B* and reproduced in quantum-mechanical *ab initio* calculations of the isolated molecule using a molecular-orbital Hartree–Fock method. Cohesion of the crystal can be attributed to van der Waals interactions and weak C—H···O hydrogen bonds.

Comment

Following our interest in preparing steroidal enzymatic inhibitors aimed at breast cancer treatment and in studying their structure–activity relationships (Cepa *et al.*, 2005), the title compound, (I), which is the acetate derivative of formestane, was prepared as previously described in the literature (Marsh *et al.*, 1985). We report here the molecular structure of (I) determined by single-crystal X-ray analysis, and compare it with that of the free molecule as given by quantum-mechanical *ab initio* calculations.



(I)

An *ORTEPII* (Johnson, 1976) plot of (I) is shown in Fig. 1. The 4-acetoxy substituent is positioned on the α face of the steroid nucleus. Average values for the atomic distances are in good agreement with reported values (Allen *et al.*, 1987), although for the Csp^3—Csp^3 bonds, extreme values of 1.514 (3) (C12—C13) and 1.569 (3) Å (C9—C10) were found, deviating significantly from the average value of 1.535 (14) Å. The abnormally large value is probably due to the severe distortion of ring *A* (C1–C5/C10). A similar C9—C10 bond length was observed for one of the non-equivalent molecules in the asymmetric unit of formestane [1.571 (3) Å; Griffin *et al.*, 1980].

As a consequence of the C4═C5 double bond present in ring *A*, this ring assumes a conformation intermediate between 1α,2β-half chair and 1α-sofa [asymmetry parameters (Duax & Norton, 1975): $\Delta C_2(1,2)$ = 12.5 (3)°, $\Delta C_s(1)$ = 13.7 (2)° and $\Delta C_s(3)$ = 45.1 (2)°]. Rings *B* (C5–C10) and *C* (C8/C9/C11–C14) have sightly distorted chair conformations, with average torsion angles of 54.0 (18) and 55 (2)°, respectively. The five-membered ring *D* (C13–C17) has a 14α conformation, most common for these 17-one steroids [puckering parameters (Cremer & Pople, 1975): q_2 = 0.417 (3) Å and φ_2 = 215.6 (4)°; pseudorotation (Altona *et al.*, 1968) and asymmetry parameters (Duax & Norton, 1975): Δ = −34.4 (4)°, φ_m = 42.7 (1)°, $\Delta C_s(14)$ = 0.7 (2)°, $\Delta C_2(13,14)$ = 20.0 (2)°]. The distance between terminal atoms O3 and O17 is 10.564 (2) Å. The C19—C10···C13—C18 pseudo-torsion angle of −0.06 (19)° indicates that the molecule is not twisted. The dihedral angle between the least-squares plane of the four non-H atoms of the acetate group and that of ring *A* is 79.78 (10)°.

In order to check whether the observed large deviations from the mean of the C9—C10 and C12—C13 bond lengths were intrinsic to the free steroid molecule or rather due to an influence of crystal packing, we have performed a quantum mechanical calculation of the equilibrium geometry of the free molecule. These calculations were performed with the computer program *GAMESS* (Schmidt *et al.*, 1993). A molecular-orbital Roothan Hartree–Fock method was used with an extended 6-31G(d,p) basis set. Tight conditions for convergence of both the self-consistent field cycles and the maximum density and energy gradients were imposed (10^{-5}

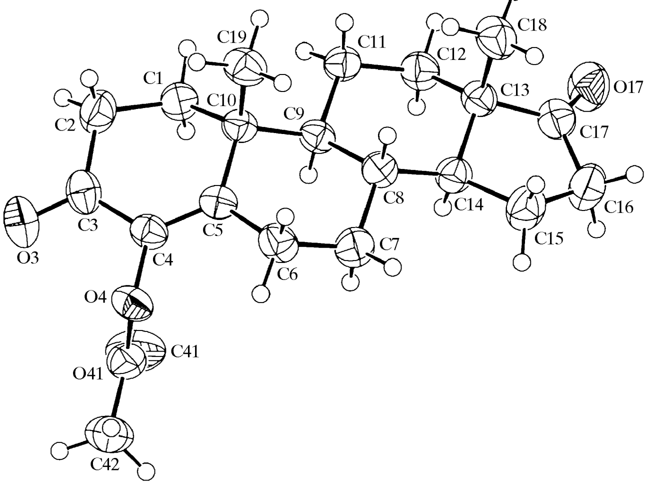


Figure 1
A plot of the title compound. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

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atomic units). The programs were run on a Pentium IV PC (3.0 GHz) running Linux. Interestingly, the calculations reproduce the long C9—C10 bond (calculated value 1.570 Å). For the shorter Csp^3—Csp^3 bond, the calculations give a slightly higher value than the observed value (calculated value 1.526 Å). Overall, there is a very good agreement between the remaining calculated and observed bond lengths. However, the equilibrium geometry of the isolated molecule has a significantly more twisted steroid nucleus (calculated pseudo-torsion angle C19—C10···C13—C18 = 4.9°). There is considerable freedom of rotation of the acetoxy group around the C4—O4 and O4—C41 bonds, as evidenced by the torsion angles C3—C4—O4—C41 [experimental 80.0 (2)°; calculated 77.0°] and C4—O4—C41—O41 [experimental 0.4 (4)°; calculated 15.4°].

Owing to the absence of a strong hydrogen-bond donor, cohesion of the structure of (I) is mainly achieved by van der Waals and weak C—H···O interactions. One intramolecular C—H···O short contact between the single-bonded O atom of the 4-acetoxy group and a neighbouring H atom of ring *B* is present [C6—H6*A*···O4 = 2.808 (5) Å]. There are, in addition, two intermolecular C—H···O short distances of 3.357 (6) and 3.459 (6) Å between H atoms of rings *B* and *C* and O atoms.

Experimental

To an ice-cooled solution of formestane (0.3 g, 0.99 mmol) in pyridine (5.0 ml), acetyl chloride (0.11 ml, 1.48 mmol) was added, and the reaction was stirred for 3 h until completion. Dichloromethane (100 ml) was then added, and the organic layer was washed with aqueous 0.25 *N* HCl (2 × 100 ml), 10% $NaHCO_3$ (2 × 100 ml) and water (2 × 100 ml), dried over anhydrous $MgSO_4$ and evaporated to dryness giving the desired title compound as a yellow crystalline solid (yield 0.335 g, 98%). Crystals of (I) of good quality suitable for X-ray crystallographic analysis were grown from ethyl acetate [m.p. 457–458 K; literature m.p. 457.0–457.5 K (Marsh *et al.*, 1985)]. IR (NaCl salt plate, ν, cm^{-1}): 1758, 1735, 1681, 1625; ^{1}H NMR ($CDCl_3$): δ 0.91 (*s*, 3H, 18-H_3), 1.27 (*s*, 3H, 19-H_3), 2.24 [*s*, 3H, $CH_3C(O)O$], 2.73 (*ddd*, 1H, $J_{6\alpha-6\beta}$ = 15.0 Hz, $J_{6\alpha-7\alpha}$ = 4.0 Hz, $J_{6\alpha-7\beta}$ = 2.5 Hz, 6α-H).

Crystal data

$C_{21}H_{28}O_4$
M_r = 344.43
Orthorhombic, $P2_12_12_1$
a = 11.5681 (3) Å
b = 12.0702 (3) Å
c = 13.512 (2) Å
V = 1886.6 (3) Å^3
Z = 4
Cu $K\alpha$ radiation
μ = 0.66 mm^{-1}
T = 294 (2) K
0.36 × 0.17 × 0.17 mm

Data collection

Enraf–Nonius MACH-3 diffractometer
Absorption correction: ψ scan (North *et al.*, 1968)
$T_{\min}$ = 0.851, $T_{\max}$ = 0.890
3577 measured reflections
2135 independent reflections
1795 reflections with $I > 2\sigma(I)$
$R_{\rm int}$ = 0.022
3 standard reflections
frequency: 300 min
intensity decay: 2.2%

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.029
$wR(F^2)$ = 0.088
S = 1.09
2128 reflections
230 parameters
H-atom parameters constrained
$\Delta\rho_{\max}$ = 0.16 e Å^{-3}
$\Delta\rho_{\min}$ = −0.15 e Å^{-3}

Table 1
Selected bond lengths (Å).

O4—C4	1.409 (3)	C4—C5	1.334 (3)
C2—C3	1.498 (3)	C9—C10	1.569 (3)
C3—C4	1.465 (3)	C12—C13	1.514 (3)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C6—H6*A*···O4	0.97	2.34	2.808 (3)	109
C6—H6*B*···O3^{i}	0.97	2.42	3.358 (3)	164
C11—H11*B*···O41^{ii}	0.97	2.54	3.459 (3)	159

Symmetry codes: (i) $-x, y-\frac{1}{2}, -z+\frac{3}{2}$; (ii) $-x+\frac{1}{2}, -y+1, z+\frac{1}{2}$.

All H atoms were refined as riding on their parent atoms, with C—H = 0.96–0.98 Å and $U_{\rm iso}$(H) = 1.2$U_{\rm eq}$(C) or 1.5$U_{\rm eq}$(methyl C). The absolute configuration was not determined from the X-ray data but was known from the synthesis route. Friedel pairs were merged before refinement.

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989); cell refinement: *CAD-4 Software*; data reduction: *PLATON* (Spek, 2003); 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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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3116). Services for accessing these data are described at the back of the journal.

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