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Conformation of 17-chloro-16-formylandrosta-5,16-dien-3β-yl acetate and 17-chloroandrosta-5,16-dien-3β-yl acetate

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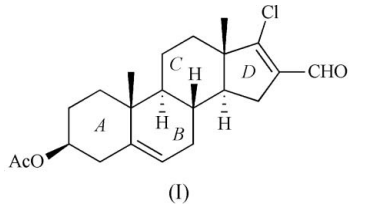
In the title compounds, $C_{22}H_{29}ClO_3$, (I), and $C_{21}H_{29}ClO_2$, (II), respectively, the *B* rings adopt a half-chair conformation and the *D* rings adopt an envelope conformation. A twist of the steroid skeleton of both compounds is observed. There is a positional disorder of the acetoxy group of (II), with the terminal atoms disordered over two positions with near equal occupancy. Quantum-mechanical *ab initio* calculations using a molecular orbital Hartree–Fock method were performed for the isolated molecules, thus allowing the distinction within the structural features of these two androstane derivatives of which characteristics are intrinsic to the molecules and which are due to packing effects. The skeletal twisting was found to be innate to the molecules, while the acetoxy disorder is due to packing effects.

Comment

Treatment of 17-oxoandrost-5-en-3β-yl acetate with $POCl_3$ and dimethylformamide (Vilsmeier reagent) afforded 17-chloro-16-formylandrosta-5,16-dien-3β-yl acetate, (I), as the major and 17-chloroandrosta-5,16-dien-3β-yl acetate, (II), as the minor reaction product (Sciaky & Pallini, 1964; Marson, 1992; Siddiqui *et al.*, 1995). Compound (I) was found to be an important precursor for the synthesis of steroidal inhibitors of cytochrome P450 17α-hydroxylase-C17,20-lyase as potential agents for prostate cancer treatment (Njar *et al.*, 1998; Handratta *et al.*, 2005; Moreira *et al.*, 2007). We report here the molecular structures of (I) and (II), determined by single-crystal X-ray analysis, and compare them with those of the free molecules given by quantum-mechanical *ab initio* calculations.

ORTEPII (Johnson, 1976) plots of (I) and (II) are shown in Figs. 1 and 2, respectively. The two compounds are very similar: both have acetoxy and chloro substituents at the 3 and 17 positions, and compound (I) has an extra formyl group at the 16 position. In both compounds, the *A*/*B* junction is quasi-*trans* and the remaining rings are *trans*-fused. The acetoxy



substituents at C3 are in equatorial positions, with angles to the normal (Cremer & Pople, 1975) of ring *A* of 68.43 (15) and 68.4 (2)°, respectively, for (I) and (II). In compound (II), the substituent is disordered, with atoms O2 and C31 and methyl group C32 occupying two positions with near-equal occupancy. Rings *A* and *C* have slightly flattened chair conformations, as shown by the mean values of their torsion angles [52.97 (12)–55.33 (14)°]. The unsaturated ring *B* adopts a half-chair conformation, with puckering parameters (Cremer & Pople, 1975) Q = 0.474 (3) Å, θ = 52.0 (4)° and φ = 210.0 (4)° for (I), and Q = 0.491 (3) Å, θ = 51.5 (3)° and φ = 211.0 (5)° for (II).

The five-membered ring *D* features a double bond at C16—C17 and shows a conformation that can be described as an envelope on C14, with P = 11.3 (3)° and τ = 36.0 (2)° [P = 12.0 (4)° and τ = 35.7 (2)° for (II)]. The value of the bowing angle, the angle between the least-squares plane of ring *A* and

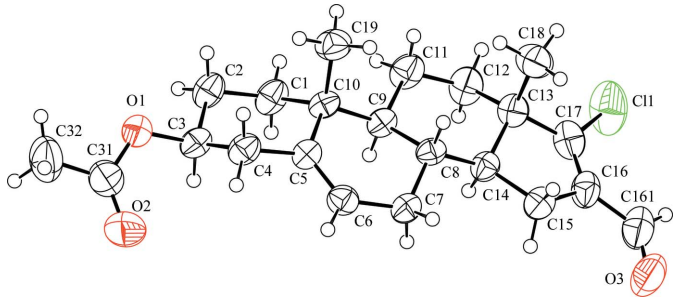


Figure 1
The molecular structure of compound (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

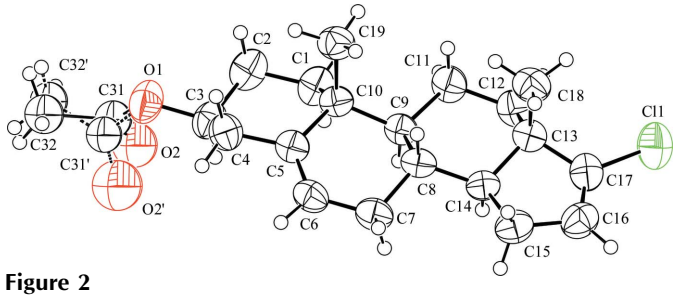


Figure 2
The molecular structure of compound (II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. The minor component of the disordered acetoxy group is shown with broken bonds.

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the least-squares plane that includes the atoms of rings *B*, *C* and *D*, is 23.43 (9)° for (I) and 21.35 (4)° for (II). The corresponding distances between terminal atoms C3 and C16 are 8.921 (5) and 8.867 (5) Å, and the values for the pseudo-torsion angle C19—C10···C13—C18 are 12.9 (5)° for (I) and 9.4 (5)° for (II).

We have performed quantum mechanical calculations of the equilibrium geometry of the free molecule using *GAMESS* (Schmidt *et al.*, 1993) under conditions described previously (Ramos Silva *et al.*, 2008). By comparing the calculated and experimental structural parameters it is possible to infer whether the molecular conformation is intrinsic to the free steroid molecule or is due to intermolecular interactions. The calculations reproduce the twist of the molecules as measured by the pseudo-torsion angle C19—C10···C13—C18, giving a slightly decreased value of 10.2° for (I) and a slightly increased value of 9.9° for (II). Such twists are therefore intrinsic to the molecule and not a packing effect, as confirmed by previous studies (Ramos Silva *et al.*, 2008; Pinto *et al.*, 2008; Paixão *et al.*, 2004). For compound (I), the geometry of the isolated molecule that corresponds to the energy minimum is quite similar to that observed in the solid state. Larger differences are found for the head and tail groups; the calculated C3—O1—C31—O2 torsion angle is 0.6° [observed 1.5 (4)°] and the calculated C15—C16—C161—O3 torsion angle is −1.7° [observed 3.2 (5)°].

There are no hydrogen bonds joining the molecules of (I). They pack in such a way that the terminal acetoxy/formyl groups come close, with the shortest intermolecular contact being O3···O1^{i} of 3.440 (3) Å [symmetry code: (i) $\frac{3}{2}-x, 1-y, -\frac{1}{2}+z$]. Without the formyl substituent, the molecules of (II) pack in a different way. They assemble head-to-tail, with the shortest intermolecular contact being C14···O2′^{ii} of 3.311 (9) Å [symmetry code: (ii) $-x+1, -\frac{1}{2}+y, \frac{1}{2}-z$].

Packing effects have a significant impact on the conformation of the molecule of (II), as seen by comparison with the calculations for the isolated molecule. The minimum energy for compound (II) is achieved with the acetoxy group in-plane with atoms C3 and C4, and C3—O1—C31—O2 converges to −0.3°, while in the solid state both alternative positions for the acetoxy group result in higher torsion angles [C3—O1—C31—O2 = −8.9 (13)° and C3—O1—C31′—O2′ = 4.7 (14)°].

Experimental

Details of the synthesis of the title compound have been reported previously (Siddiqui *et al.*, 1995; Njar *et al.*, 1998; Moreira *et al.*, 2007). Compounds (I) and (II) were each crystallized from a solution in a mixture of ethyl acetate and *n*-hexane (1:1 *v*/*v*) by slow evaporation.

Compound (I)

Crystal data

$C_{22}H_{29}ClO_3$
M_r = 376.90
Orthorhombic, $P2_12_12_1$
a = 6.0689 (2) Å
b = 13.2879 (4) Å
c = 24.7664 (8) Å
V = 1997.24 (11) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.21 mm^{-1}
T = 293 (2) K
0.42 × 0.17 × 0.09 mm

Data collection

Bruker APEX CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2000)
T_{min} = 0.863, T_{max} = 0.98
38455 measured reflections
3757 independent reflections
2563 reflections with $I > 2\sigma(I)$
R_{int} = 0.084

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.044
$wR(F^2)$ = 0.105
S = 1.03
3757 reflections
238 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.14 e Å^{-3}
$\Delta\rho_{min}$ = −0.23 e Å^{-3}
Absolute structure: Flack (1983), with 1551 Friedel pairs
Flack parameter: 0.02 (10)

Compound (II)

Crystal data

$C_{21}H_{29}ClO_2$
M_r = 348.89
Orthorhombic, $P2_12_12_1$
a = 6.0271 (2) Å
b = 15.4064 (6) Å
c = 20.6081 (9) Å
V = 1913.58 (13) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.21 mm^{-1}
T = 293 (2) K
0.36 × 0.13 × 0.09 mm

Data collection

Bruker APEX CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2000)
T_{min} = 0.861, T_{max} = 0.98
35093 measured reflections
3615 independent reflections
2487 reflections with $I > 2\sigma(I)$
R_{int} = 0.076

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.063
$wR(F^2)$ = 0.165
S = 1.26
3615 reflections
219 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.42 e Å^{-3}
$\Delta\rho_{min}$ = −0.25 e Å^{-3}
Absolute structure: Flack (1983), with 1496 Friedel pairs
Flack parameter: −0.14 (13)

All H atoms were refined as riding on their parent atoms, with C—H = 0.93–0.98 Å and U_{iso}(H) = 1.2U_{eq}(C) or 1.5U_{eq}(methyl C). Atoms O2, C31 and C32 (and their riding H atoms) are disordered over two alternative conformations. The final refined occupancy of the major components was 0.504 (9). The disordered atoms were refined isotropically. The absolute configuration known from the synthesis route was confirmed from the X-ray data.

For both compounds, data collection: *SMART* (Bruker, 2003); cell refinement: *SAINT* (Bruker, 2003); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); 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: GD3236). Services for accessing these data are described at the back of the journal.

References

Bruker (2003). *SMART* and *SAINT*. Bruker AXS Inc., Madison, Wisconsin, USA.

Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.

Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.

Handratta, V. D., Vasaitis, T. S., Njar, V. C., Gediya, L. K., Kataria, R., Chopra, P., Newman, D., Farquhar, R., Guo, Z., Qiu, Y. & Brodie, A. M. (2005). *J. Med. Chem.* **48**, 2972–2984.

Johnson, C. K. (1976). *ORTEPII*. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.

Marson, C. M. (1992). *Tetrahedron*, **48**, 3659–3726.

Moreira, V. M., Vasaitis, T. S., Njar, V. C. & Salvador, J. A. R. (2007). *Steroids*, **72**, 939–948.

Njar, V. C., Kato, K., Nnane, I. P., Grigoryev, D. N., Long, B. J. & Brodie, A. M. (1998). *J. Med. Chem.* **41**, 902–912.

Paixão, J. I. F., Salvador, J. A. R., Paixão, J. A., Matos Beja, A., Ramos Silva, M. & Rocha Gonsalves, A. M. d'A. (2004). *Acta Cryst.* C**60**, o630–o632.

Pinto, R. M. A., Salvador, J. A. R. & Paixão, J. A. (2008). *Acta Cryst.* C**64**, o279–o282.

Ramos Silva, M., Moreira, V. M., Cardoso, C., Matos Beja, A. & Salvador, J. A. R. (2008). *Acta Cryst.* C**64**, o217–o219.

Schmidt, M. W., Baldrige, K. K., Boatz, J. A., Elbert, S. T., Gordon, M. S., Jensen, J. J., Koseki, S., Matsunaga, N., Nguyen, K. A., Sue, S., Windus, T. L., Dupuis, M. & Montgomery, J. A. (1993). *J. Comput. Chem.* **14**, 1347–1363.

Sciaky, R. & Pallini, U. (1964). *Tetrahedron Lett.* **28**, 1839–1845.

Sheldrick, G. M. (2000). *SADABS*. University of Göttingen, Germany.

Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.

Siddiqui, A. U., Rao, V. U. M., Maimirani, M. & Siddiqui, A. H. (1995). *J. Heterocycl. Chem.* **32**, 353–354.