Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

3-Oxoandrosta-4,6-dien-17β-yl 2-methyl-1*H*-imidazole-1-carboxylate and 3-oxo-5α-androst-17β-yl 2-methyl-1*H*-imidazole-1-carboxylate: C—H$\cdots\pi$ and π–π intermolecular interactions

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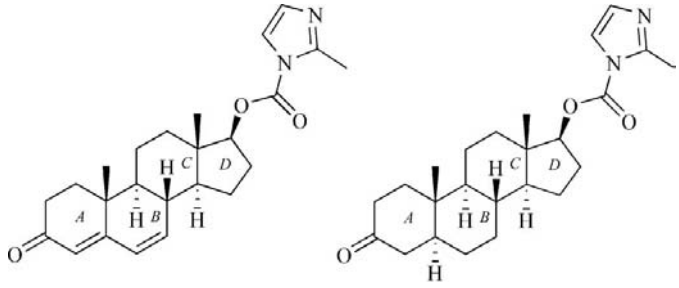
Received 10 December 2008
Accepted 27 January 2009
Online 7 February 2009

The title compounds, $C_{24}H_{30}N_2O_3$, (I), and $C_{24}H_{34}N_2O_3$, (II), both contain an androstane backbone and a 2-methylimidazole-1-carboxylate moiety at the 17-position. Compound (I) contains two symmetry-independent molecules (denoted 1 and 2), while compound (II) contains just one molecule in the asymmetric unit. The C—C—O—C torsion angle that reflects the twisting of the 2-methylimidazole-1-carboxylate moiety from the mean steroid plane is 143.1 (2)° for molecule 1 of (I), 73.1 (3)° for molecule 2 of (I) and 86.63 (17)° for (II). The significance of this study lies in its observation of significant differences in both molecular conformation and supramolecular aggregation between the molecules of the title compounds. The solid-state conformations compared with those obtained theoretically from *ab initio* methods for the isolated molecules show large differences, especially in the orientation of the methylimidazole substituent.

Comment

Hormonal treatments for prostate cancer therapy are based on the Nobel Prize-winning discovery by Huggins & Hodges (1941) that the growth and progression of prostate cancer cells depends on androgen levels in the body. Cytochrome 17α-hydroxylase-C17,20-lyase, CYP17, is one of the enzymes involved in androgen biosynthesis in the human body (Nakajin & Hall, 1981; Hall, 1991). Its inhibition has traditionally been recognized as an important strategy for prostate cancer treatment as a way of lowering androgen levels and thus inhibiting disease progression (Barrie & Jarman, 1996; Njar & Brodie, 1999; Hartmann *et al.*, 2002; Moreira, Salvador *et al.*, 2008). The present work is within a project aiming to synthesize and characterize new steroidal compounds bearing heteroatom-containing moieties at C17 as potential inhibitors for CYP17 and thus to contribute to the field of prostate cancer treatment (Ramos Silva *et al.*, 2008*a*,*b*; Moreira, Vasaitis *et al.*, 2008; Moreira *et al.*, 2007). Both title compounds, namely 3-oxoandrosta-4,6-dien-17β-yl 2-methyl-1*H*-imidazole-1-carboxylate, (I), and 3-oxo-5α-androst-17β-yl 2-methyl-1*H*-imidazole-1-carboxylate, (II), have previously been tested for biological activity and show very good affinity towards important receptors (Moreira, Vasaitis *et al.*, 2008). We report here the molecular structures of (I) and (II), as determined by single-crystal X-ray analysis, and compare them with those of the free molecules as given by quantum mechanical *ab initio* calculations.



An *ORTEPII* (Johnson, 1976) plot of (I) is shown in Fig. 1 and a plot of (II) is shown in Fig. 2. The two compounds are very similar, both having a nearly planar 2-methylimidazole-1-carboxylate moiety at the 17-position.

Compound (I) has two molecules in the asymmetric unit that differ in the orientation of the methylimidazole mean plane with respect to the steroid nucleus. In both molecules, the *A*/*B* ring junction is quasi-*trans*, whereas rings *B*/*C* and *C*/*D* are *trans*-fused. The five-membered ring *D* has an envelope conformation, with atom C13 at the flap position displaced by 0.738 (3) Å from the best plane of the other four C atoms of the ring (C14–C17); the corresponding atom C37 lies 0.733 (3) Å from the plane through C38–C41. The C16—C17—O2—C20 torsion angle is 143.1 (2)° in molecule 1 and the corresponding angle (C40—C41—O5—C44) is 73.1 (3)° in molecule 2, reflecting the large difference in the orientation of the methylimidazole plane for the two independent molecules. Rings *A* and *B* have half-chair conformations, while ring *C* has a chair conformation, with endocyclic torsion-angle magnitudes in the range 54.6 (3)–58.7 (3)° for molecule 1 and 55.5 (3)–58.1 (3)° for molecule 2. The molecules are slightly convex towards the β side. The value of the pseudo-torsion angle C19—C10$\cdots$C13—C18 is −8.9 (3)° for molecule 1 and the corresponding angle in molecule 2 is −7.4 (3)°. The corresponding distances between terminal atoms C3 and C16 are 8.895 (5) and 8.838 (5) Å, respectively, for molecules 1 and 2. The molecules pack in stacks with the aromatic tail substituents interacting *via* π–π interactions; the π–π distances are 3.6527 (18) and 3.9315 (18) Å, consecutively. These stacks are further joined by C—H$\cdots$O interactions to form layers (Fig. 3 and Table 1).

  doi:10.1107/S0108270109003278

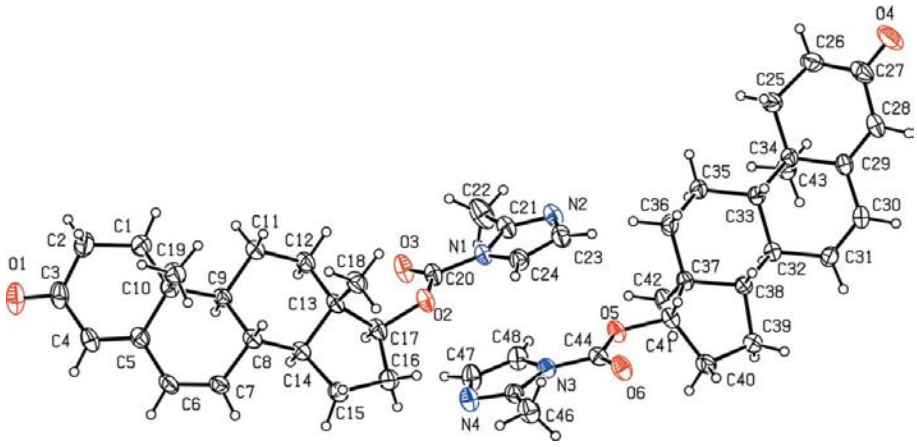


Figure 1
The two independent molecules of compound (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

Compound (II) crystallizes with just one independent molecule in the asymmetric unit. All six-membered rings are saturated and adopt chair conformations. They are all *trans*-fused. The five-membered ring *D* has an envelope conformation, with atom C13 at the flap position displaced by 0.7128 (14) Å from the best plane of the other four C atoms. The molecule is slightly convex towards the β side. The pseudo-torsion angle C19—C10···C13—C18 is 1.1 (2)° and the distance between terminal atoms C3 and C16 is 9.084 (2) Å. The C16—C17—O2—C20 torsion angle is 86.63 (17)°. The molecular packing is influenced by a C—H···π interaction of type III, as described by Malone *et al.* (1997), with a C4···π^{iii} distance of 3.670 (2) Å [Fig. 4; symmetry code: (iii) $-x+\frac{3}{2}, -y+1, z-\frac{1}{2}$]; atom H4*A* is above the centre of the N1/C21/N2/C23/C24 aromatic ring, but the C4—H4*A* bond points towards the ring edge. Further intermolecular C—H···O interactions join all the molecules into a three-dimensional network, reinforcing crystal cohesion (Table 2).

In order to check if the orientation of the 2-methylimidazole-1-carboxylate moiety is intrinsic to the free steroid molecule or rather due to intermolecular interactions, we have performed quantum mechanical calculations of the equilibrium geometries of the free molecules. These calculations were performed using the *GAMESS* computer program (Schmidt *et al.*, 1993) starting with the solid-state conformations. A molecular-orbital Roothan–Hartree–Fock method

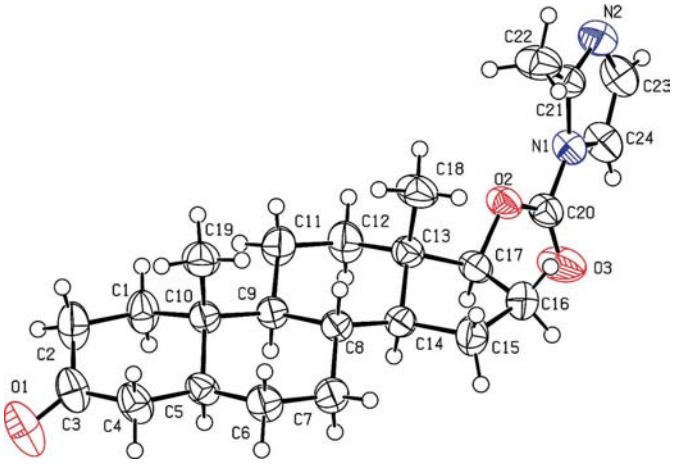


Figure 2
The molecular structure of compound (II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

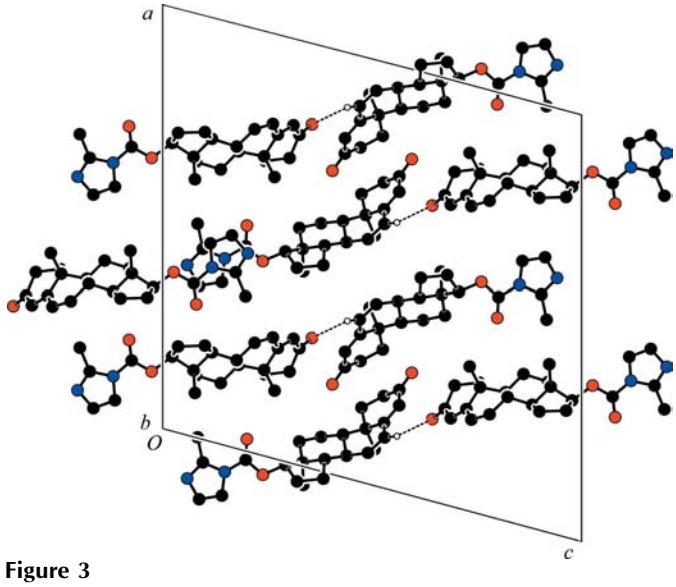


Figure 3
A partial packing diagram for compound (I), with C—H···O interactions shown as dashed lines.

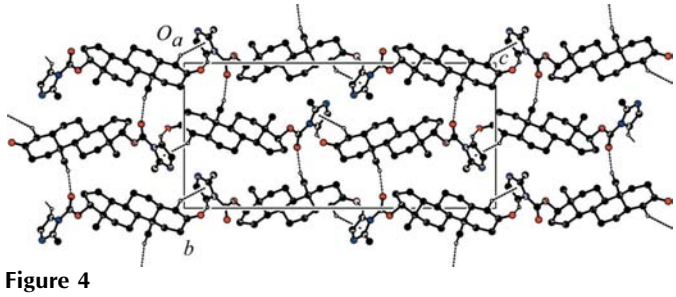


Figure 4
The packing of compound (II), with intermolecular interactions shown as dashed lines.

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} atomic units). Before engaging in heavier calculations, we computed the energy of the molecule simply by changing the orientation of the 2-methylimidazole-1-carboxylate moiety (changing the C16—C17—O2—C20 torsion angle in steps of 10°) without relaxing the molecular geometry. This preliminary calculation shows a global minimum near the conformation of molecule 2 in (I) and a local minimum near the conformation of molecule 1 in (I). The geometries of both molecules 1 and 2 were then relaxed. For molecules 1 and 2, the calculated geometries differ more significantly in the conformation of ring *B* and on the orientation of the methylimidazole mean plane. The geometry that corresponds to the local energy minimum of molecule 1 shows a ring *B* with an average torsion angle of 29.4° [observed mean value = 36.05 (14)°]. The orientation of the methylimidazole plane converges to a C16—C17—O2—C20 torsion angle of 141.7°. The geometry that corresponds to the global energy minimum of molecule 2 shows a ring *B* with an average torsion angle of 29.4° [observed mean value = 34.74 (13)°]. The orientation of the methylimidazole plane converges to a C16—C17—O2—C20 torsion angle of 81.4°. We can therefore conclude that supramolecular aggregation plays an important role in stabilizing the two observed geometries. The minimum energy for compound (II) is achieved with a C16—C17—O2—C20 torsion angle of 86.6°, equal to the experimental value. The remaining calculated structural features agree well with those determined experimentally.

Experimental

Both compounds were synthesized as described previously (Moreira, Vasaitis *et al.*, 2008). Compounds (I) and (II) were crystallized from acetone and acetonitrile, respectively, by slow evaporation.

Compound (I)

Crystal data

$C_{24}H_{30}N_2O_3$
M_r = 394.50
Monoclinic, *C*2
a = 24.5935 (5) Å
b = 7.03510 (10) Å
c = 24.9875 (4) Å
β = 105.1160 (11)°
V = 4173.69 (12) Å^3
Z = 8
Mo *Kα* radiation
μ = 0.08 mm^{-1}
T = 293 (2) K
0.36 × 0.15 × 0.04 mm

Data collection

Bruker APEX CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2000)
T_{min} = 0.906, T_{max} = 0.997
45077 measured reflections
5398 independent reflections
3688 reflections with $I > 2\sigma(I)$
R_{int} = 0.052

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.042
$wR(F^2)$ = 0.102
S = 1.01
5398 reflections
529 parameters
1 restraint
H-atom parameters constrained
Δρ$_{max}$ = 0.13 e Å^{-3}
Δρ$_{min}$ = −0.20 e Å^{-3}

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C6—H6···O4^{i}	0.93	2.58	3.468 (4)	161

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

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C24—H24···O1^{ii}	0.93	2.54	3.301 (2)	139

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

Compound (II)

Crystal data

$C_{24}H_{34}N_2O_3$
M_r = 398.53
Orthorhombic, $P2_12_12_1$
a = 6.5828 (2) Å
b = 12.3368 (5) Å
c = 26.4702 (10) Å
V = 2149.66 (14) Å^3
Z = 4
Mo *Kα* radiation
μ = 0.08 mm^{-1}
T = 293 (2) K
0.35 × 0.33 × 0.13 mm

Data collection

Bruker APEX CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2000)
T_{min} = 0.963, T_{max} = 0.990
65343 measured reflections
5844 independent reflections
3709 reflections with $I > 2\sigma(I)$
R_{int} = 0.043

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.046
$wR(F^2)$ = 0.144
S = 1.01
5844 reflections
265 parameters
H-atom parameters constrained
Δρ$_{max}$ = 0.24 e Å^{-3}
Δρ$_{min}$ = −0.16 e Å^{-3}

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). The absolute configuration was not determined from the X-ray data but was known from the synthesis route. Friedel pairs were merged before refinement.

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*.

VMM thanks the Fundação para a Ciência e a Tecnologia for supporting this work (grant No. BD/12508/2003). JARS thanks the Universidade de Coimbra for financial support. VMM and JARS also thank the Fundação Luso-Americana for sponsoring trips to the USA that have greatly contributed to this work.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SF3097). Services for accessing these data are described at the back of the journal.

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