Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Two androsterone derivatives as inhibitors of androgen biosynthesis

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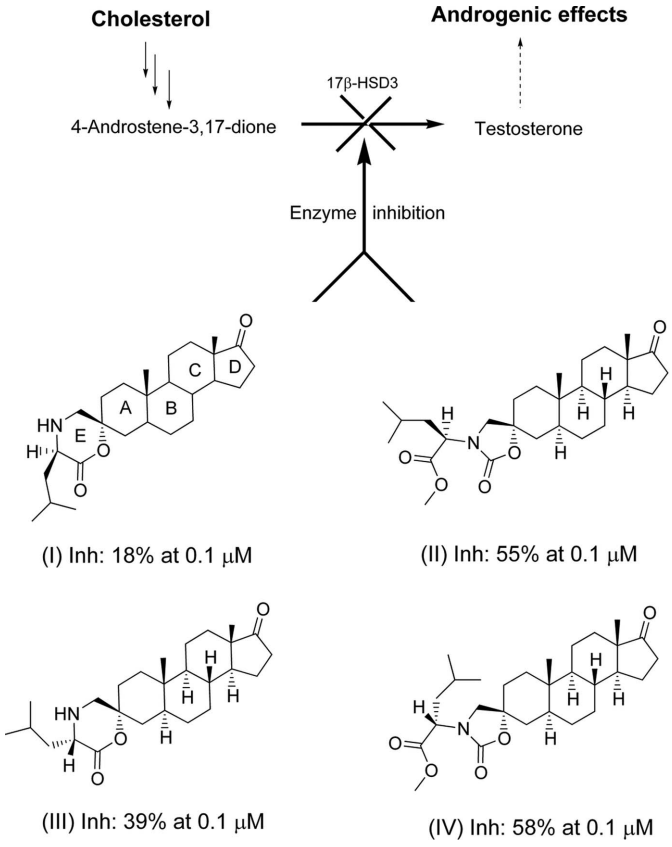
Received 29 February 2012
Accepted 9 May 2012
Online 16 May 2012

The title compounds, (3*R*,5*S*,5′*R*,8*R*,9*S*,10*S*,13*S*,14*S*)-10,13-dimethyl-5′-(2-methylpropyl)tetradecahydro-6′*H*-spiro[cyclopenta[*a*]phenanthrene-3,2′-[1,4]oxazinane]-6′,17(2*H*)-dione, $C_{26}H_{41}NO_3$, (I), and methyl (2*R*)-2-[(3*R*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*)-10,13-dimethyl-2′,17-dioxohexadecahydro-3′*H*-spiro[cyclopenta[*a*]phenanthrene-3,5′-[1,3]oxazolidin-3′-yl]]-4-methylpentanoate, $C_{28}H_{43}NO_5$, (II), possess the typical steroid shape (*A*–*D* rings), but they differ in their extra *E* ring. The azalactone *E* ring in (I) shows a half-chair conformation, while the carbamate *E* ring of (II) is planar. The orientation of the *E*-ring substituent is clearly established and allows a rationalization of the biological results obtained with such androsterone derivatives.

Comment

17β-Hydroxysteroid dehydrogenase type 3 (17β-HSD3) is an enzyme that catalyzes the reduction of 4-androstene-3,17-dione into the androgen testosterone (Poirier, 2010; Mohler *et al.*, 2007; Maltais *et al.*, 2011). This latter steroid hormone, as well as its natural metabolite dehydrotestosterone, is known to stimulate the proliferation of prostate cancer cells; the Scheme shows the biosynthesis of the androgenic hormone testosterone and a representation of azalactones (I) and (III) and carbamates (II) and (IV) tested as inhibitors of 17β-HSD3 (Inh = inhibition) (Poirier, 2008). Since 17β-HSD3 contributes to the production of androgens in men, inhibiting this enzyme is an interesting strategy to block androgen biosynthesis and to treat prostate cancer. Androsterone (ADT) derivatives substituted at position C3 were previously reported as inhibitors of 17β-HSD3 and it was established that a hydrophobic group is required to obtain good inhibition of 17β-HSD3 (Maltais *et al.*, 2002), a β-oriented group producing a better inhibition than an α-oriented group (Tchedam-Ngatcha *et al.*, 2005).

In our synthetic search for inhibitors of 17β-HSD3, we recently focused on the preparation of new ADT derivatives having an extra azalactone or carbamate *E* ring. For a better understanding of the structure–activity relationship (SAR) of



these new inhibitors, especially the side-chain orientation, we analyzed the structures of the representative compounds (I) and (II) (see Scheme and Fig. 1).

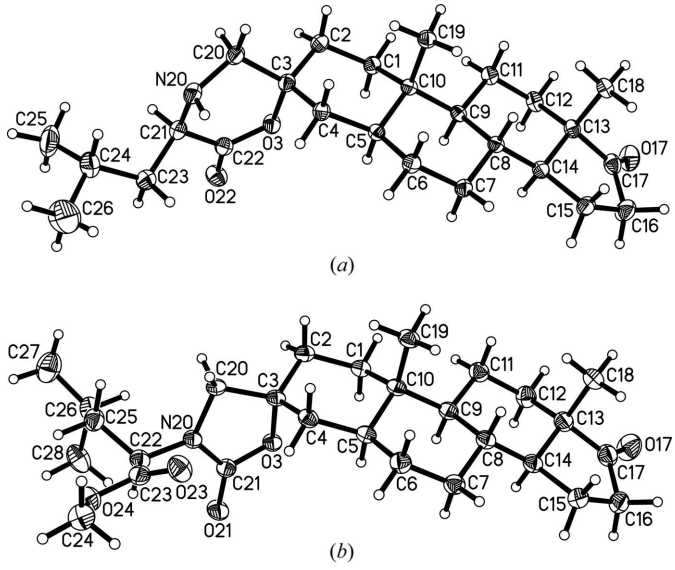


Figure 1
The molecular structures of (*a*) azalactone (I) and (*b*) carbamate (II), with non-H atoms represented by 50% probability displacement ellipsoids.

 doi:10.1107/S0108270112021099

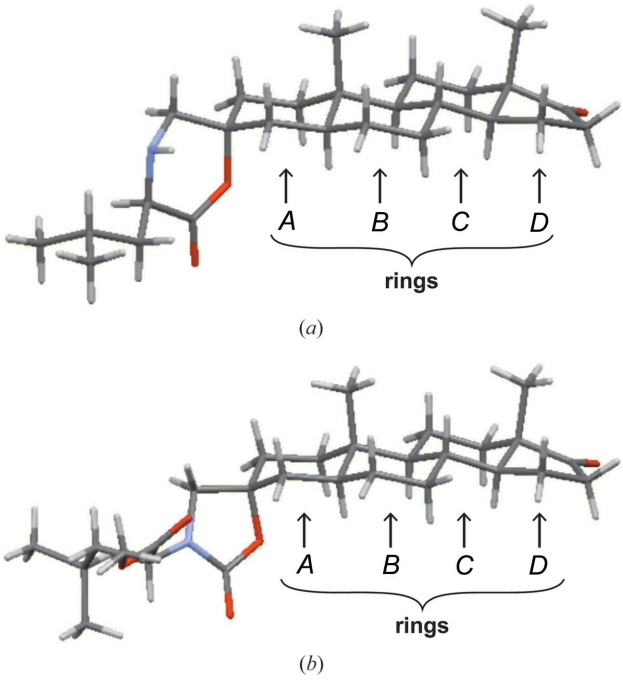


Figure 2
The structures of (*a*) (I) and (*b*) (II), showing the conformations of the steroid *A*, *B*, *C* and *D* rings.

The two compounds show fixed conformations of their extended side chains; no disorder is apparent in the structure analyses. Packing diagrams with van der Waals radii give the impression that these structures are not very tightly packed, in agreement with the low densities [1.162 Mg m^{-3} in (I) and 1.200 Mg m^{-3} in (II)]. The packing appears to be efficient enough, however, to be linked to the appearance of just one conformation of the side chain in each case.

The correct enantiomers, already known from the starting materials, were checked against the absolute structure parameters (Flack, 1983). For compound (I), the absolute structure parameter was found to be 0.12 (18) for 1747 Friedel pairs (83% Friedel coverage). For compound (II), it was 0.06 (18) for 2087 (100%) Friedel pairs. These two values are better than might have been expected considering that the highest anomalous contribution comes from O atoms (Flack & Bernardinelli, 2008). A Bayesian statistics analysis on Bijvoet differences was also performed using the program *PLATON* (Spek, 2009). The Hooft parameters obtained (Hooft *et al.*, 2008), *viz.* −0.04 (7) and −0.05 (6) for compounds (I) and (II), respectively, are also in very good agreement with the known molecular absolute configurations, and were perhaps influenced positively by the use of copper radiation. Probability levels of having a false attribution, *P*3(false), are essentially zero for both compounds.

The steroid six-membered *A*, *B* and *C* rings appear as the well known fused-ring system, all in chair conformations, while the five-membered *D* ring is in a slightly twisted envelope conformation in both azalactone (I) and carbamate (II) (Yan *et al.*, 2009) (Fig. 2). The heterocyclic ring of (I) is a half-chair perpendicular to the steroid backbone, while the heterocyclic

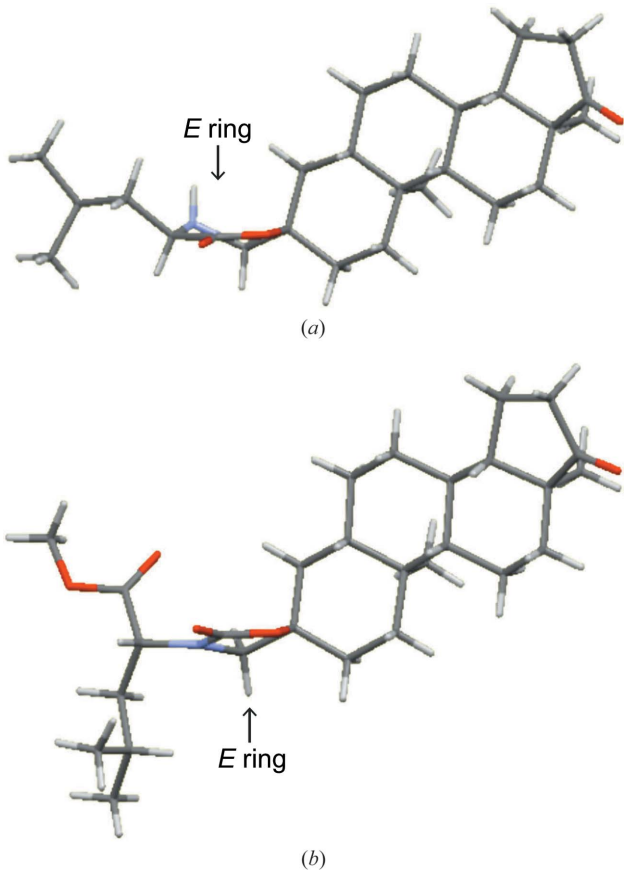


Figure 3
The *E*-ring conformation in (*a*) (I) and (*b*) (II).

ring of carbamate (II) is almost planar [maximum deviation = 0.147 (1) Å] and is perpendicular to the steroidal plane (Fig. 3). These extra heterocyclic *E* rings provide a restricted orientation to the isobutyl group in the azalactones (I) and (III) (see Scheme). In carbamates (II) and (IV), the methyl pentanoate group has a higher degree of liberty owing to the free rotation around the exocyclic bond to the N atom. In azalactone (I), the hydrophobic side chain has a distal orientation with respect to the longitudinal axis of the four-ring steroid system (to the right in Fig. 4*a*). Consequently, the isobutyl group of the other isomer, the azalactone (III), would be oriented to the left in a similar drawing, or in other words in a proximal disposition to the centerline of the four-ring system. Since the present compound (I) is a less potent inhibitor than its stereoisomer (III), it appears that the side chain must be proximal (on the left side in Fig. 4*a*) for better enzyme inhibition. The isobutyl group would thus point toward a hypothetical hydrophobic pocket of 17β-HSD3, which was previously deduced from SAR studies (Tchedam-Ngatcha *et al.*, 2005; Maltais *et al.*, 2011) but not confirmed because this membrane enzyme was never crystallized. In the case of carbamates (II) (Fig. 4*b*) and (IV), the inhibitory activity is the same (55 and 58% of inhibition at 0.1 μM) for both compounds due to the free rotation of the methyl pentanoate group, which promotes interaction with a hydrophobic pocket of the enzyme.

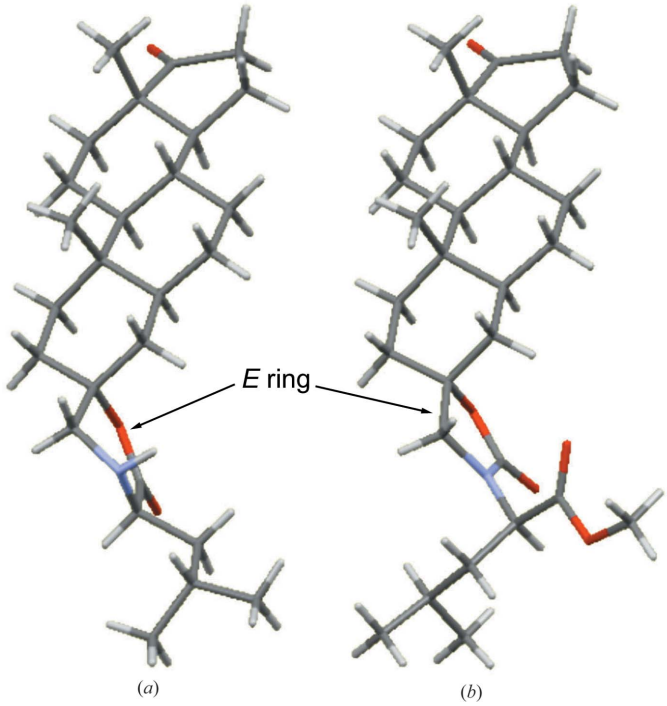


Figure 4
The *E*-ring substituent conformation in (*a*) azalactone (I) and (*b*) carbamate (II). The isobutyl group of (I) is oriented away from the longitudinal axis of the steroid ring system, while the methyl pentanoate group of (II) has free rotation.

Experimental

Compounds (I) and (III) were synthesized by modification of an approach developed in our laboratory (Rouillard *et al.*, 2008). Briefly, aminolysis of the oxirane at C3 of androsterone with L- and D-isoleucine methyl esters provided the corresponding amino alcohols, which were treated with sodium methoxide to afford azalactones (I) and (III). Compounds (II) and (IV) were prepared according to the method of Maltais *et al.* (2002) by treatment of each amino alcohol with triphosgene. X-ray quality crystals of (I) and (II) were obtained by slow diffusion of hexane into a methylene chloride solution of the compound (hexane–methylene chloride 1:1 *v*/*v*) followed by slow evaporation.

Azalactone (I)

Crystal data

$C_{26}H_{41}NO_3$
M_r = 415.60
Monoclinic, $P2_1$
a = 13.07929 (17) Å
b = 5.82873 (8) Å
c = 16.3140 (2) Å
β = 107.3095 (6)°
V = 1187.37 (3) Å^3
Z = 2
Cu $K\alpha$ radiation
μ = 0.58 mm^{-1}
T = 150 K
0.25 × 0.11 × 0.05 mm

Data collection

Bruker SMART 6000 diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2008)
T_{min} = 0.810, T_{max} = 0.971
36176 measured reflections
4334 independent reflections
4159 reflections with $I > 2\sigma(I)$
R_{int} = 0.038

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.040
$wR(F^2)$ = 0.107
S = 1.07
4334 reflections
279 parameters
1 restraint
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.18 e Å^{-3}
$\Delta\rho_{min}$ = −0.22 e Å^{-3}
Absolute structure: Flack (1983), 1733 Friedel pairs
Flack parameter: 0.12 (18)

Carbamate (II)

Crystal data

$C_{28}H_{43}NO_5$
M_r = 473.63
Orthorhombic, $P2_12_12_1$
a = 6.3941 (2) Å
b = 18.1440 (7) Å
c = 22.6047 (9) Å
V = 2622.47 (17) Å^3
Z = 4
Cu $K\alpha$ radiation
μ = 0.65 mm^{-1}
T = 150 K
0.12 × 0.05 × 0.05 mm

Data collection

Bruker Microstar diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2008)
T_{min} = 0.787, T_{max} = 0.968
43157 measured reflections
4933 independent reflections
4697 reflections with $I > 2\sigma(I)$
R_{int} = 0.052

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.037
$wR(F^2)$ = 0.101
S = 1.06
4933 reflections
312 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.23 e Å^{-3}
$\Delta\rho_{min}$ = −0.14 e Å^{-3}
Absolute structure: Flack (1983), 2087 Friedel pairs
Flack parameter: 0.06 (18)

H atoms were treated as riding, with C—H = 1.00 (methyl), 0.99 (methylene) and 0.98 Å (remaining H atoms), and with U_{iso}(H) = 1.5U_{eq}(C) for methyl H atoms and 1.2U_{eq}(C) otherwise. The N-bound H atom of (I) was located by difference Fourier synthesis; its coordinates were refined and its U_{iso}(H) value was constrained to 1.2U_{eq}(N).

Data collection: *APEX2* (Bruker, 2011); cell refinement: *SAINT* (Bruker, 2011); data reduction: *XPREP* (Bruker, 2008); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *SHELXTL* (Sheldrick, 2008); software used to prepare material for publication: *UdMX* (Maris, 2004).

The authors thank the Canadian Institutes of Health Research (CIHR) for financial support. LCK thanks the Faculty of Medicine (Laval University) for a fellowship.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FA3273). Services for accessing these data are described at the back of the journal.

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