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Structure–activity relationships in 4- and 5-androstene: 3β-acetoxy-17-methyl-17-oxo-16,17-seco-5-androstene-16-carbonitrile and 17-methyl-3,17-dioxo-16,17-seco-4-androstene-16-carbonitrile

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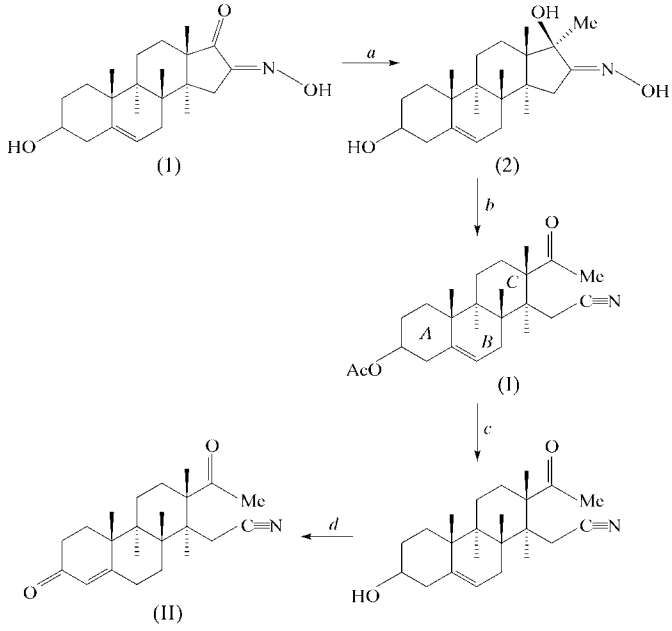
The title compounds, $C_{22}H_{31}NO_3$ and $C_{20}H_{27}NO_2$, have similar conformations except in the molecular geometry and the bonding of two of the rings. These differences lead to marked differences in the biological activities of these compounds. Molecules of both compounds are linked by weak C—H···O hydrogen bonds in the crystal structures.

Comment

With the aim of studying anti-aromatase activity of some ring-*D*-modified steroids, we have synthesized several new androstane derivatives (Penov-Gaši *et al.*, 2001). Potent steroid aromatase inhibitors are mainly the ring-*A*- and ring-*B*-modified steroids, whereas the ring-*D*-modified steroids (with the exception of testololactone) have received little research attention. Aromatase is a cytochrome P450 enzyme that catalyzes the conversion of androgens into estrogens at the last step of estrogen biosynthesis (Thomson & Süteri, 1974). Compounds that inhibit aromatase have potential applications in the treatment of advanced estrogen-dependent tumors, such as breast cancer, dometrial cancer, prostatic hyperplasia and prostate cancer. Within the framework of this project, we have performed the structure analysis of the title compounds, *viz*. (I) and (II) (see scheme). The original basic crystallographic data have been deposited in the Cambridge Structural Database [CSD refcodes WULGAL, (I), and WULGEP, (II); Allen, 2002].

The structures of both compounds, deduced from chemical spectroscopic evidence, were confirmed by X-ray diffraction analyses. Molecular-mechanics calculations using *PCMODEL* (Serena Software, 1989) were also performed in order to define the conformations of the molecules in terms of energy minima. Since the starting materials were synthesized from the natural androstene derivative, the absolute stereochemistry of which is known (Fieser & Fieser, 1967), the X-ray structures are described for the appropriate enantiomer.



Perspective views of the molecules of (I) and (II) are shown in Figs. 1 and 2, respectively. The puckering (Cremer & Pople, 1975) and asymmetry parameters (Duax *et al.*, 1976) reveal the following conformations. In (I), ring *A* has a 1α,4β-chair conformation, ring *B* has a 9α,8β-half-chair conformation and ring *C* adopts a 8β,12α-chair conformation. In (II), ring *A* exhibits a form intermediate between 1α-envelope and 1α,2β-half-chair, while rings *B* and *C* have 5α,8β- and 8β,12α-chair conformations, respectively.

The different conformations of rings *A* and *B* in (I) and (II), caused by the shifting of the double bond from C4═C5 in (I)

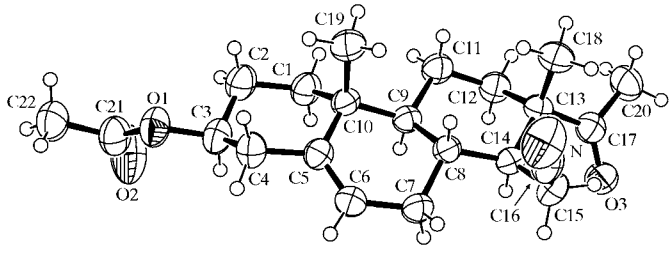


Figure 1
A perspective view of the molecule of (I) with the atomic labeling. Displacement ellipsoids are shown at the 30% probability level and H atoms are drawn as spheres of arbitrary radii.

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to C5═C6 in (II), lead to significant differences in the steroid skeleton geometry in the region of rings *A* and *B* (Tables 1 and 3, and Fig. 3). Introducing the double bond into ring *A* of (I) and ring *B* of (II) also causes the twisting of the steroidal skeleton of each compound along the molecular principal axis, characterized by the values of the non-bonded C19—C10···C13—C18 torsion angles [5.7 (2) and 10.3 (2)° for (I) and (II), respectively]. The steroid geometries in the region of the C15 and C17 substituents (Fig. 3) are similar. In the energy-minimized models, this similarity is even more pronounced; ring *A* in (II) adopts an almost ideal ^1E form, while the conformations of the other rings in (I) and (II) are not altered.

In the crystal packing of both compounds, molecules related by the screw axes are linked by weak hydrogen bonds, forming coils. In (I), C20—H20*B*···O2 bonds form coils along the *c* axis (Table 2); in (II), C2—H2*A*···O2 and C20—H29*B*···O1 bonds, in a 'head-to-tail' and 'tail-to-head' relationship, form coils along the *b* axis (Table 4).

The compounds were tested for possible anti-aromatase activity in the denucleated ovarian fractions from PMSG-pretreated female rats. For screening purposes, the compounds were tested in a single concentration (50 μ*M*). The results showed that (I) exhibited very low potency, while (II) completely inhibited aromatase activity in the presence of a subsaturated dose of testosterone, as well as in the presence of a saturated concentration (Penov-Gaši *et al.*, 2001). The markedly greater biological activity of (II) can be interpreted as being due to the different molecular geometry in the region of rings *A* and *B* of the compounds, *i.e.* the presence of the 4-ene-3-one system instead of 5-ene-3-acetoxy.

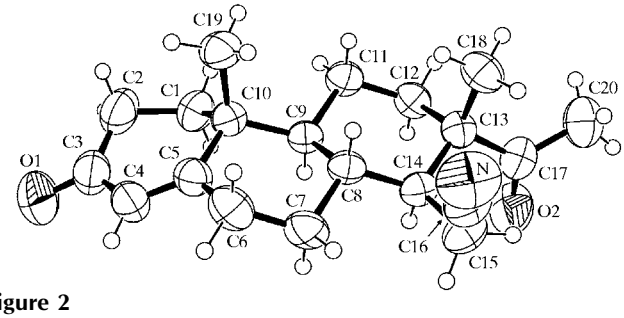

Figure 2
A perspective view of the molecule of (II) with the atomic labeling. Displacement ellipsoids are shown at the 30% probability level and H atoms are drawn as spheres of arbitrary radii.

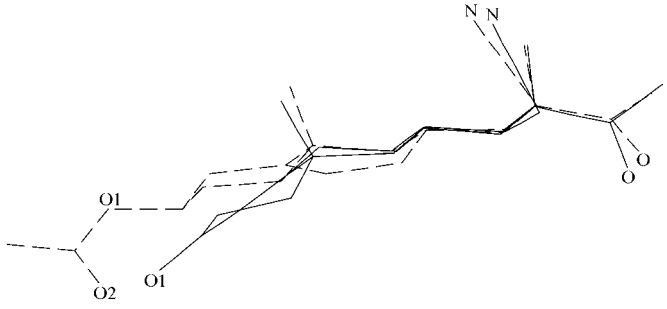

Figure 3
A superimposed fit for molecules of (I) (solid lines) and (II) (dashed lines) in the crystalline state, viewed perpendicular to the C8—C14 bond.

Experimental

The preparation of (1) and (2) (see scheme) was described by Miljković *et al.* (1997). Treatment of (2) with acetic anhydride in pyridine (*b*) afforded the fragmentation product (I). By further treatment with sodium ethoxide in ethanol (*c*), (I) was transformed into 3β-hydroxy-17-methyl-17-oxo-16,17-seco-5-androstene-16-carbonitrile. Oppenauer oxidation of this compound using aluminium(III) *tert*-butoxide in cyclohexanone (*d*) gave (II) (Penov-Gaši *et al.*, 2001). M.p.: 398–401 K for (I) and 406–409 K for (II).

Compound (I)

Crystal data

$C_{22}H_{31}NO_3$
M_r = 357.48
Orthorhombic, $P2_12_12_1$
a = 5.946 (2) Å
b = 16.120 (2) Å
c = 20.746 (3) Å
V = 1988.5 (8) Å^3
Z = 4
D_x = 1.194 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 15.0–23.9°
μ = 0.62 mm^{-1}
T = 293 (2) K
Plate, colorless
0.20 × 0.18 × 0.04 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
6350 measured reflections
2354 independent reflections
1621 reflections with $I > 2\sigma(I)$
R_{int} = 0.037
θ_{max} = 74.7°
$h = -6 \rightarrow 7$
$k = -20 \rightarrow 20$
$l = -25 \rightarrow 25$
3 standard reflections
frequency: 120 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.040
$wR(F^2)$ = 0.136
S = 0.99
2354 reflections
240 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0734P)^2 + 0.1452P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.035
$\Delta\rho_{max}$ = 0.21 e Å^{-3}
$\Delta\rho_{min}$ = −0.17 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0015 (4)

Table 1
Selected torsion angles (°) for (I).

C10—C1—C2—C3	−55.8 (4)	C10—C5—C6—C7	3.1 (6)
C1—C2—C3—C4	56.6 (4)	C5—C6—C7—C8	12.6 (5)
C2—C3—C4—C5	−54.5 (4)	C6—C7—C8—C9	−44.1 (4)
C2—C1—C10—C5	49.6 (4)	C7—C8—C9—C10	63.2 (3)
C3—C4—C5—C10	52.5 (4)	C6—C5—C10—C9	14.5 (4)
C4—C5—C10—C1	−48.5 (4)	C8—C9—C10—C5	−47.2 (3)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C20—H20*B*···O2^{i}	0.96	2.55	3.447 (5)	155

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

Compound (II)

Crystal data

$C_{20}H_{27}NO_2$
M_r = 313.43
Orthorhombic, $P2_12_12_1$
a = 8.929 (2) Å
b = 10.022 (3) Å
c = 19.651 (9) Å
V = 1758.5 (10) Å^3
Z = 4
D_x = 1.184 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 25.0–29.6°
μ = 0.59 mm^{-1}
T = 293 (2) K
Plate, colorless
0.45 × 0.40 × 0.06 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
4254 measured reflections
2073 independent reflections
1723 reflections with $I > 2\sigma(I)$
R_{int} = 0.054
θ_{max} = 74.6°
$h = -11 \rightarrow 11$
$k = -12 \rightarrow 12$
$l = -24 \rightarrow 24$
3 standard reflections
frequency: 120 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.036
$wR(F^2)$ = 0.119
S = 0.91
2073 reflections
212 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0788P)^2 + 0.1175P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.19 e Å^{-3}
$\Delta\rho_{min}$ = −0.14 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0033 (7)

Table 3
Selected torsion angles (°) for (II).

C10—C1—C2—C3	−54.3 (3)	C10—C5—C6—C7	−53.8 (3)
C1—C2—C3—C4	33.0 (4)	C5—C6—C7—C8	57.7 (3)
C2—C3—C4—C5	−5.2 (4)	C6—C7—C8—C9	−56.6 (2)
C2—C1—C10—C5	45.5 (3)	C7—C8—C9—C10	51.3 (2)
C3—C4—C5—C10	−2.8 (4)	C6—C5—C10—C9	46.3 (3)
C4—C5—C10—C1	−17.6 (3)	C8—C9—C10—C5	−44.8 (2)

H atoms were placed in idealized positions and treated as riding, with U_{iso}(H) values fixed at 1.3U_{eq} of the parent atoms, or 1.5U_{eq} for methyl H atoms. In the absence of significant anomalous scattering, the values of the Flack (1983) parameter were indeterminate (Flack & Bernardinelli, 2000). Accordingly, the Friedel-equivalent reflections were merged prior to the final refinements.

Table 4
Hydrogen-bonding geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
C2—H2A···O2^{ii}	0.97	2.58	3.402 (4)	142
C20—H20B···O1^{ii}	0.96	2.49	3.422 (4)	167

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

For both compounds, data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: *CAD*-4 *Software*; program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 *for Windows* (Version 1.074; Farrugia, 1997); software used to prepare material for publication: *CSU* (Vicković, 1988).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GA1054). Services for accessing these data are described at the back of the journal.

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