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Two androst-5-ene derivatives: 16-[4-(3-chloropropoxy)-3-methoxybenzylidene]-17-oxoandrost-5-en-3β-ol and 16-[3-methoxy-4-(2-pyrrolidin-1-ylethoxy)benzylidene]-3β-pyrrolidinoandrost-5-en-17β-ol monohydrate

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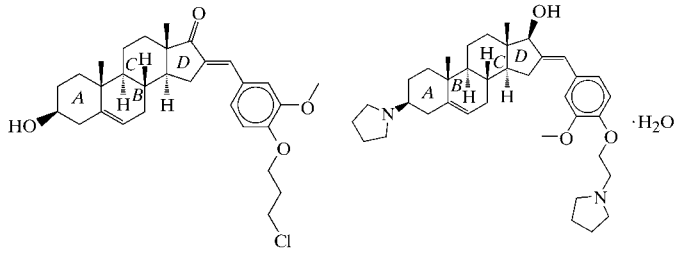
In the steroidal nucleus of 16-[4-(3-chloropropoxy)-3-methoxybenzylidene]-17-oxoandrost-5-en-3β-ol, $C_{30}H_{29}ClO_4$, (I), the outer two six-membered rings are in chair conformations, while the five-membered ring and the central six-membered ring of the steroidal nucleus adopt half-chair and envelope conformations, respectively. In 16-[3-methoxy-4-(2-pyrrolidin-1-ylethoxy)benzylidene]-3β-pyrrolidinoandrost-5-en-17β-ol monohydrate, $C_{37}H_{54}N_2O_3\cdot H_2O$, (II), one C atom of one of the outer six-membered rings of the steroid nucleus and the four C atoms of the ethoxypyrrolidine ring are disordered over two sites. The five-membered ring, and the central and one of the outer six-membered rings of the steroidal nucleus exhibit distorted half-chair, chair and envelope conformations, respectively. In (I), intermolecular O—H···O hydrogen bonds link the molecules into chains *via* a co-operative O—H···O—H···O—H pattern. In (II), intermolecular O—H···O and O—H···N hydrogen bonds link the steroid and water molecules alternately into extended chains.

Comment

It is well known that minor changes in the basic composition of steroids significantly alter their chemical and biological activities (Duax & Norton, 1975). The present crystallographic analyses of 16-[4-(3-chloropropoxy)-3-methoxybenzylidene]-17-oxoandrost-5-en-3β-ol, (I), and 16-[3-methoxy-4-(2-pyrrolidin-1-ylethoxy)benzylidene]-3β-pyrrolidinoandrost-5-en-17β-ol monohydrate, (II), have been carried out to study the influence of different functionalities on the steroid skeleton, in particular substituents at the C3, C16 and C17 positions. This study extends ongoing investigations into a series of similar synthetic androstene derivatives (Thamotharan *et al.*, 2002, and references therein; Hema *et al.*, 2003).



(I) (II)

Compounds (I) and (II) are androstene steroid derivatives in which rings *A*, *B* and *C* are essentially rigid, whereas ring *D* has a flexible conformation with respect to the side chain. Both compounds have the normal 8β,9α,10β,13β,14α configuration, and the *B*/*C* and *C*/*D* ring junctions have *trans* configurations (Figs. 1 and 2). The crystals of (I) are enantiomerically pure and the absolute configuration of the molecule has been confirmed independently by the X-ray diffraction experiment. In (II), the absence of any significant anomalous scatterers in the compound prevented the determination of the absolute configuration and the enantiomer used in the refinement was assigned to correspond with the known chiral centres in a precursor molecule, which remained unchanged during the synthesis of (II).

In compound (I) (Fig. 1), rings *A* and *C* are in chair conformations, as shown by the Cremer & Pople (1975) puckering parameters [ring *A*: Q = 0.550 (3) Å, q_2 = 0.078 (3) Å, q_3 = 0.545 (3) Å, θ = 7.9 (3)° and φ_2 = 107 (2)° for the atom sequence C1–C5/C10; ring *C*: Q = 0.577 (3) Å, q_2 = 0.053 (3) Å, q_3 = 0.575 (3) Å, θ = 5.2 (3)° and φ_2 = 269 (3)° for the atom sequence C8/C9/C11–C14]. Thus, the presence of a hydroxy group at C3 has not disturbed the usual chair conformation of ring *A* of the steroid nucleus. The C3—O3 bond is oriented equatorially and (−)synclinal to the C3—C4 bond. In contrast, it lies (+)antiperiplanar to the C3—C4 bond in a related structure reported from our laboratory (Hema *et al.*, 2003). In ring *B*, the C5═C6 (Csp^2—Csp^2) distance of 1.324 (3) Å confirms the localization of a double bond at this position. This double bond imposes an 8β,9α-half-chair conformation on ring *B*, with puckering parameters of Q = 0.468 (3) Å, q_2 = 0.365 (3) Å, q_3 = 0.292 (3) Å, θ = 51.5 (3)° and φ_2 = 211.4 (4)° for the atom sequence C5–C10. Similar observations on the conformation of ring *B* in related structures have been reported by Caira *et al.* (1995), Hema *et al.* (2002), Vasuki *et al.* (2002) and Thamotharan *et al.* (2002). Ring *D* has a 14α-envelope conformation, with a pseudorotation angle of 12.4 (2)° and a maximum torsion angle of 42.5 (1)° (Rao *et al.*, 1981) for the atom sequence C13–C17.

† Deceased.

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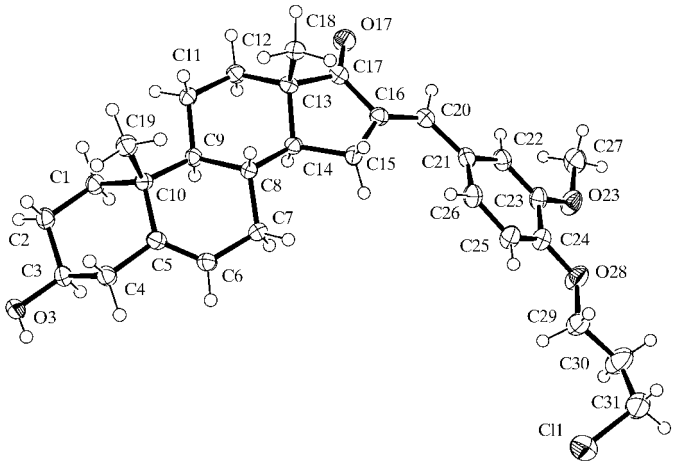

Figure 1
A view of the molecule of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small circles of arbitrary radii.

Atom C14 is 0.142 (2) Å from the plane containing the four remaining atoms.

In compound (II) (Fig. 2), atom C4 in ring *A* of the steroid nucleus is disordered over two sites, so that ring *A* adopts two alternate conformations, with the major conformation existing in 78.8 (7)% of the molecules. As seen from the puckering parameters, the major disordered component has a chair conformation [Q = 0.558 (3) Å, q_2 = 0.087 (3) Å, q_3 = 0.551 (3) Å, θ = 9.0 (3)° and φ_2 = 113 (2)° for the atom sequence C1–C4*A*/C5/C10], while the minor disordered component has a boat conformation distorted towards that of a screw-boat [Q = 0.569 (5) Å, q_2 = 0.556 (6) Å, q_3 = 0.120 (5) Å, θ = 77.8 (5)° and φ_2 = 8.8 (3)° for the atom sequence C1–C4*B*/C5/C10]. Ring *B* exhibits a slightly flattened half-chair conformation [Q = 0.454 (3) Å, q_2 = 0.281 (3) Å, q_3 = 0.356 (3) Å, θ = 38.3 (4)° and φ_2 = 208.7 (6)° for the atom sequence C5–C10], while ring *C* adopts a chair conformation [Q = 0.581 (3) Å, q_2 = 0.084 (3) Å, q_3 = 0.574 (3) Å, θ = 8.7 (3)° and φ_2 = 268.4 (18)° for the atom sequence C8/C9/C11–C14]. Ring *D* of the steroid exhibits an envelope conformation, as is evident from the pseudorotation angle of 345.0 (2)° and maximum torsion angle of 45.4 (1)° for the atom sequence C13–C17.

In (II), the four ring C atoms of the ethoxypyrrolidine ring are disordered over two almost equally occupied conformations. Both disordered components exhibit envelope conformations, as can be seen from the pseudorotation angles of 344.8 (8) and 346.8 (8)° and maximum torsion angles of 44.2 (6) and 44.3 (5)° for the atom sequences N30/C31*A*/C32*A*/C33*A*/C34*A* and N30/C31*B*/C32*B*/C33*B*/C34*B*, respectively. The pyrrolidine-ring substituent at C3 has an envelope conformation, with a pseudorotation angle of 348.0 (3)° and a maximum torsion angle of 42.7 (2)° for the atom sequence N37/C38–C41.

The C17—C16—C20—C21 torsion angles of −173.5 (2)° in (I) and 179.2 (2)° in (II) indicate that the benzylidene moiety has an *E* configuration with respect to the carbonyl or hydroxy substituted atom, C17. The chloropropoxy group in (I) projects in a planar zigzag fashion slightly away from the plane of the methoxybenzylidene ring [C25—C24—O28—C29 = 6.9 (4)°].

The C19—C10···C13—C18 pseudo-torsion angle, which gives a quantitative measure of the molecular twist, is 13.84 (18)° in (I) and 11.34 (19)° in (II). These values are comparable with those of related structures with bulky substitutions at C3 and C16 (Hema *et al.*, 2002; Thamotharan *et al.*, 2002). The C16—C20—C21—C22 torsion angle of 160.8 (3)° in (I) and 5.7 (4)° in (II) indicate that the benzylidene moiety has been flipped by almost 180° about the C20—C21 bond in (II) with respect to its orientation in (I), thus bringing the methoxy group to the other side of the molecule. The *A*/*B*/*C*/*D* ring systems of both (I) and (II) can be superimposed on each other, with a small r.m.s. deviation of the atoms of 0.084 Å.

In (I), the hydroxy substituent on atom C3 forms an intermolecular hydrogen bond with hydroxy atom O3 of a symmetry-related molecule (Table 1). This interaction leads

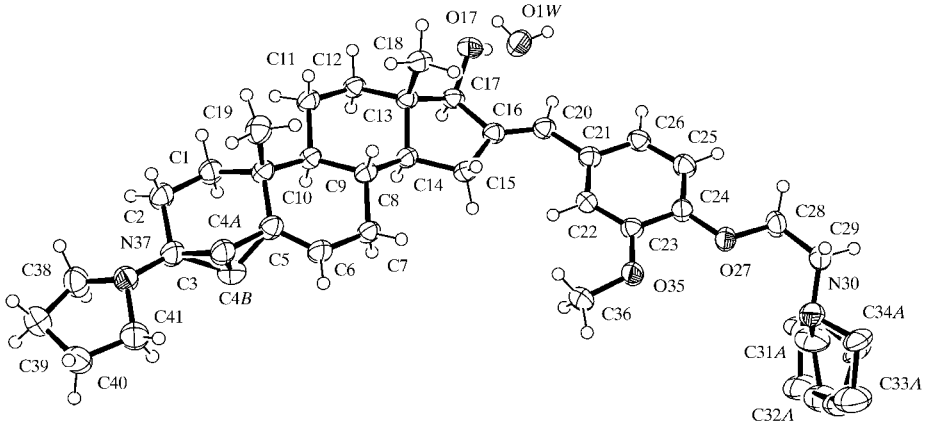

Figure 2
A view of the molecule of (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level. For clarity, all H atoms of the disordered rings have been omitted. The other H atoms are shown as small circles of arbitrary radii.

co-operatively to an O—H···O—H···O—H pattern, producing a chain which runs parallel to the [001] direction and has a graph-set motif of $C(2)$ (Bernstein *et al.*, 1995). As can be seen from Table 2, the hydroxy substituent on atom C17 in (II) forms an intermolecular O—H···O hydrogen bond with the O atom of the water molecule. In turn, the water molecule forms two intermolecular O—H···O and one intermolecular O—H···N hydrogen bonds with the methoxy, ethoxy and ethoxypyrrolidine O and N atoms, respectively, of a single adjacent steroid molecule. These three acceptor atoms form a pocket into which the water molecule is bound. The combination of all these interactions links the steroid and water molecules alternately into extended chains which run in the $[10\bar{1}]$ direction. Binary graph-set motifs (Bernstein *et al.*, 1995) of $C_2^2(11)$, $C_2^2(12)$ and $C_2^2(15)$ are present for the chain routes through acceptor atoms O37, O25 and N30, respectively. Ring motifs of $R_1^2(5)$, $R_2^2(7)$ and $R_2^2(10)$ are also formed by the various combinations of donor–acceptor interactions between the water molecule and the single acceptor steroid molecule.

Experimental

To a solution of dehydroepiandrosterone (0.75 g, 2.60 mmol) in methanol (10 ml), sodium hydroxide pellets (1.5 g) were added and dissolved. 4-(3-Chloropropoxy)-3-methoxybenzaldehyde (1 g, 4.373 mmol) was added dropwise and stirred for 2 h. The completion of the reaction was monitored using thin-layer chromatography. Ice-cold water was added to the reaction mixture and the precipitate obtained was filtered off, washed, dried and crystallized from acetone to afford (I) (institution code: DPJ-RG-1150; yield: 1.5 g, 86.7%; m.p. 483–485 K). To a stirred suspension of 16-[3-methoxy-4-(2-pyrrolidin-1-ylethoxy)benzylidene]-3-pyrrolidino-3,5-androstadien-17-one (0.5 g, 0.871 mmol) in methanol (75 ml), sodium borohydride (1.0 g) was added in small amounts over a period of 2 h at room temperature. Stirring was continued for a further 4 h. Excess solvent was removed under vacuum and the reaction mixture was poured into ice-cold water (100 ml). The precipitate obtained was filtered off, washed with water, dried and crystallized from methanol–acetone (9:1) to afford (II) (institution code: DPJ-RG-1122; yield: 0.38 g, 75.54%; m.p. 469–472 K).

Compound (I)

Crystal data

$C_{30}H_{39}ClO_4$
M_r = 499.09
Trigonal, $R\bar{3}$
a = 34.3749 (8) Å
b = 34.3749 (8) Å
c = 5.7585 (1) Å
V = 5892.8 (2) Å^3
Z = 9
D_x = 1.266 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 19 304 reflections
θ = 2.0–27.5°
μ = 0.18 mm^{-1}
T = 160 (2) K
Prism, colourless
0.30 × 0.12 × 0.10 mm

Data collection

Nonius KappaCCD area-detector diffractometer
φ and ω scans with κ offsets
Absorption correction: multi-scan (*SORTAV*; Blessing, 1995)
T_{min} = 0.909, T_{max} = 0.984
29 761 measured reflections
5990 independent reflections
5077 reflections with $I > 2\sigma(I)$
R_{int} = 0.062
θ_{max} = 27.5°
$h = -44 \rightarrow 41$
$k = -44 \rightarrow 44$
$l = -7 \rightarrow 7$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.049
$wR(F^2)$ = 0.127
S = 1.02
5987 reflections
324 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0672P)^2 + 7.0766P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.60 e Å^{-3}
$\Delta\rho_{min}$ = −0.34 e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.00078 (19)
Absolute structure: Flack & Bernardinelli (2000)
Flack parameter = −0.21 (7)

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

D—H···A	D—H	H···A	D···A	D—H···A
O3—H3A···O3^{i}	0.76 (3)	1.95 (3)	2.710 (2)	177 (3)

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

Compound (II)

Crystal data

$C_{37}H_{54}N_2O_3{\cdot}H_2O$
M_r = 592.86
Monoclinic, $P2_1$
a = 6.4219 (1) Å
b = 32.4115 (5) Å
c = 8.0981 (1) Å
β = 99.6510 (7)°
V = 1661.71 (4) Å^3
Z = 2
D_x = 1.185 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3313 reflections
θ = 2.0–26.0°
μ = 0.08 mm^{-1}
T = 160 (2) K
Prism, colourless
0.28 × 0.18 × 0.15 mm

Data collection

Nonius KappaCCD area-detector diffractometer
φ and ω scans with κ offsets
36 139 measured reflections
3302 independent reflections
2865 reflections with $I > 2\sigma(I)$
R_{int} = 0.052
θ_{max} = 26.0°
$h = -7 \rightarrow 7$
$k = -39 \rightarrow 39$
$l = -9 \rightarrow 9$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.037
$wR(F^2)$ = 0.092
S = 1.04
3299 reflections
451 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0500P)^2 + 0.1844P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.23 e Å^{-3}
$\Delta\rho_{min}$ = −0.22 e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.017 (5)

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

D—H···A	D—H	H···A	D···A	D—H···A
O17—H17A···O1W	0.85 (4)	1.90 (4)	2.748 (3)	172 (3)
O1W—H1W···N30^{i}	0.87 (2)	1.95 (2)	2.813 (3)	169 (4)
O1W—H2W···O35^{i}	0.88 (2)	1.96 (2)	2.835 (3)	170 (4)
O1W—H2W···O27^{i}	0.88 (2)	2.47 (4)	2.987 (3)	118 (3)

Symmetry code: (i) $x - 1, y, 1 + z$.

For compound (II), atom C4 on ring *A* of the steroid nucleus is disordered over two sites. The four ring C atoms of the ethoxypyrrolidine moiety are also disordered over two conformations and two sets of positions were defined for pyrrolidine ring atoms C31–C34. Constrained refinement of the site-occupation factors for the two disordered regions led to values of 0.788 (7) and 0.510 (13), respectively, for the major conformations. Chemically equivalent bonds involving the disordered C atoms were constrained to have similar lengths and the 1,3-distances within each conformation of the pyrrolidine ring were also restrained to be similar. Neighbouring disordered atoms within and between each conformation of the disordered region were also restrained to have similar atomic displacement parameters. The position of the hydroxy H atom in (I) was determined from a difference Fourier map and refined freely along with its isotropic displacement parameters. The positions of the water H atoms in (II) were also determined from a difference Fourier map and were refined along with their isotropic displacement parameters, while restraining the O—H bond length to 0.82 Å. The methyl H atoms in both compounds were constrained to an ideal geometry (C—H = 0.98 Å), with U_{iso}(H) = 1.5U_{eq}(C), but were allowed to rotate freely about the C—C bonds. All remaining H atoms were placed in geometrically idealized positions (C—H = 0.95–1.00 Å) and were constrained to ride on their parent atoms. The presence of Cl in compound (I) permitted the determination of the absolute configuration of the molecule by refining the Flack parameter [−0.21 (7), 2982 Friedel pairs; Flack, 1983; Flack & Bernardinelli, 2000]. Due to the absence of any significant anomalous scatterers in (II), attempts to confirm the absolute structure by refinement of the Flack parameter in the presence of 3177 sets of Friedel equivalents led to an inconclusive value of 0.0 (8). Therefore, the Friedel pairs were merged before the final refinement and the absolute configuration was assigned to correspond with the known chiral centres in a precursor molecule, which remained unchanged during the synthesis of (II). Reflections $\bar{1}1\bar{2}$, 012 and $\bar{1}11$ in (I), and 021, 011 and 040 in (II) were partially obscured by the beam stop and were omitted.

For both compounds, data collection: *COLLECT* (Nonius, 2000); cell refinement: *DENZO–SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO–SMN* and *SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 (Farrugia, 1999); software used to prepare material for publication: *SHELXL*97 and *PLATON* (Spek, 2003).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1678). Services for accessing these data are described at the back of the journal.

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