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Two azasteroidal [3,2-*c*]pyrazole derivatives: 2′-(*p*-fluorophenyl)-4-azapyrazolo[4′,3′:2,3]-5α-androstan-17β-yl acetate and 2′-(*p*-fluorophenyl)-4-azapyrazolo[4′,3′:2,3]-5α-androstan-17β-ol

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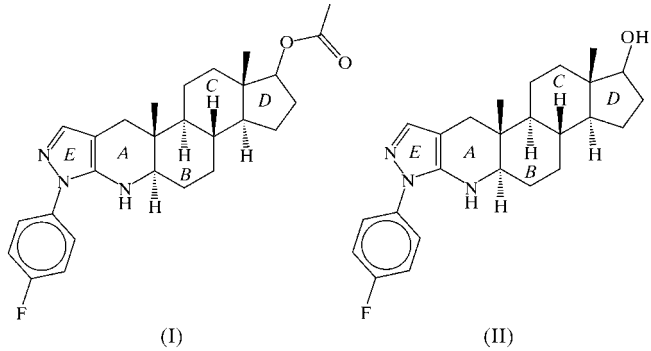
In both the title aza-steroids, 2′-(*p*-fluorophenyl)-4-azapyrazolo[4′,3′:2,3]-5α-androstan-17β-yl acetate, $C_{27}H_{34}FN_3O_2$, (I), and 2′-(*p*-fluorophenyl)-4-azapyrazolo[4′,3′:2,3]-5α-androstan-17β-ol, $C_{25}H_{32}FN_3O$, (II), the tetrahydropyridine ring adopts a half-chair conformation and is considerably strained as a consequence of the presence of the fused planar pyrazole ring. In both compounds, both cyclohexane rings have chair conformations, while the cyclopentane ring has an envelope conformation. All the rings of the steroid nucleus are *trans* fused. In (I), intermolecular N—H···O, C—H···F, C—H···O and C—H···N interactions are observed in the solid state, while intermolecular N—H···O and O—H···N hydrogen bonds are observed in (II).

Comment

There has been considerable interest in the synthesis and biological study of several heterocyclic steroids as extremely potent anti-inflammatory agents (Gupta *et al.*, 1996, and references therein). It is known that 2′-phenyl-11β,17α,21-trihydroxy-16α-methyl-20-oxo-4-pregneno[3,2-*c*]pyrazol-21-yl acetate and its *p*-flurophenyl analogue are, respectively, 60 and 100 times more active than hydrocortisone (Hirschmann *et al.*, 1963, 1964), and the importance of the [3,2-*c*]pyrazole function has been demonstrated by a number of investigators (Fried *et al.*, 1963; Hirschmann *et al.*, 1963; Hannah *et al.*, 1975). Both cortivazol and nivazol have the [3,2-*c*]pyrazole structural component, and the 3-keto function is absent, while both have been described as potent anti-inflammatory steroids (Gupta *et al.*, 1996, and references therein). In this paper, we report the crystal and molecular structures of the ring-*A*-modified steroids 2′-(*p*-fluorophenyl)-4-azapyrazolo[4′,3′:2,3]-5α-androstan-17β-yl acetate, (I), and 2′-(*p*-fluorophenyl)-4-azapyrazolo[4′,3′:2,3]-5α-androstan-17β-ol, (II). Although both (I) and (II) were found to be more active than hydrocortisone, the acetoxy derivative, (I), was found to be less active than the hydroxy derivative, (II) (Gupta *et al.*, 1996). Crystallographic analyses have been carried out in order to study the influence of the fused pyrazole moiety on the steroid skeleton. The present study extends our ongoing investigation of a series of similar ring-*A*- or ring-*D*-modified steroids.



Figs. 1 and 2 show the asymmetric units of (I) and (II), respectively, with the atomic numbering schemes. All the rings of the steroid skeleton are *trans* connected. The corresponding bond lengths and angles in (I) and (II) are almost equivalent and are comparable to those found in similar ring-*A*-modified steroids (Lisgarten & Palmer, 1998; Lisgarten *et al.*, 2003).

In (I), ring *A* of the steroid nucleus adopts a half-chair conformation, being considerably strained as a consequence of the presence of the fused planar pyrazole ring *E* [the puckering parameters (Cremer & Pople, 1975) are Q = 0.493 (2) Å, q_2 = 0.391 (2) Å, q_3 = 0.300 (2) Å, θ = 52.5 (2)° and φ_2 = 260.2 (3)° for the atom sequence N4—C3—C2—C1—C10—C5]. Steroidal rings *B* and *C* exhibit chair conformations [ring *B*: Q = 0.571 (2) Å, q_2 = 0.033 (2) Å, q_3 = 0.571 (2) Å, θ = 3.4 (2)° and φ_2 = 276 (3)° for the atom sequence C5—C6—C7—C8—C9—C10; ring *C*: Q = 0.580 (2) Å, q_2 = 0.052 (2) Å, q_3 = 0.578 (2) Å, θ = 4.9 (2)° and

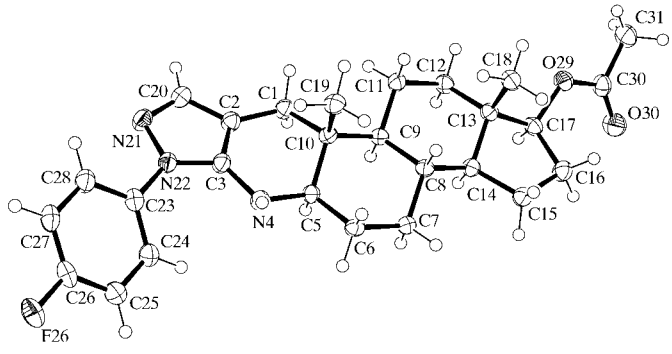


Figure 1
A view of the molecule of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are represented by circles of arbitrary radii.

† Deceased.

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φ_2 = 270 (2)° for the atom sequence C8—C9—C11—C12—C13—C14]. Similar conformations have been reported in related structures (Lisgarten & Palmer, 1998; Lisgarten *et al.*, 2003). Five-membered ring *D* of the steroid skeleton has a 13β-envelope conformation. The pseudo-rotation angle is 350.0 (1)° and the maximum torsion angle is 47.6 (1)° for the atom sequence C13—C14—C15—C16—C17 (Rao *et al.*, 1981). In (II), steroidal ring *A* also exhibits a half-chair conformation, being strained as a consequence of the presence of the fused pyrazole ring *E*, as in (I) [Q = 0.466 (2) Å, q_2 = 0.367 (2) Å, q_3 = 0.287 (2) Å, θ = 52.0 (3)° and φ_2 = 267.5 (3)° for the atom sequence N4—C3—C2—C1—C10—C5]. The puckering parameters of steroidal rings *B* and *C* [ring *B*: Q = 0.579 (2) Å, q_2 = 0.050 (2) Å, q_3 = 0.577 (2) Å, θ = 4.8 (2)° and φ_2 = 327 (2)° for the atom sequence C5—C6—C7—C8—C9—C10; ring *C*: Q = 0.581 (2) Å, q_2 = 0.031 (2) Å, q_3 = 0.580 (2) Å, θ = 3.0 (2)° and φ_2 = 310 (4)° for the atom sequence C8—C9—C11—C12—C13—C14] are indicative of chair conformations. Five-membered ring *D* of the steroid nucleus has a 13β-envelope conformation, with a pseudo-rotation angle of 348.3 (1)° and a maximum torsion angle of 48.9 (1)° for the atom sequence C13—C14—C15—C16—C17. The presence of either an acetoxy or a hydroxy substituent on atom C17 does not affect the conformation of ring *D* in (I) and (II). In related structures (Lisgarten & Palmer, 1998; Lisgarten *et al.*, 2003), steroidal ring *D* also has a half-chair conformation, even when atom C17 is disubstituted (17β-hydroxy and 17α-methyl).

The C19—C10···C13—C18 pseudo-torsion angle, which provides a quantitative measure of the twist about the length of the molecule, is 0.73 (14)° in (I) and 1.36 (16)° in (II). The dihedral angle between the plane of the fluorophenyl ring and the average molecular plane through rings *E*, *A*, *B*, *C* and *D* is 28.29 (5)° in (I) and 29.05 (5)° in (II). The *E*/*A*/*B*/*C*/*D* ring systems of the two compounds can be superimposed on one another and exhibit a small r.m.s. deviation of the equivalent atoms (0.168 Å), which indicates that the change in substituent on atom C17 of ring *D* (from acetoxy to hydroxy) does not affect the overall conformation of the steroidal nucleii.

In (I), atom N4 forms an intermolecular N—H···O hydrogen bond with carbonyl atom O30 of an adjacent molecule. This interaction links the molecules into a chain that runs parallel to the *z* axis and has a graph-set motif of *C*(12) (Bernstein *et al.*, 1995). Atom C15 acts as a donor for a weak intermolecular C—H···F interaction with atom F26 of an adjacent molecule. This interaction links the molecules into a chain that runs parallel to the *y* axis and has a graph-set motif of *C*(15). Atom C20 is involved in an intermolecular C—H···O interaction with carbonyl atom O30 of a different adjacent molecule. This interaction links the molecules into a continuous chain that runs parallel to the *x* axis and has a graph-set motif of *C*(13). Atom C25 acts as a donor for a weak intermolecular C—H···N interaction with atom N21 of the pyrazole moiety of a symmetry-related molecule. This weak interaction links the molecules into a chain that runs parallel to the *x* axis and has a graph-set motif of *C*(6) (Table 1). Atom C31 (*via* atom H31*C*) is involved in an intermolecular C—H···π interaction with pyrazole ring *E* of a neighbouring molecule [H31*C*···*Cg* = 2.75 Å, C31···*Cg* = 3.665 (2) Å and C31—H31*C*···*Cg* = 155°, where *Cg* is the centroid of ring *E* at ($x-\frac{1}{2}, \frac{1}{2}-y, -z$)].

In (II), atom N4 forms an intermolecular N—H···O hydrogen bond with hydroxy atom O17 of an adjacent molecule. This interaction links the molecules into a chain that runs parallel to the *z* axis and has a graph-set motif of *C*(10). Hydroxy atom O17 participates in an intermolecular O—H···N hydrogen bond with atom N21 of the pyrazole moiety of a different adjacent molecule. This interaction links the molecules into a continuous chain that runs parallel to the *y* axis and has a graph-set motif of *C*(12) (Table 2). There is a short intermolecular contact between atoms H16*B* and H19*B*($\frac{1}{2}-x, -y, -\frac{1}{2}+z$) (H···H = 2.15 Å), which is smaller than the sum of the van der Waals radii of the corresponding atoms.

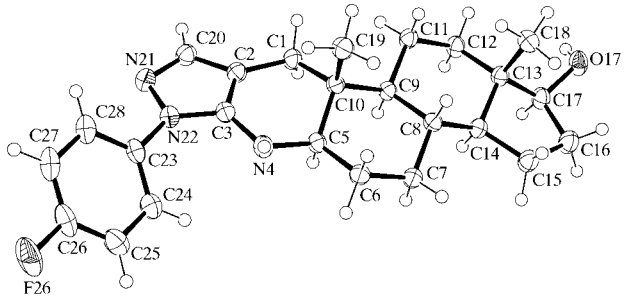

Figure 2
A view of the molecule of (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are represented by circles of arbitrary radii.

Experimental

To a refluxing solution of 17β-acetoxy-3-chloro-4-aza-5-androst-2-ene-2-carbaldehyde (0.5 g, 1.32 mmol) in aldehyde-free ethanol (250 ml), glacial acetic acid (1.5 ml) was added dropwise. The solution was refluxed for 10 min and then *p*-fluorophenylhydrazine hydrochloride (0.25 g) was added; the resulting solution was refluxed for 5 h. The solution was concentrated to ~20 ml and then poured into ice-cold water and dried. The resulting solid, (I) (institution code DPJ-308), was crystallized from acetone (yield 0.25 g, 41.9%; m.p. 511–513 K). A mixture of (I) (0.2 g, 0.443 mmol) and potassium carbonate (0.5 g) in aqueous methanol (10%, 50 ml) was stirred at room temperature for 3 h. The resulting slurry was poured into ice-cold water, and the precipitated product was filtered, washed and dried. The resulting solid, (II) (institution code DPJ-309), was crystallized from acetone (yield 0.125 g, 68.9%; m.p. 513–515 K).

Compound (I)

Crystal data

$C_{27}H_{34}FN_3O_2$
M_r = 451.57
Orthorhombic, $P2_12_12_1$
a = 7.2545 (1) Å
b = 13.5417 (2) Å
c = 23.6387 (4) Å
V = 2322.23 (6) Å^3
Z = 4
D_x = 1.292 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3850 reflections
θ = 2.0–30.0°
μ = 0.09 mm^{-1}
T = 160 (2) K
Prism, colourless
0.25 × 0.10 × 0.08 mm

Data collection

Nonius KappaCCD diffractometer	$R_{int} = 0.062$
φ and ω scans with κ offsets	$\theta_{max} = 30.0^\circ$
42 805 measured reflections	$h = 0 \rightarrow 10$
3830 independent reflections	$k = 0 \rightarrow 19$
3157 reflections with $I > 2\sigma(I)$	$l = 0 \rightarrow 33$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0503P)^2 + 0.2409P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.043$	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2) = 0.103$	$\Delta\rho_{max} = 0.23$ e Å^{-3}
$S = 1.04$	$\Delta\rho_{min} = -0.20$ e Å^{-3}
3825 reflections	Extinction correction: *SHELXL*97
306 parameters	Extinction coefficient: 0.0093 (19)
H atoms treated by a mixture of independent and constrained refinement	

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

D—H···A	D—H	H···A	D···A	D—H···A
N4—H4···O30^{i}	0.90 (3)	2.31 (3)	3.208 (2)	177 (2)
C15—H15B···F26^{ii}	0.99	2.53	3.455 (2)	155
C20—H20···O30^{iii}	0.95	2.56	3.477 (3)	162
C25—H25···N21^{iv}	0.95	2.58	3.399 (3)	145

Symmetry codes: (i) $\frac{3}{2} - x, 1 - y, \frac{1}{2} + z$; (ii) $2 - x, \frac{1}{2} + y, \frac{1}{2} - z$; (iii) $x - \frac{1}{2}, \frac{1}{2} - y, -z$; (iv) $1 + x, y, z$.

Compound (II)

Crystal data

$C_{25}H_{32}FN_3O$	Mo $K\alpha$ radiation
$M_r = 409.54$	Cell parameters from 2816 reflections
Orthorhombic, $P2_12_12_1$	$\theta = 2.0$–27.5°
$a = 7.0990$ (2) Å	$\mu = 0.08$ mm^{-1}
$b = 14.8153$ (4) Å	$T = 160$ (2) K
$c = 20.2961$ (4) Å	Prism, colourless
$V = 2134.62$ (9) Å^3	0.25 × 0.23 × 0.10 mm
$Z = 4$	
$D_x = 1.274$ Mg m^{-3}	

Data collection

Nonius KappaCCD diffractometer	$R_{int} = 0.063$
φ and ω scans with κ offsets	$\theta_{max} = 27.5^\circ$
34 805 measured reflections	$h = 0 \rightarrow 9$
2798 independent reflections	$k = 0 \rightarrow 19$
2390 reflections with $I > 2\sigma(I)$	$l = 0 \rightarrow 26$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0501P)^2 + 0.2133P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.037$	$(\Delta/\sigma)_{max} = 0.001$
$wR(F^2) = 0.092$	$\Delta\rho_{max} = 0.22$ e Å^{-3}
$S = 1.04$	$\Delta\rho_{min} = -0.17$ e Å^{-3}
2797 reflections	Extinction correction: *SHELXL*97
282 parameters	Extinction coefficient: 0.0114 (15)
H atoms treated by a mixture of independent and constrained refinement	

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

D—H···A	D—H	H···A	D···A	D—H···A
N4—H4···O17^{iv}	0.88 (2)	2.14 (2)	3.021 (2)	172.7 (18)
O17—H17A···N21^{v}	0.83 (3)	2.26 (3)	3.086 (2)	177 (3)

Symmetry codes: (iv) $\frac{1}{2} - x, -y, \frac{1}{2} + z$; (v) $\frac{1}{2} + x, \frac{1}{2} - y, -z$.

The positions of the amine H atoms in (I) and (II) and of the hydroxy H atom in (II) were determined from a difference Fourier map and refined freely, along with their isotropic displacement parameters. For both compounds, the methyl H atoms were constrained to an ideal geometry [C—H = 0.98 Å and 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 idealized positions (C—H = 0.95–1.00 Å) and were constrained to ride on their parent atoms. The crystals of (I) and (II) are enantiomerically pure. However, because of the absence of any significant anomalous scatterers in (I) and (II), attempts to confirm the absolute structure by refinement of the Flack (1983) parameter in the presence of 2940 sets of Friedel equivalents for (I) [2094 for (II)] led to an inconclusive value (Flack & Bernardinelli, 2000) of 0.1 (8) [−0.1 (9) for (II)]. Therefore, the Friedel pairs were merged before the final refinement and the absolute configuration of (I) was assigned to correspond to that of the known chiral centres in a precursor molecule, which remained unchanged during the synthesis of (I). Since (I) was the starting material for the synthesis of (II), the absolute configuration of (II) was assumed to correspond to that of the known chiral centres in (I), which remained unchanged during the synthesis of (II). Reflections 013, 020, 111, 112 and 041 in (I), and 012 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); structure solution: *SIR*92 (Altomare *et al.*, 1994); structure refinement: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 (Farrugia, 1997); 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: SK1673). Services for accessing these data are described at the back of the journal.

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