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An aza-steroidal [17,16-*c*]pyrazole derivative: 2′-(*p*-fluorophenyl)-17a-aza-2′*H*-pyrazolo[4′,3′:16,17]-*D*-homoandrost-4-en-3-one

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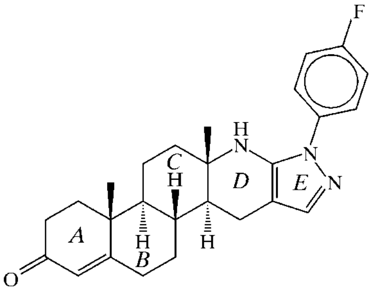
The asymmetric unit of the title compound, $C_{26}H_{30}FN_3O$, contains two crystallographically independent molecules, the core skeletons of which have the same absolute configuration and almost identical conformations, except for differences in the orientation of the *p*-fluorophenyl ring. The tetrahydropyridine ring adopts a half-chair conformation, while the cyclohexenone ring has a slightly distorted envelope conformation. The cyclohexane rings have chair conformations, sometimes slightly distorted. Intermolecular N—H···O, N—H···N and C—H···F interactions and an intramolecular C—H···N interaction are observed.

Comment

There has been considerable interest in the synthesis and biological activity of several heterocyclic steroids as extremely potent anti-inflammatory agents (Gupta *et al.*, 1996, and references therein). In the 17a-aza series, the presence of an α,β-unsaturated ketone group produces compounds with good activity, while hydroxy and acetoxy derivatives are found to be inactive. The fusion of pyrazole ring systems at the 2,3- and/or 16,17-positions of aza-steroids affords compounds with enhanced anti-inflammatory activity compared with standard drugs in the androstane series (Gupta *et al.*, 1996). Crystal structure 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. In a previous paper, we reported two ring-*A*-modified steroids, namely 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 (Thamotharan *et al.*, 2003). In this paper, we report the crystal and molecular structure of a ring-*D*-modified steroid, namely2′-(*p*-fluorophenyl)-17a-aza-2′*H*-pyrazolo[4′,3′:16,17]-*D*-homoandrost-4-en-3-one, (I).



(I)

The crystals of (I) are enantiomerically pure. However, due to the absence of any significant anomalous scatterers in the compound, the absolute configuration of the molecule has not been determined by the present X-ray diffraction experiment. The enantiomer used in the refinement was assumed to correspond with the configuration of the known chiral centres in a precursor molecule, which remained unchanged during the synthesis of (I).

There are two symmetry-independent molecules, *A* and *B*, in the asymmetric unit of (I), and these are depicted in Fig. 1. The corresponding bond lengths and angles for the independent molecules agree well with each other. Excluding the atoms of the *p*-fluorophenyl group, the core skeletons of the two molecules have the same absolute configuration and almost identical conformations, with only very minor differences in the puckering of some rings. The unweighted r.m.s. fit of the remaining non-H atoms of molecule *A* with the corresponding atoms of molecule *B* is 0.12 Å. The main difference between the conformations of the two molecules is the orientation of the plane of the *p*-fluorophenyl ring in molecule *B*, which is tilted by approximately 63° with respect to its orientation in molecule *A*. The angle between the mean planes through the *p*-fluorophenyl ring (excluding the F atom) and the pyrazole ring is 38.85 (11)° for molecule *A* and −23.86 (11)° for molecule *B*. Another difference between the two symmetry-independent molecules is that the positions of the lone electron pair and the H atom on atom N17*B* in molecule *B* are reversed with respect to their positions on atom N17*A* in molecule *A*. This effective inversion of the configuration at this N atom also has consequences for the hydrogen-bonding interactions, as described below.

In both independent molecules, the methyl groups C18 and C19 lie in the expected β orientation, while the geometry at the *B*/*C* and *C*/*D* ring junctions is in each case all-*trans*. The C4═C5 distances of 1.343 (3) and 1.346 (3) Å in molecules *A* and *B*, respectively, confirm the localization of the double bond at this position.

The cyclohexenone ring *A* adopts a slightly distorted envelope conformation in both independent molecules, with

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‡ Deceased.

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the distortion being more severe and slightly towards a half-chair conformation in molecule *A*. Atoms C1*A* and C1*B* form the envelope flap in the respective molecules and the conformation of this ring is a consequence of the C4=C5 alkene bond. The puckering parameters (Cremer & Pople, 1975) for this ring (atom sequence C1*A*–C5*A*/C10*A*) in molecule *A* are Q = 0.436 (2) Å, q_2 = 0.347 (2) Å, q_3 = 0.265 (2) Å, θ = 52.7 (3)° and φ_2 = 12.2 (4)°, while for molecule *B* (atom sequence C1*B*–C5*B*/C10*B*), Q = 0.450 (2) Å, q_2 = 0.371 (2) Å, q_3 = 0.254 (2) Å, θ = 55.7 (3)° and φ_2 = 8.2 (3)°.

The steroidal ring *B* exists in a slightly distorted chair conformation in both molecules, with puckering parameters for molecule *A* [molecule *B* in brackets] of Q = 0.543 (2) Å [0.529 (2) Å], q_2 = 0.099 (2) Å [0.082 (2) Å], q_3 = 0.534 (2) Å [0.522 (2) Å], θ = 10.6 (2)° [9.2 (2)°] and φ_2 = 195.1 (12)° [192.7 (14)°] for the atom sequence C5*A*–C10*A* [C5*B*–C10*B*].

Ring *C* has a chair conformation in both molecules, although it is slightly more distorted in molecule *A* than in molecule *B*. The puckering parameters for molecule *A* [molecule *B* in brackets] are Q = 0.559 (2) Å [0.570 (2) Å], q_2 = 0.077 (2) Å [0.041 (2) Å], q_3 = 0.554 (2) Å [0.568 (2) Å], θ = 7.6 (2)° [3.9 (2)°] and φ_2 = 218.0 (15)° [207 (3)°] for the atom sequence C8*A*/C9*A*/C11*A*–C14*A* [C8*B*/C9*B*/C11*B*–C14*B*]. The tetrahydropyridine ring *D* of the steroid nucleus adopts a half-chair conformation in both molecules *A* and *B*, twisted at C13*A*—C14*A* and C13*B*—C14*B*, respectively. The ring is considerably strained as a consequence of the presence of the fused planar pyrazole ring. The puckering parameters for ring *D* in molecule *A* [molecule *B* in brackets] are Q = 0.497 (2) Å [0.480 (2) Å], q_2 = 0.379 (2) Å [0.377 (2) Å], q_3 = 0.323 (2) Å [0.297 (2) Å], θ = 49.6 (2)° [51.8 (2)°] and φ_2 = 83.5 (3)° [94.4 (3)°] for the atom sequence N17*A*/C13*A*–C17*A* [N17*B*/C13*B*–C17*B*].

The pseudo-torsion angle C19*A*—C10*A*···C13*A*—C18*A* [−1.31 (15)°] in molecule *A* and C19*B*—C10*B*···C13*B*—C18*B* [1.88 (17)°] in molecule *B* provide a quantitative measure of the twist about the length of the molecule and show that the molecules in (I) are not twisted to any significant degree and, with the exception of the tilted *p*-fluorophenyl group, that the entire molecule is quite flat. The values are comparable with those of related structures (Thamotharan *et al.*, 2003).

In (I), atom C24*B* forms a weak intramolecular C—H···N interaction (Table 1) with atom N17*B* of molecule *B*, which leads to a loop with a graph-set motif of *S*(6) (Bernstein *et al.*, 1995). Atoms C27*A* and C27*B* are involved in weak intermolecular C—H···F interactions with atoms F26*A* and F26*B*, respectively, of two different adjacent molecules, and each interaction links the *A* and *B* molecules independently into chains which have graph-set motifs of *C*(4) and run parallel to the *y* axis. Atoms N17*A* and N17*B* participate in intermolecular N—H···O or N—H···N hydrogen bonds with atoms O3*B* and N21*A*, respectively, of two different neighbouring molecules. These interactions serve to crosslink molecules *A* with *B*, and act co-operatively to produce chains of alternating *A* and *B* molecules which have a graph-set motif of $C_2^2(16)$ and run parallel to the *y* axis. Atom C4*A* acts as donor for a weak intermolecular C—H···N interaction with atom N21*B* of an adjacent molecule.

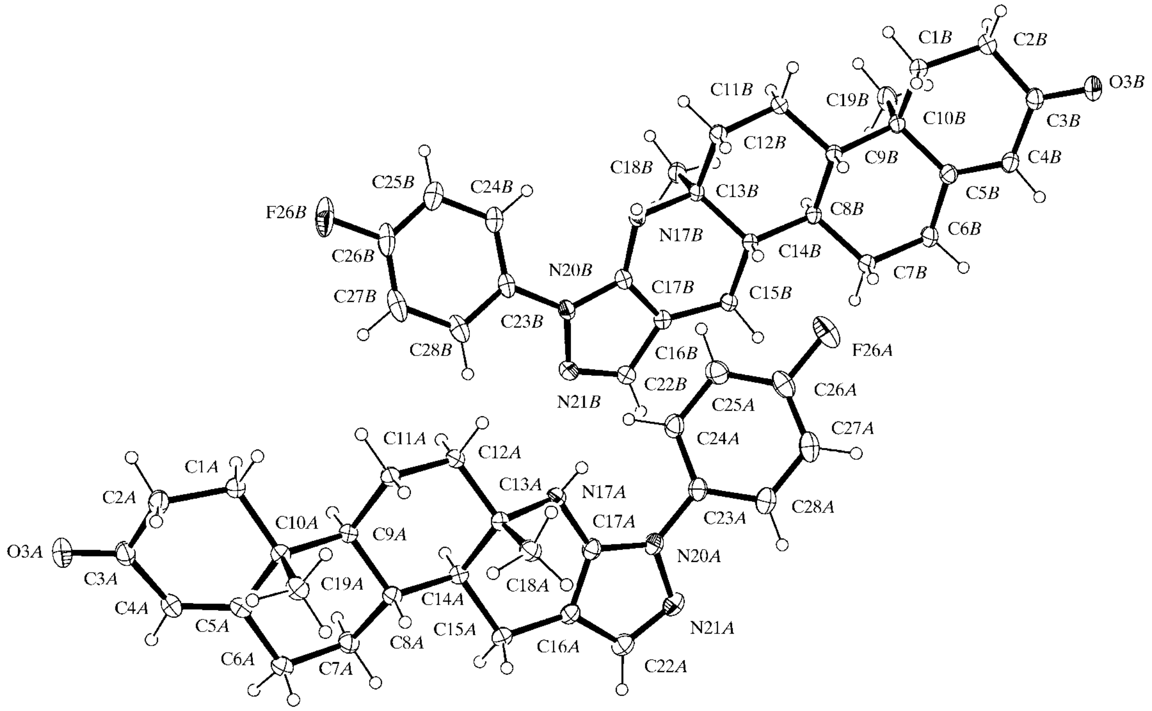

Figure 1

A view of the two independent molecules of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are represented by spheres of arbitrary radii.

Experimental

A solution of 2′-(*p*-fluorophenyl)-17a-aza-*D*-homo-5-androsteno-[17,16-*c*]pyrazol-3β-ol (0.5 g, 1.186 mmol) in cyclohexanone (5 ml) and toluene (100 ml) was distilled slowly while aluminium isopropoxide (1 g) in toluene (10 ml) was added to remove moisture. Distillation was continued for 30 min. The reaction mixture was refluxed for 4 h and allowed to stand overnight. The solution was filtered, the filtrate was steam distilled and the residue obtained was crystallized from ethyl acetate to afford (I) (institution code DPJ-255) (yield 0.35 g, 70.42%; m.p. 499–501 K).

Crystal data

$C_{26}H_{30}FN_3O$
$M_r = 419.53$
Monoclinic, $P2_1$
$a = 13.5243$ (2) Å
$b = 7.3983$ (1) Å
$c = 21.8934$ (3) Å
$\beta = 102.1562$ (8)°
$V = 2141.47$ (5) Å^3
$Z = 4$
$D_x = 1.301$ Mg m^{-3}

Mo *K*α radiation
Cell parameters from 6708 reflections
$\theta = 1.0$–30.0°
$\mu = 0.09$ mm^{-1}
$T = 160$ (2) K
Prism, colourless
0.30 × 0.28 × 0.15 mm

Data collection

Nonius KappaCCD area-detector diffractometer
φ and ω scans with κ offsets
64 206 measured reflections
6714 independent reflections
5595 reflections with $I > 2\sigma(I)$

$R_{\rm int} = 0.055$
$\theta_{\rm max} = 30.0°$
$h = 0 \rightarrow 19$
$k = 0 \rightarrow 10$
$l = -30 \rightarrow 30$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.041$
$wR(F^2) = 0.100$
$S = 1.02$
6704 reflections
571 parameters
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0503P)^2 + 0.2257P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\rm max} < 0.001$
$\Delta\rho_{\rm max} = 0.23$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.19$ e Å^{-3}

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C24*B*—H242···N17*B*	0.95	2.36	2.990 (2)	123
N17*A*—H171···O3*B*$^{\rm i}$	0.86 (2)	2.16 (2)	2.975 (2)	158.6 (19)
N17*B*—H172···N21*A*$^{\rm ii}$	0.83 (2)	2.54 (2)	3.281 (2)	149 (2)
C4*A*—H41···N21*B*$^{\rm iii}$	0.95	2.61	3.467 (2)	151
C27*A*—H271···F26*A*$^{\rm i}$	0.95	2.41	3.320 (2)	161
C27*B*—H272···F26*B*$^{\rm iii}$	0.95	2.42	3.365 (3)	171

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

The positions of the amine H atoms were determined from a difference Fourier map and refined freely along with their isotropic displacement parameters. The methyl H atoms were constrained to an ideal geometry (C—H = 0.98 Å), with $U_{\rm iso}({\rm H}) = 1.5U_{\rm eq}({\rm C})$, 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. Due to the absence of any significant anomalous scatterers in (I), attempts to confirm the absolute structure by refinement of the Flack (1983) parameter in the presence of 5710 sets of Friedel equivalents led to an inconclusive value (Flack & Bernardinelli, 2000) of 0.2 (6). Therefore, the Friedel pairs were merged before the final refinement and the absolute configuration was assigned to correspond with that of the known chiral centres in a precursor molecule, which remained unchanged during the synthesis of (I). Reflections 003, $\overline{1}03$, 012, 101, 110, 011, 002, $\overline{1}11$, $\overline{1}02$ and $\overline{1}01$ were partially obscured by the beam stop and were omitted.

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, 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: SK1692). Services for accessing these data are described at the back of the journal.

References

Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.
Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.
Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Flack, H. D. & Bernardinelli, G. (2000). *J. Appl. Cryst.* **33**, 1143–1148.
Gupta, R., Pathak, D. & Jindal, D. P. (1996). *Eur. J. Med. Chem.* **31**, 241–247.
Nonius (2000). *COLLECT*. Nonius BV, Delft, The Netherlands.
Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
Sheldrick, G. M. (1997). *SHELXL*97. University of Göttingen, Germany.
Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.
Thamotharan, S., Parthasarathi, V., Gupta, R., Jindal, D. P. & Linden, A. (2003). *Acta Cryst.* C**59**, o724–o726.