Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

(8*R*,9*S*,13*S*,14*S*)-17-Butyl-16,17a-dioxo-17-aza-*D*-homoestra-1,3,5(10)-trien-3-ol

R. Hema,[a] V. Parthasarathi,[a]* Ranju Bansal[b] and Anthony Linden[c]

[a]Department of Physics, Bharathidasan University, Tiruchirappalli 620 024, India, [b]University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh 160 014, India, and [c]Institute of Organic Chemistry, University of Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland

Correspondence e-mail: vpsarati@yahoo.com

Key indicators

Single-crystal X-ray study
T = 160 K
Mean σ(C–C) = 0.004 Å
R factor = 0.047
wR factor = 0.122
Data-to-parameter ratio = 8.2

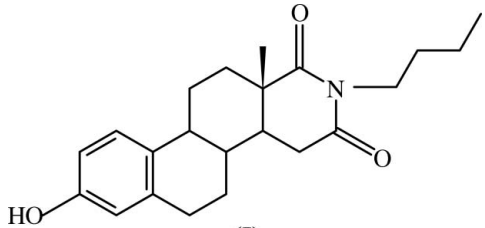
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

In the title compound, $C_{22}H_{29}NO_3$, a modified synthetic D-homo steroid, the cyclohexene ring adjacent to the aromatic ring adopts a half-chair conformation, while the cyclohexane ring has an ideal chair conformation. The heterocyclic ring adopts a 14β-sofa conformation. The butyl substituent is nearly planar, this plane lying almost perpendicular to the least-squares plane of the heterocyclic ring. Intermolecular O—H···O hydrogen bonds link the molecules into extended chains and the compound also exhibits some weak intermolecular C—H···O interactions.

Received 22 August 2005
Accepted 25 August 2005
Online 31 August 2005

Comment

The activity of steroid hormones is dependent on a number of factors, including solubilization, motility, transport, metabolism, and complementarity of fit between hormone and receptor. Functional differences caused by structural modifications may be due to an influence of the modification upon any or all of these factors. In many cases, structural changes in one part of a steroid alter the rate of reaction at a distant point, a phenomenon known as conformational transmission (Duax *et al.*, 1979). Compounds that bind to the estrogen receptor exhibit remarkable variability in composition and stereochemistry. They include non-steroidal compounds, semi-synthetic unnatural steroids and simple one- or two-ring compounds. The only structural element that all of these compounds have in common is a phenolic ring (Duax *et al.*, 1984). It is known that intrinsic free radical scavenging contributes to the receptor-independent neuroprotective effects of estrogens and this activity is inherently associated with the presence of a phenolic *A* ring in the steroid (Prokai *et al.*, 2003). As a continuation of our previous studies on *D*-homoestra-1,3,5(10)-triene derivatives (Hema *et al.*, 2004; 2005), an X-ray crystal structure determination of the title compound, (I), has been undertaken in order to better understand the influence of structural modifications upon overall molecular geometry and conformation. Compound (I) possesses a bulky substituent at the N atom of the heterocyclic ring and a hydroxy substituent at C3.



(I)

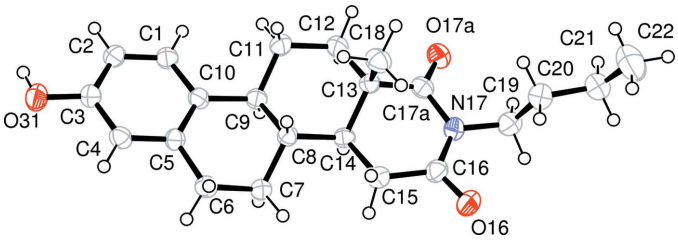


Figure 1
View of the molecule of (I), showing the atom-labelling scheme. Displacement ellipsoids for the non-H atoms are drawn at the 50% probability level.

A view of the molecule of (I) with the atom-labelling scheme is shown in Fig. 1. The bond lengths and bond angles are comparable to those in the structures of the related 17-butyl- and 17-allyl-16,17a-dioxo-17-aza-*D*-homoestra-1,3,5(10)-trien-3-yl acetate derivatives (Hema *et al.*, 2004; 2005). The cyclohexene ring, *B*, adjacent to the aromatic ring adopts a 7α,8β-half-chair conformation [puckering parameters (Cremer & Pople, 1975) Q = 0.518 (3) Å, θ = 50.5 (3)°, φ = 158.4 (4)°] as a result of the fusion with the planar aromatic ring, *A*. The cyclohexane ring, *C*, has an ideal chair conformation [Q = 0.576 (3) Å, θ = 4.0 (3)°, φ = 326 (5)°].

The butyl substituent at N17 of (I) is nearly planar, this plane lying almost perpendicular to the least-squares plane of the heterocyclic ring, *D*. The r.m.s. deviation of the butyl group atoms N17, C19, C20, C21 and C22 from their mean plane is 0.035 Å, and the dihedral angle between the plane of the butyl group and the least-squares plane through ring *D* is 89.91 (16)°.

The corresponding values observed in the 17-butyl- and 17-allyl-3yl acetate analogues are 82.1 (2) and 84.5 (5)°, respectively (Hema *et al.*, 2004, 2005). Ring *D* in (I) adopts a flattened 14β-sofa conformation [Q = 0.495 (3) Å, θ = 59.2 (3)°, φ = 215.9 (4)°]. The flattening of ring *D* is indicated by the torsion angles C13—C17*a*—N17—C16 [10.8 (4)°] and C17*a*—N17—C16—C15 [11.3 (4)°] The flattening is associated with the constraints to the ring conformation introduced by the normal planar arrangement about the amide N—C bond (sum of the angle at N17 = 359.6°). The *B*/*C* and *C*/*D* rings are *trans* fused.

In (I), the hydroxy group forms an intermolecular O—H···O hydrogen bond with the carbonyl atom O16 of an adjacent molecule (Table 1). This interaction links the molecules into extended chains, which run parallel to the [010] direction and have a graph-set motif of $C(12)$ (Bernstein *et al.*, 1995). Atom C15 acts as a donor for a weak intermolecular C—H···O interaction with carbonyl atom O17*a* of a different neighbouring molecule and thereby links the molecules into continuous chains, which run parallel to the [100] direction and can be described by the graph-set motif $C(6)$. Finally, atom C18 is involved in a weak intermolecular C—H···O interaction with the carbonyl atom O17*a* of yet another adjacent molecule, which produces continuous chains that also run parallel to the [100] direction and have a graph-set motif $C(5)$.

Experimental

A mixture of 17-butyl-16,17a-dioxo-17-aza-*D*-homo-1,3,5(10)-estratrien-3-yl acetate (0.5 g, 1.26 mmol), potassium carbonate (1.0 g) and 10% aqueous methanol (50 ml) was stirred at room temperature for 1 h. The reaction mixture was poured into water, and the precipitated material was filtered and dried. The solid obtained was crystallized from methanol to afford crystals of compound (I) (yield 0.3 g, 67.35%; m.p. 483–485 K).

Crystal data

$C_{22}H_{29}NO_3$
M_r = 355.46
Orthorhombic, $P2_12_12_1$
a = 6.2505 (2) Å
b = 13.3718 (4) Å
c = 22.9703 (7) Å
V = 1919.87 (10) Å^3
Z = 4
D_x = 1.230 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 1995 reflections
θ = 2.0–25.0°
μ = 0.08 mm^{-1}
T = 160 (2) K
Prism, colourless
0.18 × 0.13 × 0.05 mm

Data collection

Nonius KappaCCD area-detector diffractometer
φ and ω scans with κ offsets
Absorption correction: none
20155 measured reflections
1982 independent reflections
1601 reflections with $I > 2\sigma(I)$
R_{int} = 0.069
θ_{max} = 25.0°
$h = -7 \rightarrow 7$
$k = -15 \rightarrow 15$
$l = -27 \rightarrow 27$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.047
$wR(F^2)$ = 0.122
S = 1.09
1979 reflections
241 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0677P)^2 + 0.1751P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.24 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
O31—H31···O16^{i}	0.81 (3)	2.00 (3)	2.792 (3)	168 (3)
C15—H151···O17A^{ii}	0.99	2.45	3.397 (4)	159
C18—H183···O17A^{iii}	0.98	2.52	3.238 (3)	130

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

The methyl H atoms 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. The hydroxy H atom was located in a difference Fourier map and its position was refined freely along with an isotropic displacement parameter. All other H atoms in the structure were placed in geometrically idealized positions (C—H = 0.95–1.00 Å) and constrained to ride on their parent atoms with U_{iso}(H) = 1.2U_{eq}(C). Owing to the absence of any significant anomalous scatterers in the molecule, attempts to confirm the absolute structure by refinement of the Flack (1983) parameter in the presence of 1404 sets of Friedel pairs led to an inconclusive value (Flack & Bernardinelli, 2000) of 1.4 (15). Therefore, the Friedel pairs were merged before the final refinement and the absolute configuration was assigned to correspond to that of the known chiral centres in a precursor molecule, which remained unchanged during the synthesis of the title compound. Three low-angle reflections (020, 021 and 022) 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: *SIR92* (Altomare *et al*., 1994); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3* (Farrugia, 1999); software used to prepare material for publication: *SHELXL97* and *PLATON* (Spek, 2003).

RH thanks UGC, India, for the award of a minor research project, and RB thanks the late Professor D. P. Jindal for his guidance and help rendered in the synthesis of the title compound.

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.
Duax, W. L., Griffin, J. F. & Rohrer, D. C. (1984). *X-ray Crystallogrphy and Drug Action*, edited by A. S. Horn & C. J. De Ranter, pp. 405–425. Oxford: Clarendon Press.
Duax, W. L., Roher, D. C., Blessing, H. & Strong, D. (1979). *Acta Cryst.* B**35**, 2656–2664.
Farrugia, L. J. (1999). *J. Appl. Cryst.* **32**, 837–838.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Flack, H. D. & Bernardinelli, G. (2000). *J. Appl. Cryst.* **33**, 1143–1148.
Hema, R., Parthasarathi, V., Bansal, R. & Linden, A. (2005). *Acta Cryst.* E**61**, o160–o162.
Hema, R., Parthasarathi, V., Gupta, R. & Linden, A. (2004). *Acta Cryst.* E**60**, o2002–o2004.
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.
Prokai, L., Prokai, K., Perjesi, P., Zarikova, A. D., Perez, E. J., Liu, R. & Simpkins, J. W. (2003). *Neuroscience*, 100, 11744–11746.
Sheldrick, G. M. (1997). *SHELXL97*, University of Göttingen, Germany.
Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.