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17-Allyl-16,17a-dioxo-17-aza-D-homoestra-1,3,5(10)-trien-3-yl acetate

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Key indicators

Single-crystal X-ray study
T = 160 K
Mean σ(C–C) = 0.003 Å
R factor = 0.047
wR factor = 0.128
Data-to-parameter ratio = 10.1

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

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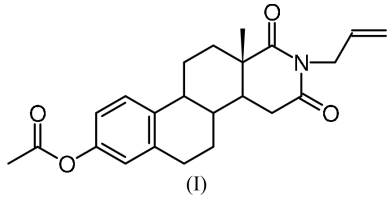
In the title compound, $C_{23}H_{27}NO_4$, a modified synthetic D-homo steroid, the cyclohexene ring adjacent to the aromatic ring adopts a half-chair conformation, while the cyclohexane ring has an ideal chair conformation and the heterocyclic ring has a sofa conformation. The plane of the allyl substituent lies almost perpendicular to the least-squares plane of the heterocyclic ring. The crystal structure contains a series of weak C—H···O intermolecular interactions.

Comment

Recently, synthetic steroids have been proposed as potential drug delivery systems targeting estrogen receptor positive breast cancer and other diseases associated with the estrogen receptor Erα (Yamamoto *et al.*, 2004, and references therein). Because of the common phenolic ring, *A*, the estradiol structures analogous to the title compound, (I), are expected to bind to the estrogen receptor (Roszak *et al.*, 1991). The title compound, however, does not possess a 17β-hydroxy function, which is important for high-affinity binding. When the 17β-hydroxy substituent is replaced with a 17-carbonyl group as, for example, in estrone, the binding affinity may be decreased (see, for example, Roszak *et al.*, 1991). It has also been suggested that the absence of an oxygen substituent, comparable to the estradiol 17-O, accounts for the inactivity or antagonistic properties observed for some ligands (Duax *et al.*, 1985). Recently, we have reported a related structure which was also a modified steroid (Hema *et al.*, 2004). As a continuation of our studies on modified steroids containing alkylating and other functional groups, the synthesis and crystal structure determination of the title compound, (I), has been undertaken.



(I)

Compound (I) is pseudo-isostructural with the related 17-butyl-16,17a-dioxo-17-aza-D-homoestra-1,3,5(10)-trien-3-yl acetate (Hema *et al.*, 2004), which possesses a 17-butyl group instead of the 17-allyl group of (I). The unit-cell dimensions for the two structures are very similar and the space groups are the same.

A view of the molecule of (I) with the atomic labeling scheme is shown in Fig. 1. In (I), the cyclohexene ring *B*, adjacent to the aromatic ring has a 7α,8β-half-chair

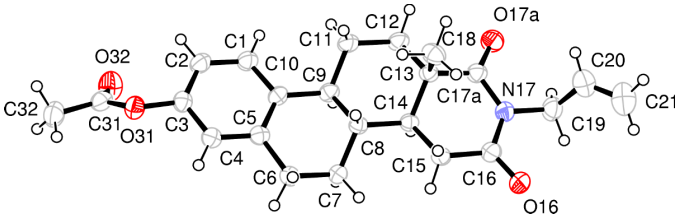


Figure 1
View of the molecule of the title compound, showing the atom-labeling scheme. Displacement ellipsoids are drawn at the 50% probability level. H atoms are represented by circles of arbitrary radius.

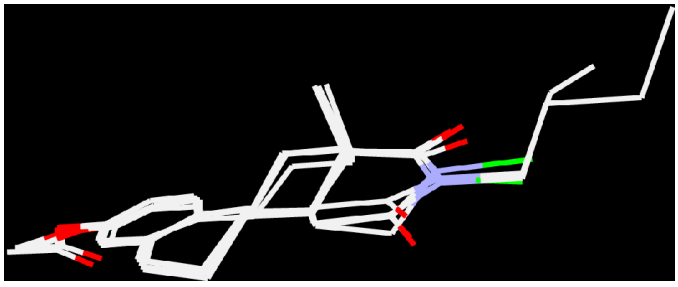


Figure 2
Superposition of the structures of the four steroid molecules discussed in the *Comment*. It was obtained by a least-squares fit of atoms C1–C18 plus N17, O16 and O17a.

conformation [puckering parameters (Cremer & Pople, 1975): Q = 0.537 (3) Å, θ = 49.7 (3)° and φ = 158.0 (4)°] as a result of the fusion with the planar aromatic ring *A*. The cyclohexane ring *C* has an ideal chair conformation [Q = 0.572 (3) Å, θ = 1.2 (3)° and φ = 310 (8)°]. With the substitution by the allyl group at N17, the heterocyclic ring *D* adopts a 14α-sofa conformation [Q = 0.505 (3) Å, θ = 56.0 (3)° and φ = 195.9 (4)°]. The dihedral angle between the plane of allyl group and the least-squares plane of ring *D* is 84.5 (5)°. The corresponding value observed in the 17-butyl analogue is 82.1 (2)° (Hema *et al.*, 2004). Ring *D* is flattened as indicated by the torsion angles for C13—C17a—N17—C16 and C17a—N17—C16—C15 of 3.1 (4) and 6.8 (4)°, respectively [−0.9 (4) and 11.0 (5)°, respectively, in the 17-butyl analogue]. This is associated with the constraints on the ring conformation introduced by the normal planar arrangement about the two amide N—C bonds (sum of the angles at N17 = 359.9°). The *B*/*C* and *C*/*D* rings are *trans*-fused. The plane of the acetate group attached to atom C3 is oriented at an angle of 44.78 (9)° [50.84 (18)° in the 17-butyl analogue] to the plane of aromatic ring *A*. Except for these small differences observed in the dihedral angles, both compounds have nearly identical conformations.

The superposition of the non-H atoms of all the four six-membered rings of the title compound with the corresponding atoms of the related structures *N*-chloro-3-methoxy-17-aza-D-homoestra-1,3,5(10)-trien-16-one and *N*-chloro-3-methoxy-17-aza-D-homoestra-1,3,5(10)-trien-17*a*-one (Roszak *et al.*, 1991) gives r.m.s. deviations of 0.093 and 0.183 Å, respectively, which shows that the structures have nearly the same conformation. The superposition of the non-H atoms common

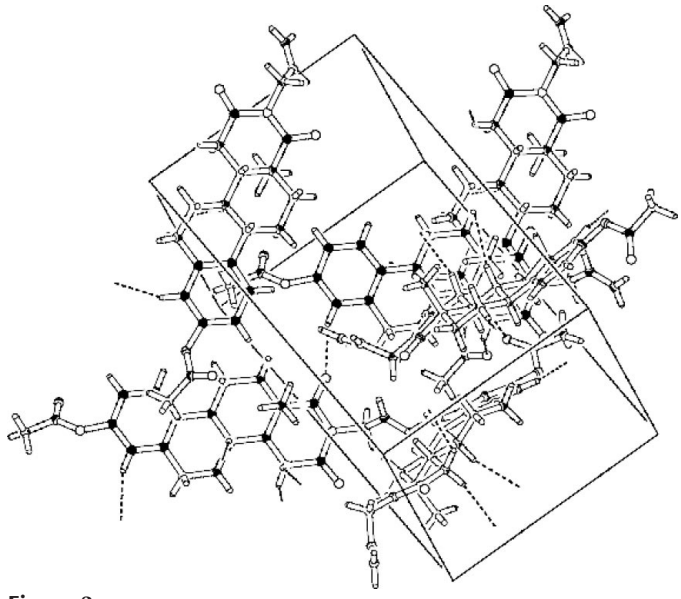


Figure 3
The packing of molecules of (I), viewed down the *a* axis. Dashed lines indicate hydrogen bonds.

to the structures of (I) and the 17-butyl analog (Hema *et al.*, 2004), gives an r.m.s. deviation of 0.06 Å, which shows that replacement of the butyl substituent at N17 by an allyl group has a negligible effect on the conformation of the steroid nucleus.

Atom C4 acts as a donor for a weak C—H···O intermolecular interaction (*via* H4) with carbonyl atom O17a of a symmetry-related molecule. This interaction links the molecules into chains which run in the [010] direction and can be described by a graph-set motif of $C(10)$ (Bernstein *et al.*, 1995; Table 1). Atom C8 is involved in a weak C—H···O interaction with carbonyl atom O16 of another adjacent molecule and thereby produces a continuous chain which runs in the [100] direction and has a graph-set motif $C(6)$. Atom C15 interacts *via* H151 and H152 with atom O32 in two other neighboring molecules, giving chains which run in the [001] and [010] directions, respectively. Each of these chains has a graph-set motif of $C(12)$. A weak C—H···π interaction is also present between atom C14 and the centroid, *Cg*1, of aromatic ring *A* of a neighboring molecule [H14···$Cg1^{iv}$ = 2.99 Å, C14···$Cg1^{iv}$ = 3.951 (3) Å and C14—H14···$Cg1^{iv}$ = 162°; symmetry code: (iv) $-x, y-\frac{1}{2}, \frac{1}{2}-z$].

Experimental

To a solution of 16,17a-dioxo-17-aza-D-homoestra-1,3,5(10)-trien-3-yl acetate (0.5 g, 1.46 mmol) in ethyl methyl ketone was added allyl bromide (2 ml) and the mixture was heated for 10 min. Anhydrous potassium carbonate (1.5 g) was then added and reaction mixture was refluxed with stirring for 3.5 h. The slurry obtained was filtered and the residue obtained after removal of solvent was crystallized from methanol to afford crystals of the title compound (yield: 0.47 g, 84%; m.p. 453–455 K).

Crystal data

$C_{23}H_{27}NO_4$
M_r = 381.46
Orthorhombic, $P2_12_12_1$
a = 9.3546 (2) Å
b = 10.7074 (2) Å
c = 19.9204 (5) Å
V = 1995.30 (8) Å^3
Z = 4
D_x = 1.270 Mg m^{-3}
Mo Kα radiation
Cell parameters from 2614 reflections
θ = 2.0–27.5°
μ = 0.09 mm^{-1}
T = 160 (2) K
Tablet, colourless
0.25 × 0.18 × 0.10 mm

Data collection

Nonius KappaCCD area-detector diffractometer
φ and ω scans with κ offsets
Absorption correction: none
30 780 measured reflections
2596 independent reflections
2063 reflections with $I > 2\sigma(I)$
R_{int} = 0.068
θ_{max} = 27.5°
$h = -12 \rightarrow 12$
$k = -13 \rightarrow 13$
$l = -25 \rightarrow 25$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.047
$wR(F^2)$ = 0.128
S = 1.06
2591 reflections
256 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0731P)^2 + 0.1695P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.004
$\Delta\rho_{max}$ = 0.25 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.012 (3)

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

D—H···A	D—H	H···A	D···A	D—H···A
C4—H4···O17A^{i}	0.95	2.32	3.204 (3)	155
C8—H8···O16^{ii}	1.00	2.45	3.404 (3)	159
C15—H151···O32^{iii}	0.99	2.53	3.428 (3)	151
C15—H152···O32^{iv}	0.99	2.44	3.181 (3)	131
C14—H14···$Cg1^{iv}$	1.00	2.99	3.591 (3)	162

Symmetry codes: (i) $x, 1+y, z$; (ii) $\frac{1}{2}+x, \frac{1}{2}-y, 1-z$; (iii) $\frac{1}{2}-x, 1-y, \frac{1}{2}+z$; (iv) $-x, y-\frac{1}{2}, \frac{1}{2}-z$. *Cg*1 is the centroid of the aromatic ring.

The structure of (I) was solved successfully by using the atomic coordinates from the structure of the pseudo-isostructural compound 17-butyl-16,17*a*-dioxo-17-aza-D-homoestra-1,3,5(10)-trien-3-yl acetate (Hema *et al.*, 2004), minus the atoms of the butyl group, as a starting model in the structure refinement. 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. All remaining H atoms 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). Due to the absence of any significant anomalous scatterers in the molecule, attempts to confirm the absolute configuration by refinement of the Flack (1983) parameter in the presence of 1958 Friedel pairs led to an inconclusive value (Flack & Bernardinelli, 2000) of 0.0 (12). Therefore, the Friedel pairs were merged before the final refinement and the absolute configuration was assigned to correspond with that of the known chiral centers in a precursor molecule, which remained unchanged during the synthesis of the title compound. Five low-angle reflections (012, 011, 002, 102 and 100) 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: coordinates taken from pseudo-isostructural compound; 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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