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Cyproterone and a comparison with its acetate ester

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.003 Å
R factor = 0.036
wR factor = 0.103
Data-to-parameter ratio = 9.1

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

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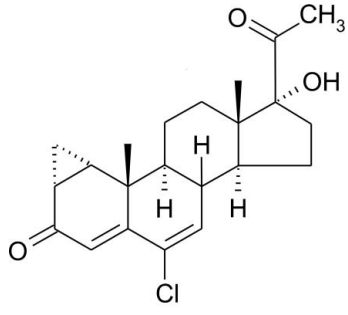
The crystal structure of cyproterone (systematic name: 6-chloro-1,2-dihydro-17-hydroxy-3′*H*-cyclopropa[*a*]pregna-1,4,6-triene-3,20-dione), $C_{22}H_{27}ClO_3$, is compared with cyproterone acetate, a potent anti-androgen steroid. The two compounds adopt a similar conformation, except for the cyclopropyl ring attached to the cyclohexenone ring (ring *A*). Cyproterone further adopts a crystal packing distinct from that of the acetate form. These differences result from hydrogen bonding between the free hydroxy group and the carbonyl group of ring *A*.

Comment

Compound (I), 6-chloro-1,2-dihydro-17-hydroxy-3′*H*-cyclopropa[*a*]pregna-1,4,6-triene-3,20-dione (called cyproterone, CPH), is an anti-androgen and is frequently used as its acetate in several pharmaceutical formulations with both anti-androgen and progestogen properties (Schneider, 2003).



(I)

By hydrolysis of the acetate group, cyproterone is considered as a by-product in the synthesis or an impurity in formulations.

The crystal structure determination of (I) was carried out in order to compare it with the previously reported structure of cyproterone acetate (CPA), its acetylated form (Chandross, 1974) [Cambridge Structural Database (Version 5.26 of November 2004; Allen, 2002) refcode CYPROT10].

The molecular structure of (I) is shown in Fig. 1. The hydroxylated cyproterone presents a reasonably strong curvature towards the α-face, similar to the cyproterone acetate conformation (Chandross, 1974). There is no significant difference in the deviations of the atoms of the steroid nucleus from the least-squares plane defined by atoms C3, C4, C5, C6, C7 and Cl1 (Table 1).

The *A* ring can best be described as a shallow boat; the *B* ring conformation is intermediate between chair and boat conformation, and the *C* ring is a normal chair as described previously (Chandross, 1974). Replacement of the acetate

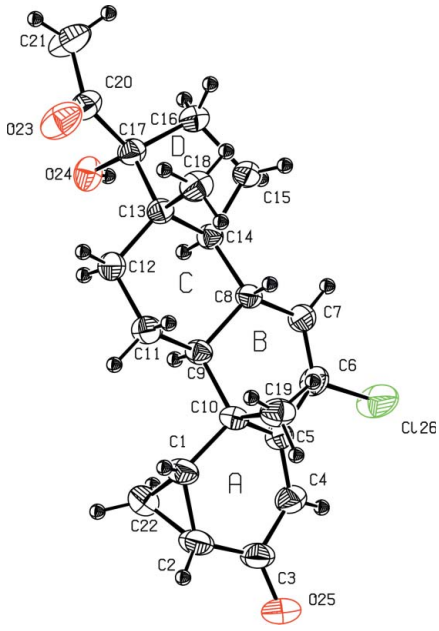


Figure 1
Structure of cyproterone, (I). Displacement ellipsoids are drawn at the 50% probability level.

group by a hydroxy group on atom C17 does not significantly affect the geometry of the various rings.

Nevertheless, the crystal packing of (I) is different (Fig. 2) from that of its acetate. In (I), we observe the formation of hydrogen bonds between the H atom on atom O24 and atom O25 of the carbonyl group from another molecule (Table 2). CPA does not exhibit any intermolecular hydrogen bonding. The hydrogen bond induces variations of torsion angles in rings *A* (containing the carbonyl group) and *D* (containing the hydroxy group) (Table 3).

Experimental

The title compound was prepared from a basic hydrolysis of the corresponding acetate. Cyproterone was obtained by hydrolysis of the corresponding acetate in 10% aqueous NaOH under reflux. Colorless prisms of compound (I) were obtained by slow evaporation of an ethyl acetate solution.

Crystal data

$C_{22}H_{27}ClO_3$
M_r = 374.89
Orthorhombic, $P2_12_12_1$
a = 6.388 (1) Å
b = 14.182 (2) Å
c = 21.107 (3) Å
V = 1912.2 (5) Å^3
Z = 4
D_x = 1.302 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 21 reflections
θ = 14.0–34.7°
μ = 1.91 mm^{-1}
T = 293 K
Prism, colorless
0.36 × 0.31 × 0.25 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: analytical (Alcock, 1970)
T_{min} = 0.546, T_{max} = 0.646
2271 measured reflections
2271 independent reflections
2223 reflections with $I > 2\sigma(I)$
θ_{max} = 75.0°
$h = 0 \rightarrow 8$
$k = 0 \rightarrow 17$
$l = 0 \rightarrow 26$
3 standard reflections
every 200 reflections
intensity decay: 2.6%

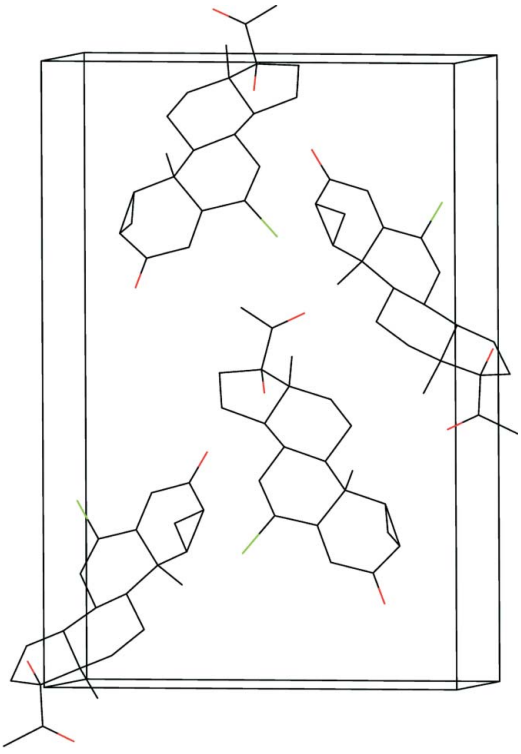


Figure 2
Crystal packing of (I). H atoms have been omitted.

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.036
$wR(F^2)$ = 0.103
S = 1.08
2271 reflections
250 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0726P)^2 + 0.2755P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.24 e Å^{-3}
$\Delta\rho_{min}$ = −0.29 e Å^{-3}
Absolute structure: (Flack, 1983)
Flack parameter: −0.06 (2)

Table 1
Deviations (Å) of the steroid nucleus from the plane defined by atoms C3, C4, C5, C6, C7 and Cl1.

Name	CPA	CPH
C1	−0.04	−0.19
C2	−0.16	−0.28
C3	+0.01	+0.01
C4	−0.04	−0.04
C5	+0.08	+0.04
C6	+0.01	+0.00
C7	−0.04	−0.02
C8	−0.07	−0.04
C9	−0.45	−0.47
C10	+0.37	+0.29
C11	−0.41	−0.40
C12	−1.30	−1.22
C13	−0.93	−0.85
C14	−1.00	−0.96
C15	−0.93	−0.86
C16	−1.70	−1.50
C17	−1.96	−1.86
C21	−1.36	−1.52
O25	+0.14	+0.27
Cl26	+0.01	+0.01

Table 2
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O24—H2A···O25	0.81 (3)	2.01 (3)	2.804 (3)	169 (3)
C4—H4···Cl26	0.93	2.54	2.994 (2)	111
C12—H12B···O24	0.97	2.48	2.905 (2)	106
C14—H14···O24	0.98	2.49	2.876 (2)	103
C15—H15B···O24	0.97	2.49	3.394 (2)	156
C22—H20A···O23	0.96	2.46	3.042 (3)	119

Table 3
Torsion angles (°) in rings A and D (°).

φA–B is the torsion angle about the A—B bond in which the other two atoms required to define the angle are those attached to either end of the bond and are within the same ring.

Ring A	φA—B (CPA)	φA—B (CPH)
C1–C2	−6.2	−4.8
C2–C3	−12.7	−17.9
C3–C4	+14.1	+18.9
C4–C5	+4.9	+4.7
C5–C10	−22.8	−26.1
C1–C10	+23.0	+25.4
Ring D		
C13—C14	+46.6	+47.3
C14—C15	−36.4	−31.2
C15—C16	+11.4	+2.3
C16—C17	+16.7	+27.1
C13—C17	−38.1	−45.0

The H atoms bound to atoms O24, C1 and C2 were located in a Fourier map and refined isotropically. The remaining H atoms were placed in idealized positions and refined with riding constraints, with C—H distances in the range 0.93–0.98 Å and with U_{iso}(H) values of 1.2 or 1.5 times U_{eq}(C).

Data collection: *CAD-4*/*MACH3* (Nonius, 2000); cell refinement: *CAD-4*/*MACH3*; data reduction: *HELENA* (Spek, 1997); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *PLATON*.

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