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21-Deoxycortisone (17α-hydroxy-4-pregnene-3,11,20-trione)

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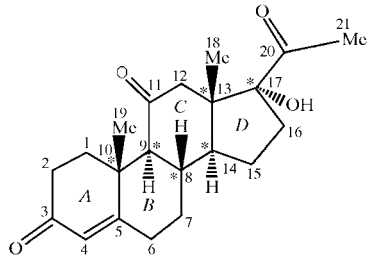
The title compound, $C_{21}H_{28}O_4$, a synthetic glucocorticoid, crystallizes with a single molecule in the asymmetric unit. Ring *A* is almost in a half-chair conformation, rings *B* and *C* are almost in chair conformations, and ring *D* is between a twist and a 13β-envelope conformation. The *A*/*B* ring junction is quasi-*trans*, whereas the *B*/*C* and *C*/*D* ring junctions both approach *trans* characteristics. The molecule as a whole is slightly convex towards the β side, with an angle of 9.60 (2)° between the C10—C19 and C13—C18 vectors. Molecular-packing and hydrogen-bonding (both intra- and intermolecular) interactions play a major role in the structural association of the compound.

Comment

The hormones of the adrenal cortex, particularly the glucocorticoids, are an essential component of adaptation to severe stress. Synthetic analogues of this class of steroid are used therapeutically (Murray *et al.*, 1990). The title compound, (I), belongs to the class of hormones which affect specific cellular processes by influencing the number of enzymes within the cell through regulation of the rate of transcription of specific genes in the target cell. The glucocorticoid complexed with its receptor plays a major role in this regulation of transcription (Murray *et al.*, 1990). Introduction of an 11-oxo group to cortisone decreases its binding affinity with human corticosteroid binding globulin (Mickelson *et al.*, 1981). Glucocorticoid receptors show high binding affinity to glucocorticoids (Westphal, 1983). The structural analysis of (I) may eventually lead to a better understanding of its mode of binding with its receptor. We have therefore elucidated the three-dimensional structure of (I). In the scheme, the asymmetric C atoms are indicated by asterisks.

In the molecule of (I), ring *A* has a nearly half-chair conformation, with an α-H atom at C4. Rings *B* and *C* are almost in chair conformations, with an α-H atom at C9 and a β-H atom at C8. Ring *D* is between a twist and a 13β-envelope conformation, with an α-H atom at C14. The conformations of the rings were calculated using *PLATON* (Spek, 2003). The *B*/*C* and *C*/*D* ring junctions approach *trans* characteristics, whereas the *A*/*B* ring junction is quasi-*trans* (Bucourt, 1974). This quasi characteristic of the *A*/*B* *trans* ring junction is due to the existence of the trigonal atom C5. A list of the endocyclic torsion angles about the three ring junctions, which support the above-mentioned ring-junction characteristics, is given in Table 2.



(I)

The twist of the molecule of (I) about its length when viewed from head to tail is determined by the C19—C10···C13—C18 pseudo-torsion angle. This has a value of −3.3 (3)°, which implies that the tail of the molecule is twisted slightly anticlockwise by that angle. Moreover, the molecule is slightly convex towards the β side, with an angle of 9.60 (2)° between the C10—C19 and C13—C18 vectors. Final bond lengths and bond angles agree well with the published values (Duax & Norton, 1975). The s.u. values for the bond lengths lie within the range 0.005–0.008 Å and those for the bond angles lie within the range 0.3–0.5°. A list of the functional groups, with their orientations and deviations from the C5–C17 mean plane (determined by all the atoms of the *B*, *C* and *D* rings) and the angles subtended at the C5–C17 mean plane, is given in Table 3. Here, the angle subtended by a functional group at the C5–C17 mean plane is obtained by calculating the angle between the normal to this mean plane towards the β side and

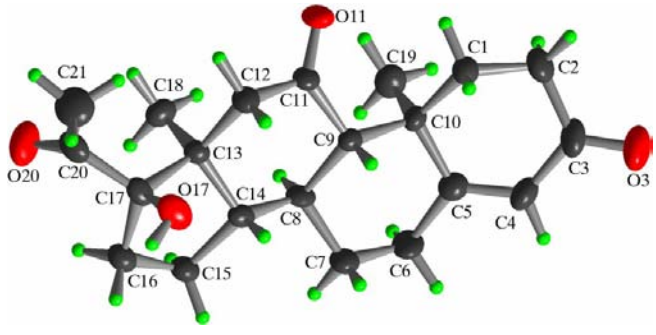


Figure 1
A three-dimensional view of (I), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

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the line joining the functional group to the bonded C atom.

It is well known that the conformation of ring *A* is considered to be a key factor in binding steroids to their receptors (Duax *et al.*, 1984). Since the pregnene molecule exhibits a certain degree of flexibility in the region of ring *A*, it can be accommodated in the ligand-binding domain of its receptor by changing the orientation of ring *A* relative to the mean plane passing through all the atoms of rings *B*, *C* and *D*. A major conformational difference between the four cortisone structures, *viz*. 17α,21-dihydroxy-4-pregnene-3,11,20-trione (PR20), 21-acetoxy-17α-hydroxy-4-pregnene-3,11,20-trione (PR21) and 4-chloro-17α,21-dihydroxy-4-pregnene-3,11,20-trione (PR22) (Duax & Norton, 1975), and 17α-hydroxy-4-pregnene-3,11,20-trione, (I), are in the conformation of ring *A*. Ring *A* has a symmetric half-chair conformation in PR20, a distorted sofa conformation in PR21, a sofa conformation in PR22 (Duax & Norton, 1975) and a nearly half-chair conformation in (I). The distance between atom O3 and the plane is usually used as a measure of the bow of a 4-en-3-one steroid molecule (Galdecki *et al.*, 1989). The bowing of ring *A* relative to the remainder of the steroid (*A*/*B*–*C*–*D*) is −32.3° for PR20, −21.5° for PR21, −15° for PR22 (Duax & Norton, 1975) and 24.8 (2)° for (I). The projection of the steroid molecule viewed parallel to the least-squares plane through atoms C5–C17 is shown in Fig. 2. The C13—C17—C20—O20 and C16—C17—C20—O20 torsion angles are 85.1 (5) and −31.7 (6)°, respectively, which suggests that atom O20 is in a synclinal position with respect to both C13 and C16 (Klyne & Prelog, 1960). Atoms C17, C20, O20 and C21 of the 17β side chain are coplanar (to within ±0.004 Å). The 17α substituent is 0.578 (5) Å from this plane. The dihedral angle between this plane and the C5–C17 reference plane is 122.0 (3)°.

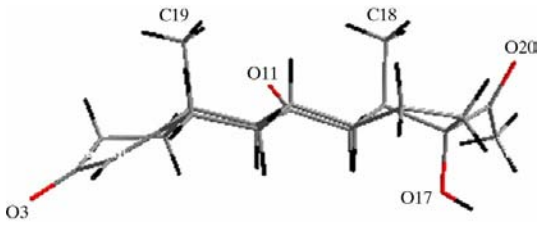

Figure 2
A projection of the structure of (I) parallel to the C5–C17 mean plane.

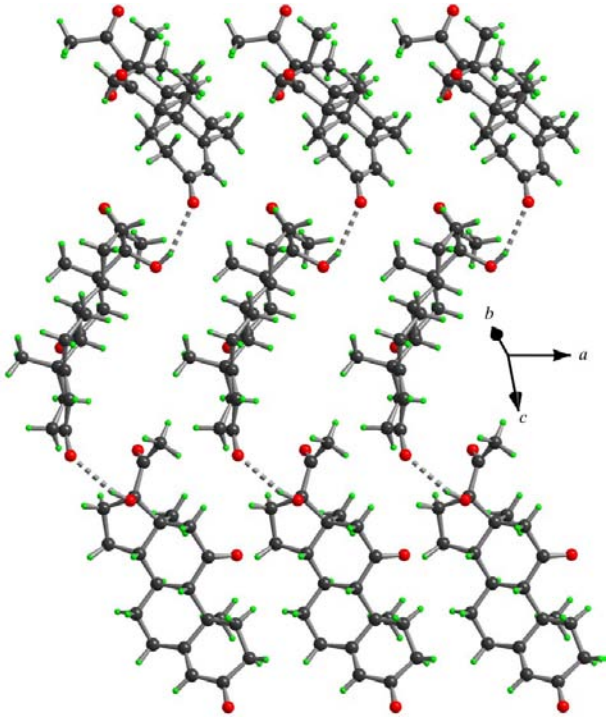

Figure 3
The molecular packing of (I), showing the hydrogen bonding joining the molecules in a helical fashion with a threefold screw axis.

The unit-cell packing of (I), including the hydrogen-bonding network, is shown in Fig. 3. In the crystal packing of (I), an infinite chain of steroid molecules is formed by hydrogen bonding in a head-to-tail fashion. Molecules are connected by means of intermolecular hydrogen bonds formed by the donor, the hydroxyl group at C17, with the common keto O-atom acceptor at C3 (Table 1). A short intermolecular contact of less than 3.5 Å playing an important role in the crystal packing is O11···O17^{ii} = 3.466 (6) Å [symmetry code: (ii) $x+1, y, z$].

Experimental

The stereospecific synthetic compound 21-deoxycortisone (17α-hydroxy-4-pregnene-3,11,20-trione), (I), was purchased from Sigma and crystallized from a solution in ethanol. The crystals are dark brown in colour and transparent, and are quite stable at room temperature.

Crystal data

$C_{21}H_{28}O_4$
M_r = 344.43
Trigonal, $P3_1$
a = 7.297 (2) Å
c = 30.304 (3) Å
V = 1397.4 (6) Å^3
Z = 3
D_x = 1.228 Mg m^{-3}
D_m = 1.25 Mg m^{-3}
D_m measured by flotation in benzene–bromoform
Mo $K\alpha$ radiation
Cell parameters from 50 reflections
θ = 3.2–25.7°
μ = 0.08 mm^{-1}
T = 153.7 (1) K
Pyramidal, brown
0.45 × 0.34 × 0.28 mm

Data collection

Marresearch image-plate diffractometer
φ scans
6746 measured reflections
1755 independent reflections
1531 reflections with $I > 2\sigma(I)$
R_{int} = 0.059
θ_{max} = 25.7°
$h = -7 \rightarrow 8$
$k = -8 \rightarrow 8$
$l = -36 \rightarrow 36$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.065
$wR(F^2)$ = 0.132
S = 1.19
1755 reflections
230 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0494P)^2 + 0.6658P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.19 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
O17—H17···O3^{i}	0.82	2.34	3.094 (5)	154

Symmetry code: (i) $-x+y+1, -x+2, z-\frac{1}{3}$.

Table 2
Endocyclic torsion angles (°) about the ring junctions in (I).

Junction	Atoms	Angle	Characteristics
A/*B*	C4—C5—C10—C1	−12.6 (7)	Quasi-*trans*
	C6—C5—C10—C9	49.1 (6)	
B/*C*	C7—C8—C9—C10	55.3 (5)	*trans*
	C14—C8—C9—C11	−49.6 (5)	
C/*D*	C12—C13—C14—C8	−61.1 (5)	*trans*
	C17—C13—C14—C15	47.6 (4)	

Table 3
Functional groups of (I), with their orientations, distances (Å) from the C5–C17 mean plane and angles (°) subtended at the C5–C17 mean plane.

Functional group	Orientation	Distance	Angle
C18	β axial	1.834 (5)	4.6 (3)
C19	β axial	1.779 (6)	7.0 (3)
O3	α axial	−1.854 (5)	123.0 (4)
O11	β equatorial	0.804 (4)	60.4 (3)
O17	α axial	−1.702 (4)	170.4 (3)
O20	β axial	1.325 (5)	31.6 (3)
C21	α equatorial	−0.436 (7)	119.1 (3)

Preliminary cell parameters and symmetry information were obtained from oscillation and Weissenberg photographs. All H atoms were included in the riding-model approximation, with C—H distances in the range 0.93–0.98 Å and an O—H distance of 0.82 Å, and with $U_{iso}(H) = 1.2U_{eq}(C,O)$.

Data collection, cell refinement and data reduction: *XDS* (Kabsch, 1988); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *DIAMOND* (Brandenburg, 2004); software used to prepare material for publication: *PLATON* (Spek, 2003).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: HJ1040). Services for accessing these data are described at the back of the journal.

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