17α,21-Dihydroxy-16β-methyl-pregna-1,4-diene-3,11,20-trione (meprednisone)

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The title compound, $C_{22}H_{28}O_5$, is a commercial therapeutic agent of the steroid class. Both independent molecules in the asymmetric unit have six-membered *A* rings that are planar, while the *B* and *C* rings adopt normal chair conformations. The five-membered *D* ring is in a 13β,14α-half-chair conformation, and the *B*/*C* and *C*/*D* ring junctions are in *trans* positions. Cohesion in the crystal is provided by O—H···O hydrogen bonds, which generate chains of molecules that are organized in a plane that lies along the crystallographic *b* axis.

Comment

Corticosteroids constitute a class of compounds that exhibit various physiological and metabolic activities. In particular, the glucocorticoids can affect the lipid, carbohydrate and protein metabolism and, with a lesser potency, the electrolyte balance (Goodman Gilman *et al.*, 1993). The title compound, meprednisone, (I), is a steroid anti-inflammatory treatment that is indicated for rheumatic, collagen and skin diseases, and is six times as potent as cortisone. Meprednisone, the 16β-methyl analog of prednisone (Δ^1 cortisone or 17α,21-di-hydroxypregna-1,4-diene-3,11,20-trione), has been developed because it was observed that replacement of the steroid *D* ring by a methyl group changes (decreases) the Na^+ retention characteristics of the compound (Rausser *et al.*, 1966). The structure of prednisone, (II), has been determined by single-crystal X-ray crystallography and the data have been deposited in the Cambridge Structural Database (Allen, 2002) with refcode PRGDOL (Tseikinsky *et al.*, 1979). The present work, which is part of an ongoing study aimed at the determination of the three-dimensional structures of biologically active compounds (Vega *et al.*, 2001), reports the structure of (I).

Compound (I) crystallized in the space group $P2_1$, with two independent molecules in the asymmetric unit (see Fig. 1). In

the steroid nucleus, the *A* ring is planar, whereas the other six-membered rings deviate significantly from planarity and adopt conformations close to chair. Selected geometric parameters are given in Table 1. The Cremer & Pople (1975) ring puckering parameters are as follows for molecules (I*A*) and (I*B*), respectively: ring *B* $Q_T = 0.547$ (4) and 0.562 (3) Å, $\theta_2 = 174.9$ (4) and 176.8 (3), and $\varphi_2 = 15$ (4) and 126 (7)°; ring *C* $Q_T = 0.589$ (4) and 0.583 (4) Å, $\theta_2 = 170.4$ (3) and 177.8 (3), and $\varphi_2 = 58$ (2) and 68 (9)°. In these four rings, the asymmetry parameters indicate the presence of three mirror planes and three twofold axes that are typical of the ideal chair conformation (Duax *et al.*, 1976). The five-membered *D* ring is in a 13β,14α-half-chair conformation [ring puckering parameters $q_2 = 0.454$ (4) and 0.484 (4) Å, and $\varphi_2 = 11.9$ (4) and 12.8 (4)° for molecules (I*A*) and (I*B*), respectively; asymmetry parameters $D_S(C13) = 0.075$ (2) and 0.085 (2), and $D_2(C13—C14) = 0.026$ (2) and 0.024 (2), for molecules (I*A*) and (I*B*), respectively].

(I)
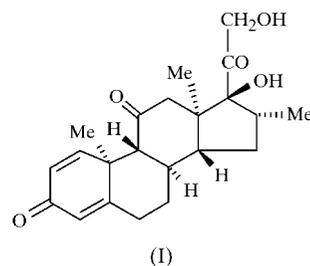
A molecular superposition of molecules (I*A*) and (I*B*), using *XP* (Sheldrick, 1991), gave an r.m.s. deviation of 0.30 Å. As shown in Fig. 2, the molecules differ considerably at atoms O3 (deviation of 0.791 Å), O11 (0.479 Å) and O21 (0.459 Å). In molecule (I*B*), the mean plane of the *A* ring lies 43.76 (7)° from the least-squares C5–C17 reference plane (Duax *et al.*, 1976). However, in molecule (I*A*), the dihedral angle is 30.95 (8)°, and consequently atom O3*B* lies ∼1 Å further from the C5–C17 reference plane than O3*A* [2.708 (3) *versus* 1.743 (2) Å]. This dissimilarity could be an effect of the intermolecular interactions in which the O3 atoms take part. The donor–acceptor distances and the angles of the hydrogen bonds differ by 0.25 Å and 25° (Table 2), thus making the O3*B* interaction stronger than that of O3*A*. In (II), atom O3 forms a weak contact with a C atom (D···A = 3.379 Å, H···A = 2.615 Å and D—H···A = 126°). Therefore, the geometry exhibited by molecule (I*A*) probably arises from the maximization of the O3*A* hydrogen-bond interaction *via* a decrease of the donor–acceptor distance, with the concomitant displacement of the *A* ring (see also Fig. 3). The deviation of the C11 plane (C9/C11/C12/O11) with respect to the main plane of the chair (C8/C9/C12/C13) is 2° greater in molecule (I*B*) than in (I*A*), the dihedral angles being 52.66 (13) and 50.61 (16)°, respectively. The weak C1···O11 and C19···O11 hydrogen bonds could exert an effect, but this seems unlikely because the bonds are comparable in both independent molecules (Table 2). Therefore, an effect caused by the corresponding *A* ring could be the most plausible explanation. The orientation of the C20 plane (C17/C20/O20/C21) with respect to the C5/C17 reference plane is similar in both independent molecules,

organic compounds
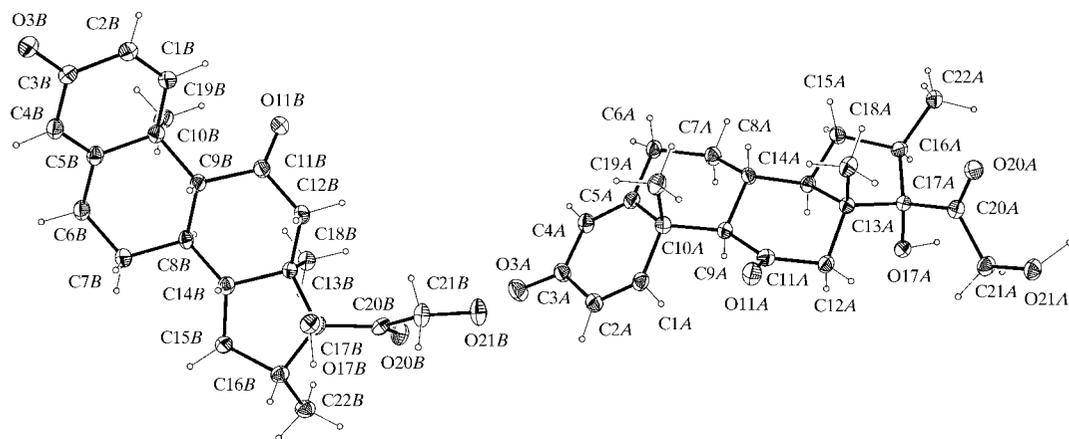
Figure 1
The structures of the two independent molecules of (I), showing the numbering schemes and displacement ellipsoids at the 30% probability level.

the values of the dihedral angles being 70.9 (1) and 70.5 (1)° in molecules (I*A*) and (I*B*), respectively; thus, atoms O17*A* and O17*B* are separated from the C20 plane by 1.593 (2) and 1.752 (3) Å, respectively. The orientation of O21, as indicated by the torsion angle O20—C20—C21—O21, is (+)synperiplanar [6.2 (5) and 3.8 (5)° for (I*A*) and (I*B*), respectively]. From Table 2, it is evident that O21*B*, unlike O21*A*, participates in an intramolecular interaction with O20*B*, thus forming a five-membered ring.

A comparison of (I) and (II) in *XP* indicated that the latter is closer to molecule (I*B*) than to (I*A*), the r.m.s. deviations being 0.14 and 0.28 Å, respectively. In the superposition for (I*B*) and (II), the major differences were encountered within the O20—C20—C21—O21 chain, namely for atoms O20 (0.319 Å), C21 (0.255 Å) and O21 (0.248 Å). However, in the superposition with (I*A*), the major deviations occurred for atoms O3 (0.824 Å), O20 (0.452 Å) and O11 (0.388 Å). Atom O20 is (+)synclinal with respect to the C16—C17 bond, the C16—C17—C20—O20 torsion angles being 44.9 (5), 47.9 (2) and 33.2° for (I*A*), (I*B*) and (II), respectively. Note that O20 is further from C16 in (I) than in (II), possibly as a result of steric hindrance introduced on the O atom by the neighboring methyl group. Weak C—H⋯O hydrogen bonds can have an effect on this distance. The C18⋯O20 interactions could be regarded as attractive contacts (Table 2), whereas, because of the bent geometry, the C22⋯O20 interactions (average *D*⋯*A* = 2.872 Å, H⋯*A* = 2.609 Å and *D*—H⋯*A* = 96°) could be considered to be repulsive, so that the net effect is the enlargement of the O20⋯C16 distance in (I). In (II), there is a

very weak C16⋯O20 interaction (*D*⋯*A* = 2.855 Å, H⋯*A* = 2.404 Å and *D*—H⋯*A* = 107°), which was not observed in (I).

The longitudinal twist of the steroid nucleus, which is measured by the value of the C19—C10⋯C13—C18 pseudo-torsion angle (Duax *et al.*, 1976), is similar in both independent molecules [2.6 (3) and 2.7 (3)° for (I*A*) and (I*B*), respectively], and this angle is somewhat smaller than that in (II) (4.6°). In addition, the mutual orientation of O17 and C18 is in good agreement in the three structures, as shown by the values of the C18—C13—C17—O17 torsion angle [164.6 (2), 166.7 (4) and 165.4° for (I*A*), (I*B*) and (II)]. The structural cohesion in the crystals of (I) is achieved through O—H⋯O hydrogen bonds. As shown in Fig. 3, chains are formed by the two independent molecules, which are linked *via* O21*B*⋯O3*A*
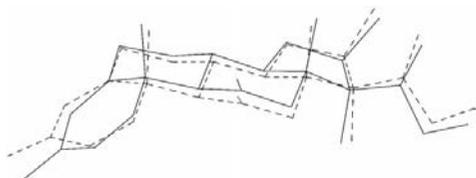
Figure 2
An *XP* (Sheldrick, 1991) plot depicting the superposition of the two independent molecules of (I), *viz.* (I*A*) (dashed lines) and (I*B*) (solid lines).
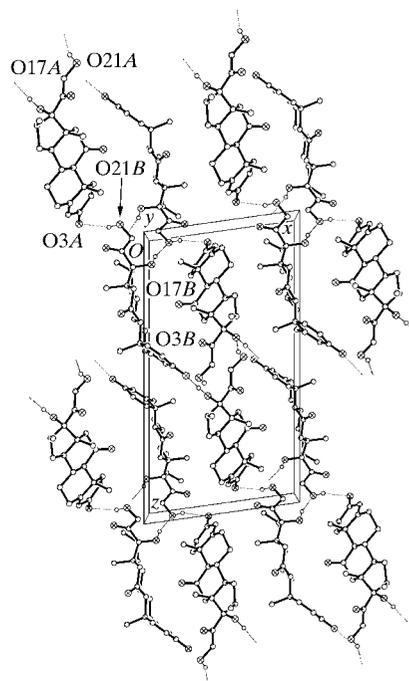
Figure 3
A partial packing diagram showing the O⋯O hydrogen bonds (dotted lines). Only H atoms attached to O atoms are shown.

and O17A···O3B($x - 1$, $y + 1$, $z - 1$) hydrogen bonds. The chains are propagated by O21A···O17A($-x$, $y + \frac{1}{2}$, $-z$) and O17B···O21B($-x + 1$, $y - \frac{1}{2}$, $-z + 1$) hydrogen bonds through two different 2_1 screw axes. The propagation direction is nearly perpendicular to the largest dimension of the steroid, and thus the chains are arranged into planes parallel to the b axis.

Experimental

Compound (I) was obtained from LABORATORIOS GADOR SA, Buenos Aires, Argentina. Crystals suitable for X-ray diffraction were obtained from an aqueous solution *via* slow evaporation.

Crystal data

$C_{22}H_{28}O_5$	$D_x = 1.31$ Mg m^{-3}
$M_r = 372.44$	Mo $K\alpha$ radiation
Monoclinic, $P2_1$	Cell parameters from 3579
$a = 11.4372$ (4) Å	reflections
$b = 7.8901$ (3) Å	$\theta = 1.0$–$25.0°$
$c = 21.1268$ (9) Å	$\mu = 0.09$ mm^{-1}
$\beta = 97.896$ (2)°	$T = 120$ (2) K
$V = 1888.42$ (13) Å^3	Needle, colorless
$Z = 4$	$0.18 \times 0.06 \times 0.02$ mm

Data collection

Nonius KappaCCD diffractometer	$R_{int} = 0.050$
φ scans and ω scans with κ offsets	$\theta_{max} = 25.0°$
6178 measured reflections	$h = -13 \rightarrow 13$
3583 independent reflections	$k = -9 \rightarrow 7$
2757 reflections with $I > 2\sigma(I)$	$l = -25 \rightarrow 24$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2)]$
$R(F) = 0.044$	$(\Delta/\sigma)_{max} = 0.001$
$wR(F^2) = 0.099$	$\Delta\rho_{max} = 0.18$ e Å^{-3}
$S = 1.05$	$\Delta\rho_{min} = -0.19$ e Å^{-3}
3583 reflections	Extinction correction: *SHELXL*97
500 parameters	Extinction coefficient: 0.033 (3)
H atoms: see below	

The positional parameters of hydroxyl atoms H17 and H21 were refined with the O—H distances restrained to 0.85 Å and with U_{iso} values equal to $1.5U_{eq}$(O). H atoms attached to C atoms were constrained (C—H distances of 0.98 Å for primary, 0.99 Å for secondary, 1 Å for tertiary and 0.95 Å for aromatic H atoms) and refined with a riding model and with the U_{iso} parameters of the H

Table 1
Selected geometric parameters (Å, °).

C3A—O3A	1.245 (5)	C17B—O17B	1.443 (4)
C3B—O3B	1.248 (4)	C20A—O20A	1.217 (5)
C11A—O11A	1.219 (4)	C20B—O20B	1.214 (4)
C11B—O11B	1.220 (5)	C21A—O21A	1.427 (4)
C17A—O17A	1.440 (4)	C21B—O21B	1.409 (4)

C4A—C5A—C10A—C9A	129.5 (4)
C4B—C5B—C10B—C9B	120.0 (4)
O17A—C17A—C20A—O20A	167.1 (3)
C16A—C17A—C20A—O20A	44.9 (5)
O17B—C17B—C20B—O20B	172.1 (4)
C16B—C17B—C20B—O20B	47.9 (5)
O20A—C20A—C21A—O21A	6.5 (5)
C17A—C20A—C21A—O21A	−172.5 (3)
O20B—C20B—C21B—O21B	3.3 (5)
C17B—C20B—C21B—O21B	−174.3 (3)

Table 2
Hydrogen-bonding and short intramolecular contact geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O17A—H17A···O3B^i	0.89 (3)	1.81 (3)	2.694 (4)	173 (4)
O17B—H17B···O21B^{ii}	0.88 (3)	2.03 (3)	2.889 (4)	165 (4)
O21A—H21A···O17A^{iii}	0.89 (3)	2.03 (3)	2.888 (4)	163 (4)
O21B—H21B···O20B	0.85 (3)	2.17 (5)	2.638 (4)	115 (4)
O21B—H21B···O3A	0.85 (3)	2.19 (4)	2.946 (4)	149 (5)
C1A—H1A···O11A	0.95	2.32	2.915 (5)	120
C1B—H1B···O11B	0.95	2.41	2.970 (5)	117
C18A—H18A···O20A	0.98	2.55	2.937 (4)	104
C18B—H18D···O20B	0.98	2.50	2.942 (4)	107
C19A—H19A···O11A	0.98	2.43	3.067 (4)	122
C19B—H19D···O11B	0.98	2.44	3.076 (5)	122

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

atoms constrained to 1.2 times those of their hosts. For the final refinement, because the molecule lacks a significant anomalous scatterer at the Mo $K\alpha$ wavelength, Friedel pairs were merged. The correct enantiomer was chosen to agree with the known chirality of the steroid (Rausser *et al.*, 1966).

Data collection: *COLLECT* (Nonius, 1997–2000); cell refinement: *HKL SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO* (Otwinowski & Minor, 1997) and *SCALEPACK*; structure solution: *SHELXS*97 (Sheldrick, 1997); structure refinement: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *XP* in *SHELXTL/PC* (Sheldrick, 1991); software used to prepare material for publication: *PARST* (Nardelli, 1995) and *WinGX* (Farrugia, 1999).

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