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16α,17α-Epoxy-20-oxopregn-5-en-3β-yl acetate

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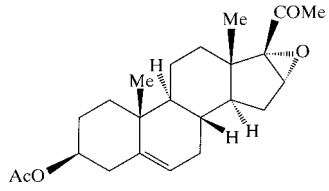
The title compound, $C_{23}H_{32}O_4$, has a 3β configuration, with the epoxy O atom at 16α,17α. Rings *A* and *C* have slightly distorted chair conformations. Because of the presence of the C5═C6 double bond, ring *B* assumes an 8β,9α-half-chair conformation slightly distorted towards an 8β-sofa. Ring *D* has a conformation close to a 14α-envelope. The acetoxy and acetyl substituents are twisted with respect to the average molecular plane of the steroid. The conformation of the molecule is compared with that given by a quantum chemistry calculation using the RHF–AM1 (RHF = Roothaan Hartree–Fock) Hamiltonian model. Cohesion of the crystal can be attributed to van der Waals interactions and weak intermolecular C—H···O interactions, which link the molecules head-to-tail along [101].

Comment

16α,17α-Epoxy-20-oxopregnanes are key intermediates in the synthesis of important steroidal compounds, ranging from such powerful anticancer agents as the cephalostins (Kim *et al.*, 1999) to steroidal metabolites (Moreno *et al.*, 1998) associated with certain pathological situations, such as adrenal carcinoma and congenital adrenal hyperplasia (Zeelen, 1990). The title compound, (I), was obtained from 20-oxopregna-5,16-dien-3β-yl acetate *via* the application of well known reactions (Kirk & Sá e Melo, 1979), namely, stereoselective epoxidation of the C16 double bond with hydrogen peroxide under alkaline conditions, which produces the simultaneous hydrolysis of the 3β-OAc group, followed by reacetylation of the 3β-hydroxy group with acetic anhydride in pyridine. The present X-ray diffraction study was undertaken to determine the stereochemistry of the epoxy O atom, which was found to be 16α,17α. This work is part of an ongoing project to study the conformation of intermolecular interactions of steroidal 16α,17α-epoxy ketones, namely those functionalized at C21 or at C15, aiming to clarify the effect of those substituents on the behaviour of the epoxide ring towards cleavage reactions (Moreno *et al.*, 1993).



(I)

An *ORTEP*II (Johnson, 1976) drawing of the molecule of (I) with the corresponding atomic numbering scheme and ring labels is shown in Fig. 1. All rings are fused *trans*. The distance between the terminal C atoms, C21 and C23, is 14.873 (4) Å, and that between the terminal O atoms, O20 and O22, is 11.898 (3) Å. Bond lengths and angles are within the expected ranges (Allen *et al.*, 1987), with average values $Csp^3—Csp^3$ = 1.531 (11), $Csp^3—Csp^2$ = 1.503 (9), $Csp^2═Csp^2$ = 1.328 (3) and C═O = 1.202 (8) Å. It is worth mentioning a small but significant asymmetry between the two C—O epoxy bond lengths [1.433 (3) and 1.453 (3) Å].

Rings *A* and *C* are slightly flattened, the mean values of their torsion angles being 53 (2) and 56 (2)°, respectively. Both ring conformations are close to chair, as shown by the values of the Cremer & Pople (1975) puckering parameters [ring *A*: Q = 0.544 (3) Å, θ = 8.2 (3) and φ = 80 (2)°; ring *C*: Q = 0.578 (2) Å, θ = 8.2 (2) and φ = 272.9 (17)°]. Thus, the presence of the acetoxy group bonded to C3 does not disturb the usual chair conformation of ring *A* of the steroidal nucleus. Due to the C5═C6 double bond, the environment of atom C5 is planar [the sum of the valence angles around this atom is 360.0 (4)°]. Hence, ring *B* is highly distorted from the normal chair conformation, assuming instead an 8β,9α-half-chair conformation slightly distorted towards an 8β-sofa [asymmetry parameters (Duax & Norton, 1975): ΔC_2[5,6] = 7.2 (3), ΔC_s(6) = 16.6 (2) and ΔC_s(7) = 43.2 (2)°]. The five-membered ring *D* assumes a 14α-envelope conformation, with puckering parameters q_2 = 0.384 (3) Å and φ_2 = 210.5 (4)° [pseudo-rotation (Altona *et al.*, 1968) and asymmetry parameters: Δ = −25.2 (5), φ_m = 39.2 (2), ΔC_s(14) = 4.4 (3) and ΔC_2(13,14) = 13.5 (3)°].

The 3β-acetoxy group attached to ring *A* is planar. The C3—O3 bond is oriented equatorially and (−)antiperiplanar to the C3—C4 bond. The dihedral angle between the plane of the acetoxy group and the mean molecular plane is 56.09 (9)°, showing that this group is twisted around the C3—O3 bond. The dihedral angle between the plane defined by the epoxy group and the average molecular plane comprising rings *A*, *B*, *C* and *D* is 89.6 (1)°.

As reported by Hazel *et al.* (1976) for the similar structure 16α,17α-epoxy-3β-hydroxypregn-5-en-20-one, we also found an unusual conformation of the substituent group at C17, where the C13—C17 bond almost eclipses the C20—O20 bond [C13—C17—C20—O20 −7.1 (4)°], which can be attributed to the epoxide link on ring *D*. In a comparison study of the molecular structures of six corticosteroids with a similar side

chain at C17 and with no epoxy rings, Weeks *et al.* (1973) report values close to 90°. The unusual eclipsed conformation may also be responsible for the relatively large value of the pseudo-torsion angle C19—C10—C13—C18 [10.4 (2)°], which measures the twist of the molecule and usually does not exceed 4.0°. Also, the 17β-acetyl group is not coplanar with the mean molecular plane, the dihedral angle being 26.70 (14)°.

In order to obtain a better insight into the effect of the substituents on the equilibrium conformation of the molecule, we have performed a semi-empirical calculation using the RHF/SCF–AM1 (RHF = Roothaan Hartree–Fock and SCF = self-consistent field) Hamiltonian model. Intermolecular interactions are weak (see below), which would validate a comparison between the conformation of an isolated molecule, as given by the calculation, and that observed in the crystal. The calculations were performed using the computer program *GAMESS* (Schmidt *et al.*, 1993). Tight conditions were applied for SCF convergence and location of the equilibrium geometry, the final electron-density variation and maximum energy gradient at the final cycle being 10^{-6} atomic units. At the end of the geometry optimization, the Hessian matrix was calculated to confirm that the stationary point was a true minimum and not a saddle point, and indeed positive frequencies were obtained for every vibrational normal mode.

The calculated geometry was in good agreement with the X-ray data; the mean deviations of bond distances and angles, excluding those involving H atoms, were 0.014 Å and 0.96°, respectively. The conformation of the steroid nucleus is well reproduced by the calculation, the average difference between the calculated and experimental endocyclic torsion angles being 1.8°, with a maximum deviation of 3.2° for the C8—C14—C13—C12 torsion angle involving the *C*/*D* ring junction. Also, at the minimum energy conformation, the 17β-acetyl group was found with an eclipsed conformation of the C13—C17 and C20—O20 bonds. The calculated C13—C17—C20—O20 torsion angle is 6.0°, which compares well in magnitude with the X-ray geometry, although the sign of the angle is opposite to that of the measured value. The fact that an eclipsed conformation is also found for the isolated molecule supports the interpretation that such a conformation is related to the steric interaction between the acetyl group and the epoxide O16 atom, rather than to intermolecular interactions or packing effects. However, weak intramolecular C—H···O interactions may also stabilize this particular conformation, as described below.

The equilibrium conformation of the 3β-acetoxy group of the isolated molecule was found to be close to that observed in the crystal, the calculated and measured C4—C3—O3—C22 torsion angles being −156.3 and −161.4 (2)°, respectively, despite the presence of a close contact in the crystal between atoms O22 and C21 of neighbouring molecules. Moreover, the large pseudo-torsion angle C19—C10—C13—C18 is well reproduced by the calculation, which gave a value of 11.8°, in good agreement with the experimental value of 10.4°.

Cohesion of the structure of (I) is achieved mainly by van der Waals interactions. No classical hydrogen bonds are present in the structure, as the molecule lacks a strong hydrogen donor. Two intramolecular C—H···O short contacts between the O atoms of the epoxy and ketone groups and a neighbouring H atom of a methyl group are present: C21—H21*B*···O16 at 2.914 (4) Å and C18—H18*A*···O20 at 3.108 (3) Å. However, in view of the rather bent angles defined by these atoms of 104.7 and 114.1°, respectively, and the rather weak acidic character of the methyl group, these interactions are probably destabilizing and should not be qualified as weak hydrogen bonds. A search for intermolecular C—H···O close contacts shows that the sole probable interaction of this type is C21—H21*C*···O22^{i} [3.482 (4) Å and 166.4°; symmetry code: (i) $x-1$, y, $z-1$], which links the molecules head-to-tail in chains parallel to the [101] direction.

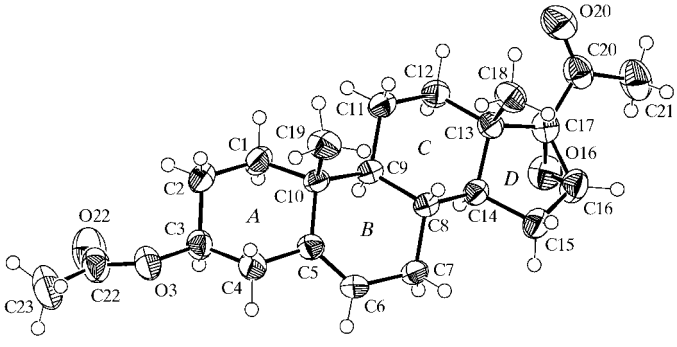


Figure 1
An *ORTEP*II (Johnson, 1976) plot of (I). Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

Experimental

Oxidation of commercially available 20-oxopregne-5,16-dien-3β-yl acetate to the 16α,17α-epoxy-3β-hydroxypregn-5-en-20-one with hydrogen peroxide under alkaline conditions, and subsequent esterification with acetic anhydride in pyridine, were performed according to the literature method of Kirk & Sá e Melo (1979). The product of this two-step procedure was isolated in very good yield and identified as (I) from IR, ^{1}H NMR and ^{13}C NMR spectra. Crystals suitable for X-ray analysis were obtained by slow evaporation of a solution of the steroid in methanol.

Crystal data

$C_{23}H_{32}O_4$
M_r = 372.49
Monoclinic, $P2_1$
a = 7.5950 (7) Å
b = 9.9731 (9) Å
c = 13.7266 (9) Å
β = 98.967 (6)°
V = 1027.02 (15) Å^3
Z = 2
D_x = 1.205 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 10.09–19.31°
μ = 0.081 mm^{-1}
T = 293 (2) K
Prism, colourless
0.58 × 0.49 × 0.12 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
Profile data from $\omega/2\theta$ scans
5324 measured reflections
2481 independent reflections
1893 reflections with $I > 2\sigma(I)$
R_{int} = 0.023
θ_{max} = 27.41°
$h = -9 \rightarrow 9$
$k = -12 \rightarrow 0$
$l = -17 \rightarrow 17$
3 standard reflections
frequency: 180 min
intensity decay: 2.6%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0578P)^2 + 0.0846P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.037$	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2) = 0.101$	$\Delta\rho_{max} = 0.19$ e Å^{-3}
$S = 1.022$	$\Delta\rho_{min} = -0.17$ e Å^{-3}
2481 reflections	
248 parameters	
H-atom parameters constrained	

Table 1
Selected geometric parameters (Å).

O3—C22	1.333 (3)	O20—C20	1.209 (4)
O3—C3	1.457 (3)	O22—C22	1.194 (4)
O16—C16	1.433 (3)	C16—C17	1.477 (4)
O16—C17	1.453 (3)		

H atoms were placed at calculated positions and refined as riding (C—H = 0.93–0.98 Å). Because the molecule lacks the presence of a significant anomalous scatterer at the Mo $K\alpha$ wavelength, Friedel pairs were merged and the correct enantiomer was chosen to agree with the known chirality of the steroid. Examination of the crystal structure with *PLATON* (Spek, 1995) showed that there was one small (14 Å^3) void in the asymmetric unit located at (0.055, 0.083, 0.764). The closest atoms to this void are the acetoxy O22 and C23 atoms of one molecule, at distances of 2.88 and 2.91 Å, respectively, and the two methyl C18 and C19 atoms of a neighbouring molecule, at 3.16 and 3.27 Å, respectively. However, both the volume and the small residual density at the void positions exclude the possibility of occupation of the void by a solvent molecule.

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: *HELENA* (Spek, 1997); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX1123). Services for accessing these data are described at the back of the journal.

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