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6β-Hydroxy-5β-methyl-20-oxo-19-norpregn-9(10)-en-3β-yl acetate

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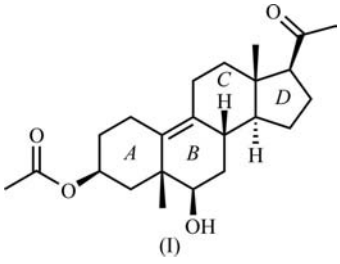
In the title compound, $C_{23}H_{34}O_4$, which is an intermediate in the synthesis of pregnane derivatives with a modified skeleton that show potent abortion-inducing activity, the conformation of ring *B* is close to half-chair due to the presence of both the C═C double bond and the axial 5β-methyl group. Rings *A* and *C* have conformations close to chair, while ring *D* has a twisted conformation around the bridgehead C—C bond. Molecules are hydrogen bonded *via* the hydroxyl and acetoxy groups into infinite chains. Quantum-mechanical *ab initio* Roothan Hartree–Fock calculations show that crystal packing might be responsible for the low values of the angles between rings *A* and *B*, and between ring *A* and rings *C* and *D*, as well as for a different steric position of the methyl ketone side chain compared to the geometry of the free molecule.

Comment

The Westphalen rearrangement is a well known reaction in steroid chemistry for the synthesis of olefinic 19-norsteroids. This classical transformation involves migration of the 10β-methyl group to the 5β-position with the formation of 5β-methyl-$\Delta^{9(10)}$-19-nor derivatives (Kamernitskii *et al.*, 1987).



(I)

As part of our current interest in the applications of bismuth(III) salts to the chemistry of epoxysteroids (Pinto *et al.*, 2006, 2007; Pinto, Salvador, Le Roux *et al.*, 2008), we have recently reported a catalytic process for the preparation of Westphalen-type compounds (Pinto, Salvador, Le Roux *et al.*, 2008). Several 5β-methyl-$\Delta^{9(10)}$-19-norsteroids from the cholestane, androstane and pregnane series were prepared by reaction of the corresponding 5β,6β-epoxysteroids in 1,4-dioxane, using a catalytic amount of bismuth trifluoromethanesulfonate (Pinto, Salvador, Le Roux *et al.*, 2008).

Of special interest was the preparation of the title 5β-methyl-$\Delta^{9(10)}$-19-norsteroid, (I). This compound is a pregnane derivative with a modified skeleton, structurally related to the endogenous hormone progesterone. In the last decade, extensive synthetic work developed by Polman and Kasal led to the preparation of analogues of progesterone possessing a 5β-methyl-$\Delta^{9(10)}$-19-nor structure, which have shown potent abortion-inducing activity (Polman & Kasal, 1990, 1991; Kasal *et al.*, 1998). The title compound, (I), can then be seen as an intermediate in the synthesis of this family of compounds. In this communication, we report the molecular structure of (I) and compare it with that of the free molecule as given by quantum mechanical *ab initio* calculations.

The structure of (I) with the corresponding atomic numbering scheme is shown in Fig. 1. This steroid compound is from the pregnane series with a double bond located in ring *B* at C9═C10. The typical C19-methyl group is absent. The acetoxy group at C3 is axial to ring *A*. The 5β-methyl group on ring *B* is also in an axial position, whereas the hydroxyl group at C6 is equatorial. The side chain attached to ring *D* is equatorial.

The dihedral angle between the least-squares planes of rings *A* and *B* is 19.43 (10)°, while the dihedral angle between the mean planes through ring *A* and through rings *C* and *D* combined is 60.37 (6)°. Rings *C* and *D* are almost coplanar, as shown by the low value of the angle between their least-squares planes of 7.53 (6)°.

Rings *A* and *C* have conformations close to chair, as shown by the Cremer & Pople (1975) parameters [for ring *A*: Q = 0.507 (2) Å, θ = 168.3 (2)° and φ = 242.7 (11)°; for ring *C*: Q = 0.5811 (19) Å, θ = 2.49 (19)° and φ = 274 (4)°]. Ring *B* has a conformation close to half-chair [Q = 0.494 (2) Å, θ = 128.1 (2)° and φ = 246.2 (3)°]. Ring *D* has a twisted conformation around the C13—C14 bond, with puckering parameters q_2 = 0.457 (2) Å and φ_2 = 194.4 (3)°, and asymmetry

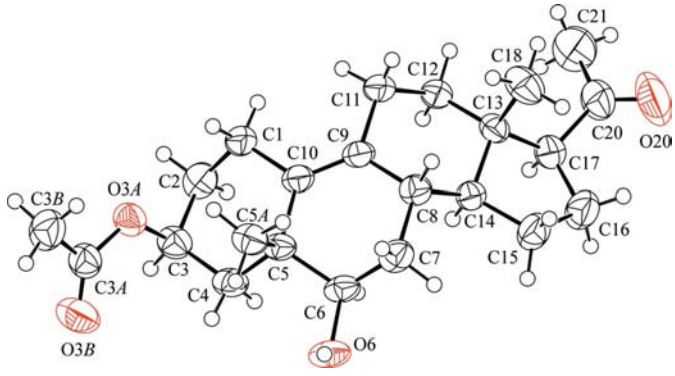


Figure 1
A view of the molecule of the title compound, with displacement ellipsoids drawn at the 50% probability level.

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parameters (Duax & Norton, 1975) $\Delta C_2(16) = \Delta C_2(13,14) = 3.9\ (3)^\circ$.

Molecules of (I) are hydrogen bonded *via* the hydroxyl and acetoxy groups into infinite chains running in the [100] direction. Two short intramolecular interactions are present in the molecule: (i) between the 5β-methyl group and the neighbouring O3*A* atom, and (ii) between the C20 carbonyl O atom (O20) and one of the H atoms bound to C16 (Table 1).

In order to gain some insight into how the crystal packing of (I) might affect the molecular geometry, we have performed quantum chemical calculations on the equilibrium geometry of the free molecule. These calculations were performed with the computer program *GAMESS* (Schmidt *et al.*, 1993). A molecular orbital Roothan Hartree–Fock method was used with an extended 6–31 G(d,p) basis set. Tight conditions for convergence of both the self-consistent field cycles and the maximum density and energy gradient variations were imposed (10^{-5} atomic units). The program was run on the Milipeia cluster of UC–LCA (using 16 Opteron cores, 2.2 GHz runing Linux).

The *ab initio* calculations reproduce well the observed experimental bond lengths and valency angles of the molecule. All valency angles match the experimental values within 2°. Calculated (calc) and experimental (exp) bond lengths agree within 0.025 Å, with the exception of the following bonds: C3—O3*A* [calc = 1.436 Å and exp = 1.467 (2) Å], C6—O6 [calc = 1.406 Å and exp = 1.432 (2) Å] and C20—C21 [calc = 1.514 Å and exp = 1.487 (4) Å].

The calculations reproduce well the small dihedral angle between the least-squares planes of rings *C* and *D* [calc = 8.3° and exp = 7.53 (6)°]. However, the calculated dihedral angles in the free molecule between the least-squares planes through rings *A* and *B* [calc = 24° and exp = 19.43 (10)°] and between the best planes through ring *A* and through rings *C* and *D* combined [calc = 71.4° and exp = 60.37 (6)°] differ significantly from those of the molecule in the crystal. These results might be interpreted as being caused by a small induced defolding of the molecule due to crystal packing. In addition, the methyl ketone side chain is almost perpendicular to ring *D* in the calculations, but a large tilt is observed in the crystal, as shown by the C13—C17—C20—C21 torsion angle [calc = −92.6° and exp = −70.5 (3)°].

One of the aims of the present study was to gain some insight into the structural differences between (I) and 5β,6β-epoxy-20-oxopregnan-3β-yl acetate, the starting compound for the preparation of (I) and whose structure we have reported recently (Pinto, Salvador & Paixão, 2008). This 5β,6β-epoxysteroid possesses a large C19—C10···C13—C18 pseudo-torsion angle of 15.74 (17)°, which indicates a significantly twisted steroid nucleus (Pinto, Salvador & Paixão, 2008).

Interestingly, the similar C5*A*—C5···C13—C18 pseudo-torsion angle for the title Westphalen-type compound is much lower, with a value of −0.94 (19)°. Calculated *ab initio* values also reproduce these findings [22.2° for 5β,6β-epoxy-20-oxopregnan-3β-yl acetate (Pinto, Salvador & Paixão, 2008) and 5.0° for (I)]. Thus, when the 5β,6β-epoxysteroid is converted into 5β-methyl-$\Delta^{9(10)}$-19-norsteroid (I), a strong relief in the twist of steroid nucleus is observed. On the other hand, low values for the C19—C10···C13—C18 pseudo-torsion angle are found in the literature for several 5α,6α-epoxysteroids (Hanson, Hitchcock & Nagaratnam, 1999; Hanson, Hitchcock & Kiran, 1999; Litvinovskaya *et al.*, 1995).

These data suggest that important steric factors, such as the above-mentioned change in the torsion of the steroid nucleus, may contribute to explaining the differential reactivity observed between 5β,6β-epoxy- and 5α,6α-epoxysteroids, which do not react under the same reaction conditions (Pinto, Salvador, Le Roux *et al.*, 2008), although similar electronic factors are present in both diastereomeric epoxides.

Experimental

The synthesis of 6β-hydroxy-5β-methyl-20-oxo-19-norpregn-9(10)-en-3β-yl acetate, (I), was carried out according to the previously reported method of Pinto, Salvador, Le Roux *et al.* (2008). The product of the reaction was isolated in 52% yield and identified as (I) from MS, IR, and one- and two-dimensional NMR analysis (Pinto, Salvador, Le Roux *et al.*, 2008). Recrystallization from acetone/*n*-hexane at room temperature gave colourless single crystals suitable for X-ray diffraction analysis.

Crystal data

$C_{23}H_{34}O_4$
$M_r = 374.50$
Orthorhombic, $P2_12_12_1$
$a = 5.8903\ (2)$ Å
$b = 9.6929\ (2)$ Å
$c = 36.9988\ (8)$ Å
$V = 2112.41\ (10)$ Å^3
$Z = 4$
Mo $K\alpha$ radiation
$\mu = 0.08$ mm^{-1}
$T = 293\ (2)$ K
0.36 × 0.23 × 0.11 mm

Data collection

Bruker APEXII CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2000)
$T_{min} = 0.882$, $T_{max} = 0.991$
59317 measured reflections
3729 independent reflections
2885 reflections with $I > 2\sigma(I)$
$R_{int} = 0.041$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.044$
$wR(F^2) = 0.133$
$S = 1.05$
3729 reflections
249 parameters
H-atom parameters constrained
$\Delta\rho_{max} = 0.18$ e Å^{-3}
$\Delta\rho_{min} = -0.17$ e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
O6—H6*A*···O3*B*^{i}	0.82	2.06	2.863 (2)	166
C5*A*—H5*A*2···O3*A*	0.96	2.50	3.104 (3)	121
C16—H16*B*···O20	0.97	2.39	2.803 (3)	105

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

All C-bound H atoms were refined as riding on their parent atoms using *SHELXL97* (Sheldrick, 2008) defaults [U_{iso}(H) = 1.2U_{eq}(C) or 1.5U_{eq}(methyl C)]. The coordinates of the hydroxy H atom were initially determined from a difference Fourier synthesis and were refined as riding on the parent O atom [U_{iso}(H) = 1.5U_{eq}(O)] using a *SHELXL97* HFIX 147 instruction with default values. The absolute

configuration was not determined from the X-ray data but was known from the synthetic route.

Data collection: *SMART* (Bruker, 2003); cell refinement: *SAINT* (Bruker, 2003); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2009); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3302). Services for accessing these data are described at the back of the journal.

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