

## 5 $\beta$ ,6 $\beta$ -Epoxy-17-oxoandrostan-3 $\beta$ -yl acetate and 5 $\beta$ ,6 $\beta$ -epoxy-20-oxopregnan-3 $\beta$ -yl acetate

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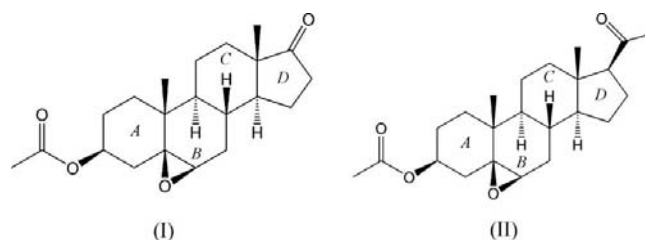
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In the title compounds, C<sub>21</sub>H<sub>30</sub>O<sub>4</sub>, (I), and C<sub>23</sub>H<sub>34</sub>O<sub>4</sub>, (II), respectively, which are valuable intermediates in the synthesis of important steroid derivatives, rings A and B are *cis*-(5 $\beta$ ,10 $\beta$ )-fused. The two molecules have similar conformations of rings A, B and C. The presence of the 5 $\beta$ ,6 $\beta$ -epoxide group induces a significant twist of the steroid nucleus and a strong flattening of the B ring. The different C17 substituents result in different conformations for ring D. Cohesion of the molecular packing is achieved in both compounds only by weak intermolecular interactions. The geometries of the molecules in the crystalline environment are compared with those of the free molecules as given by *ab initio* Roothan Hartree–Fock calculations. We show in this work that quantum mechanical *ab initio* methods reproduce well the details of the conformation of these molecules, including a large twist of the steroid nucleus. The calculated twist values are comparable, but are larger than the observed values, indicating a possible small effect of the crystal packing on the twist angles.

### Comment

The 5 $\beta$ ,6 $\beta$ -epoxide functionality (Salvador *et al.*, 2006) is present in several naturally occurring steroids, of which withanolides are a representative example. These compounds have been studied for anti-inflammatory (Jayaprakasam & Nair, 2003), antitumour (Kuroyanagi *et al.*, 1999), cytotoxic (Veras *et al.*, 2004) and immunomodulatory (Leyon & Kuttan, 2004) activities, as well as for cancer chemoprevention by inducing phase-II enzymes (Misico *et al.*, 2002). Cytotoxic activity against several cell lines has been reported for other naturally occurring 5 $\beta$ ,6 $\beta$ -epoxysteroids (Watanabe *et al.*, 1996; Anta *et al.*, 2002). 5 $\beta$ ,6 $\beta$ -Epoxy steroids are also valuable intermediates for the synthesis of important compounds, such as brassinosteroid derivatives (Ramírez *et al.*, 2000), laxogenin

(Iglesias-Arteaga *et al.*, 2005) and an analogue of squalamine (Cai & Zhou, 2004). In fact, the stereochemistry of these compounds rules their ring opening by nucleophilic agents, which leads to 5 $\alpha$ -substituted 6 $\beta$ -hydroxysteroids (Pinto *et al.*, 2006; Pinto, Salvador & Le Roux, 2007; Leitão *et al.*, 2008). Recently, we reported the molecular structure of 5 $\alpha$ -acetamido-6 $\beta$ -hydroxy-17-oxoandrostan-3 $\beta$ -yl acetate (Pinto, Ramos Silva *et al.*, 2007) obtained from the reaction of 5 $\beta$ ,6 $\beta$ -epoxy-17-oxoandrostan-3 $\beta$ -yl acetate, (I), with acetonitrile catalyzed by BiBr<sub>3</sub> (Pinto *et al.*, 2006). (I) and 5 $\beta$ ,6 $\beta$ -epoxy-20-oxopregnan-3 $\beta$ -yl acetate, (II), were also used as substrates for the synthesis of new olefinic 18-nor and 18,19-dinorsteroids (Pinto *et al.*, 2008). Thus, mindful of the biological and synthetic importance of such molecules, we report here the molecular structures of the title 5 $\beta$ ,6 $\beta$ -epoxysteroids, (I) and (II), determined by single-crystal X-ray diffraction, and compare them with those of the free molecules as given by quantum mechanical *ab initio* calculations.

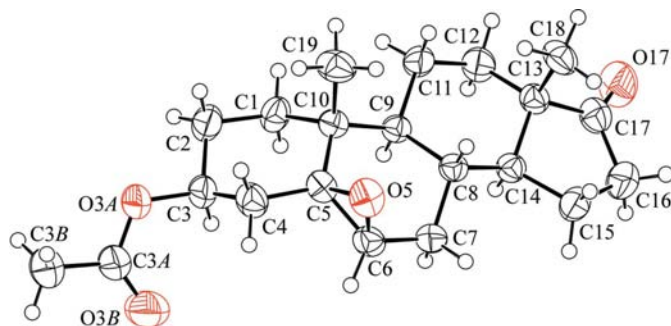


The structures of compounds (I) and (II) with the corresponding atomic numbering schemes are shown in Figs. 1 and 2, respectively. These two 5 $\beta$ ,6 $\beta$ -epoxides are from different steroid series: (I) is from androstane with a C17 carbonyl group at ring D, and (II) is from the pregnane series with a methyl ketone group at the side chain. In both molecules, the 3 $\beta$ -acetoxy group is equatorial to ring A, as is the 17 $\beta$ -COCH<sub>3</sub> group to ring D of (II).

Rings A and B are *cis*-(5 $\beta$ ,10 $\beta$ )-fused [C1–C10–C5–C4 = –39.6 (2)° in (I) and –37.9 (2)° in (II), and C9–C10–C5–C6 = 4.5 (2)° in (I) and 6.2 (3)° in (II)], with bowing angles between the least-squares planes of rings A and B of 35.43 (9) and 34.23 (9)° for (I) and (II), respectively.

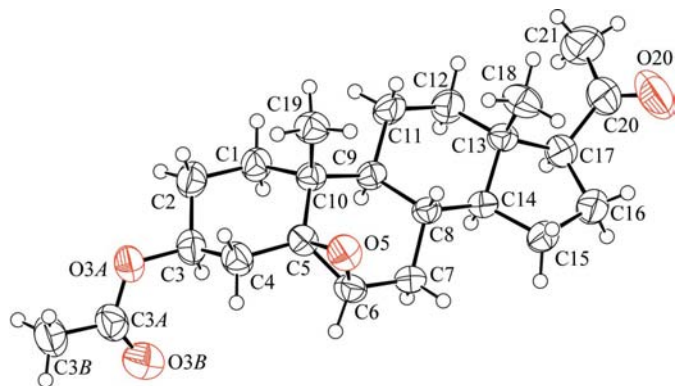
The pseudo-torsion angle C19–C10···C13–C18 deviates greatly from zero in both compounds [18.97 (17)° in (I) and 15.74 (17)° in (II)], showing that the steroid nucleus is significantly twisted. Comparably large pseudo-torsion angles have been observed in other 5 $\beta$ ,6 $\beta$ -epoxysteroids (Hanson *et al.*, 2003). This feature appears to be related to the presence of the 5 $\beta$ ,6 $\beta$ -epoxide group, as it is absent in other *cis*-(5 $\beta$ ,10 $\beta$ )-fused steroids without this functional group (Andrade *et al.*, 2003; Andrade, Paixão, de Almeida, Tavares da Silva & Fernandes Roleira, 2005).

Average values for the atomic distances are in good agreement with reported values (Allen *et al.*, 1987), although for the Csp<sup>3</sup>–Csp<sup>3</sup> bond lengths extreme values were found for C5–C6 [1.472 (3) Å in (I) and 1.464 (3) Å in (II)] and C9–C10 [1.567 (3) Å in (I) and 1.566 (2) Å in (II)], deviating significantly from the average values of 1.526 (3) and



**Figure 1**

The molecular structure of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.



**Figure 2**

The molecular structure of (II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

1.528 (3) Å for compounds (I) and (II), respectively. Short C2–C3 bonds, common to related steroids (Andrade, Paixão, de Almeida, Fernandes Roleira & Tavares da Silva, 2005), were also found [1.495 (3) Å in (I) and 1.499 (3) Å in (II)].

In both compounds, rings A and C have slightly flattened conformations intermediate between chair and half-chair, with average torsion angles of 51 (4) and 55 (2)°, respectively, for (I), and 52 (4) and 55 (2)°, respectively, for (II). Ring B of both 5 $\beta$ ,6 $\beta$ -epoxysteroids adopts a strongly flattened conformation intermediate between half-chair and envelope, with Cremer & Pople (1975) parameters of  $Q = 0.5010$  (19) Å,  $\theta = 53.1$  (2)° and  $\varphi = 190.7$  (3)° for (I), and  $Q = 0.501$  (2) Å,  $\theta = 52.1$  (2)° and  $\varphi = 193.1$  (3)° for (II). In fact, as a consequence of the presence of the 5 $\beta$ ,6 $\beta$ -epoxide group, atoms C7, C6, C5 and C10 are almost coplanar, as shown by the C7–C6–C5–C10 torsion angle of 1.2 (3)° in (I) and 0.5 (3)° in (II), which results in very low average torsion angles of 34 (10) and 38 (10)° for (I) and (II), respectively.

Ring D of (I) features a C14-envelope conformation, as shown by the Cremer & Pople [ $q_2 = 0.424$  (2) Å and  $\varphi_2 = 212.2$  (3)°] and asymmetry parameters (Duax & Norton, 1975) [ $\Delta C_s(14) = \Delta C_s(16,17) = 3.4$  (2)°]. In molecule (II), five-membered ring D has a twisted conformation around the C13–C14 bond [ $q_2 = 0.463$  (2) Å,  $\varphi_2 = 192.4$  (3)° and  $\Delta C_2(16) = \Delta C_2(13,14) = 6.6$  (2)°].

Owing to the absence of any strong hydrogen donors, cohesion of the crystal structures of both compounds is mainly achieved by van der Waals and weak C–H $\cdots$ O interactions. In both structures, one weak C–H $\cdots$ O interaction between ring A and epoxide atom O5 links molecules along the *a* axis. In compound (II), another short contact is found between carbonyl atom O20 and an H atom of a neighbouring C21 methyl group. In addition, an intramolecular C–H $\cdots$ O interaction is present between the same carbonyl atom O20 and a H atom of ring D.

In order to gain some insight into how the crystal packing of (I) and (II) might affect the molecular geometry, and to check whether the large twist of the steroid nucleus is present in the isolated molecules, we have performed a quantum chemical calculation of the equilibrium geometry of the free molecules.

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 6-31G(d,p) basis set. Tight conditions for convergence of both the self-consistent field cycles and the maximum density and energy gradients were imposed ( $10^{-5}$  atomic units). The programs were run on the Milipeia cluster of UC-LCA (16 Opteron cores, 2.2 GHz) running Linux.

Overall, there is very good agreement between the calculated and observed bond lengths, with the exception of the  $Csp^3$ –O bond lengths of the epoxide group, where the calculated (calc) values were systematically shorter than the observed (exp) values: for (I), O5–C5 calc = 1.414 Å and exp = 1.456 (2) Å, O5–C6 calc = 1.407 Å and exp = 1.435 (3) Å; for (II), O5–C5 calc = 1.413 Å and exp = 1.454 (2) Å, and O5–C6 calc = 1.407 Å and exp = 1.429 (3) Å.

The calculated pseudo-torsion angles C19–C10 $\cdots$ C13–C18 were significantly higher than the observed values for both compounds [calc = 22.7° and exp = 18.97 (17)° for (I), and calc = 22.2° and exp = 15.74 (17)° for (II)], showing that the crystal packing somehow affects the steroid nucleus. Interestingly, the calculations reproduce the short C5–C6 bond [calc = 1.459 Å and exp = 1.472 (3) Å for (I), and calc = 1.459 Å and exp = 1.464 (3) Å for (II)] and the long C9–C10 bond [calc = 1.574 Å and exp = 1.567 (3) Å for (I), and calc = 1.574 Å and exp = 1.566 (2) Å for (II)]. In both molecules, a shorter calculated value for the C3–O3A bond binding the 3 $\beta$ -acetoxy substituent to ring A is found [calc = 1.428 Å and exp = 1.462 (2) Å for (I), and calc = 1.429 Å and exp = 1.464 (3) Å for (II)].

## Experimental

The syntheses of (I) and (II) were efficiently accomplished by epoxidation with  $KMnO_4/Fe_2(SO_4)_3 \cdot nH_2O$  (Salvador *et al.*, 1996). Recrystallization from methanol at room temperature gave colourless single crystals of both compounds suitable for X-ray analysis. Analytical data for compounds (I) and (II) are in accordance with the literature (Salvador *et al.*, 1996).

**Table 1**

Selected bond lengths (Å) for (I).

O5—C6	1.435 (3)	C5—C6	1.472 (3)
O5—C5	1.456 (2)	C9—C10	1.567 (3)
C2—C3	1.495 (3)		

**Table 2**

Hydrogen-bond geometry (Å, °) for (I).

<i>D</i> —H··· <i>A</i>	<i>D</i> —H	H··· <i>A</i>	<i>D</i> ··· <i>A</i>	<i>D</i> —H··· <i>A</i>
C1—H1B···O5 <sup>i</sup>	0.97	2.58	3.490 (3)	156

Symmetry code: (i)  $x + 1, y, z$ .

## Compound (I)

### Crystal data

$C_{21}H_{30}O_4$	$V = 1914.47 (6) \text{ \AA}^3$
$M_r = 346.45$	$Z = 4$
Orthorhombic, $P2_12_12_1$	Mo $K\alpha$ radiation
$a = 5.88620 (10) \text{ \AA}$	$\mu = 0.08 \text{ mm}^{-1}$
$b = 15.0988 (3) \text{ \AA}$	$T = 293 (2) \text{ K}$
$c = 21.5413 (4) \text{ \AA}$	$0.37 \times 0.12 \times 0.11 \text{ mm}$

### Data collection

Bruker APEX CCD area-detector diffractometer	62065 measured reflections
Absorption correction: multi-scan (SADABS; Sheldrick, 2000)	2609 independent reflections
$T_{\min} = 0.928, T_{\max} = 1.000$ (expected range = 0.920–0.991)	2155 reflections with $I > 2\sigma(I)$
	$R_{\text{int}} = 0.029$

### Refinement

$R[F^2 > 2\sigma(F^2)] = 0.040$	229 parameters
$wR(F^2) = 0.123$	H-atom parameters constrained
$S = 1.02$	$\Delta\rho_{\text{max}} = 0.28 \text{ e \AA}^{-3}$
2609 reflections	$\Delta\rho_{\text{min}} = -0.19 \text{ e \AA}^{-3}$

## Compound (II)

### Crystal data

$C_{23}H_{34}O_4$	$V = 2091.90 (5) \text{ \AA}^3$
$M_r = 374.50$	$Z = 4$
Orthorhombic, $P2_12_12_1$	Mo $K\alpha$ radiation
$a = 6.29550 (10) \text{ \AA}$	$\mu = 0.08 \text{ mm}^{-1}$
$b = 11.89300 (10) \text{ \AA}$	$T = 293 (2) \text{ K}$
$c = 27.9396 (4) \text{ \AA}$	$0.30 \times 0.28 \times 0.17 \text{ mm}$

### Data collection

Bruker APEX CCD area-detector diffractometer	56880 measured reflections
Absorption correction: multi-scan (SADABS; Sheldrick, 2000)	2940 independent reflections
$T_{\min} = 0.955, T_{\max} = 1.000$ (expected range = 0.942–0.987)	2530 reflections with $I > 2\sigma(I)$
	$R_{\text{int}} = 0.025$

### Refinement

$R[F^2 > 2\sigma(F^2)] = 0.041$	248 parameters
$wR(F^2) = 0.127$	H-atom parameters constrained
$S = 1.04$	$\Delta\rho_{\text{max}} = 0.20 \text{ e \AA}^{-3}$
2940 reflections	$\Delta\rho_{\text{min}} = -0.20 \text{ e \AA}^{-3}$

All H atoms were refined as riding on their parent atoms, with C—H = 0.96–0.98 Å and  $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$  or  $1.5U_{\text{eq}}(\text{methyl C})$ . The absolute configuration was not determined from the X-ray data but

**Table 3**

Selected bond lengths (Å) for (II).

C2—C3	1.499 (3)	C5—C6	1.464 (3)
C5—O5	1.454 (2)	C9—C10	1.566 (2)

**Table 4**

Hydrogen-bond and short-contact geometry (Å, °) for (II).

<i>D</i> —H··· <i>A</i>	<i>D</i> —H	H··· <i>A</i>	<i>D</i> ··· <i>A</i>	<i>D</i> —H··· <i>A</i>
C1—H1B···O5 <sup>i</sup>	0.97	2.53	3.329 (3)	139
C16—H16A···O20	0.97	2.39	2.791 (3)	105
C21—H21C···O20 <sup>ii</sup>	0.96	2.60	3.389 (3)	140

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

was known from the synthetic route. Friedel pairs were merged before refinement.

For both compounds, 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, 2003); 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: SK3212). Services for accessing these data are described at the back of the journal.

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