Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

20-Oxopregn-5-ene-3β,16α-diyl diacetate

L. C. R. Andrade,[a] J. A. Paixão,[a]* M. J. M. de Almeida,[a] M. M. Cruz Silva,[b] M. J. S. M Moreno,[b] M. L. Sá e Melo[b] and A. S. Campos Neves[b]

[a]CEMDRX, Departamento de Física, Faculdade de Ciências e Tecnologia, Universidade de Coimbra, P-3004-516 Coimbra, Portugal, and [b]Centro de Estudos Farmacêuticos, Laboratório de Química Farmacêutica, Faculdade de Farmácia, Universidade de Coimbra, P-3004-295 Coimbra, Portugal

Correspondence e-mail: jap@pollux.fis.uc.pt

Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.004 Å
Disorder in main residue
R factor = 0.043
wR factor = 0.124
Data-to-parameter ratio = 8.8

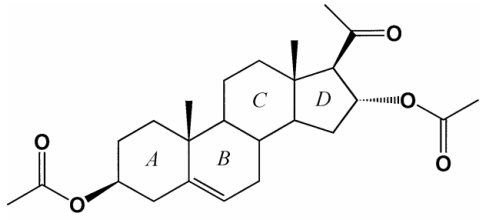
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Received 9 July 2002
Accepted 16 July 2002
Online 19 July 2002

The title compound, $C_{25}H_{36}O_5$, has two independent molecules in the asymmetric unit with similar geometry. The main difference between the two molecules relates to the conformation of the 17β-methyl ketone and 3β-acetoxy groups, the latter being disordered in one of the molecules. The five-membered ring adopts an unusual 13β-envelope conformation.

Comment

In the course of our research on the development of mild and catalytic methods for the chemi-, regio- and stereoselective transformation of polyfunctionalized molecules we directed our attention to the enormous potential of biocatalytic methodologies. In this regard, the 20-oxopregn-5-ene-3β,16α-diyl diacetate, (I), is an interesting substrate for study in acyl transfer reactions catalysed by commercially available enzymes. Compound (I) was prepared from 20-oxopregna-5,16-dien-3β-yl acetate, by application of synthetic methods already described: stereoselective epoxidation of the C-16 double bond with hydrogen peroxide under alkaline conditions, followed by sonochemical reductive opening of the corresponding 16α,17α-epoxide with aluminium amalgam and acetylation of the 3β- and 16α-hydroxyl groups using acetic anhydride in pyridine.



(I)

The X-ray diffraction study of (I) shows that the asymmetric unit contains two symmetry-independent molecules, 1 and 2, with almost identical geometry, although with some disorder on the side chains. An *ORTEP*II (Johnson, 1976) drawing of the molecules, with the corresponding atomic numbering scheme, is shown in Fig. 1. A study of isostructurality between the ordered parts of both molecules (Kálmán *et al.*, 1991) gives the following values: I_D^{29} (distances) = 99.3% and I_D^{23} (valency angles) = 99.6%. All rings are fused *trans*. Bond lengths and angles are within the range of expected values (Allen *et al.*, 1987), apart from some minor deviations in the disordered 3β-acetoxy group.

Both molecules show a larger than usual Csp^2—Csp^3 bond C5—C10, 1.527 (3) and 1.523 (3) Å for molecules 1 and 2,

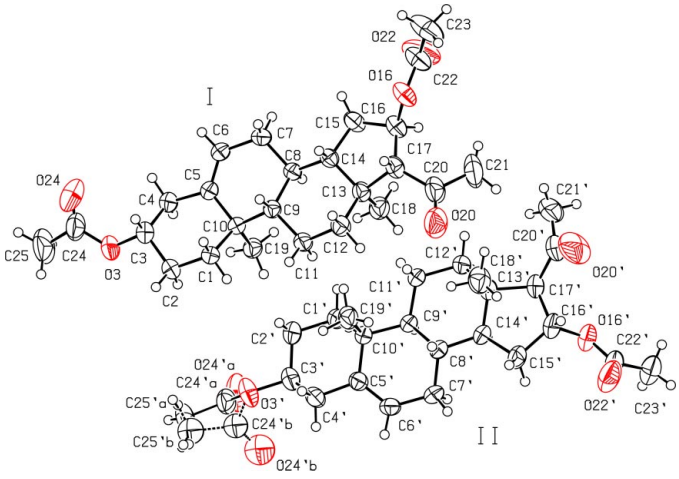


Figure 1
View of two symmetry-independent molecules of the title compound, with 50% probability ellipsoids and the atom-numbering scheme.

respectively, a feature already found in the similar structure of 16α-hydroxy-20-oxopregn-5-en-3β-yl-acetate (Andrade, Paixão, de Almeida, Martins, Soares, Moreno *et al.*, 2001). Rings *A* and *C* have slightly flattened chair conformations, the mean values of the torsion angles being 52 (3) and 54 (5)° for molecule 1, and 53 (3) and 54 (5)° for molecule 2, respectively. As a result of the double bond C5═C6, the C5 environment is planar; the sum of valency angles is 359.9 (4)° for both molecules. Thus, ring *B* is highly distorted, assuming a conformation between 8β,9α-half chair and 8β-sofa [asymmetry parameters (Duax & Norton, 1975) are ΔC_2(5,6) = 3.2 (3), ΔC_S(6) = 20.3 (3), ΔC_2(5,10) = 48.9 (3)° and ΔC_2(5′,6′) = 1.9 (4), ΔC_S(5′) = 21.0 (3), ΔC_2(6′,7′) = 48.1 (4)°, respectively, for molecules 1 and 2]. The five-membered *D* ring assumes an unusual 13β-envelope conformation, with puckering parameters (Cremer & Pople, 1975) q_2 = 0.460 (3) Å, φ_2 = 185.5 (3)° for molecule 1, and q_2 = 0.455 Å, φ_2 = 183.9 (4)° for molecule 2 [pseudo-rotation (Altona *et al.*, 1968) and asymmetry parameters (Duax & Norton, 1975): Δ = 24.3 (5), φ_m = 46.6 (2), ΔC_S(13) = 6.0 (3), ΔC_s(14) = 28.5 (3)° for molecule 1, and Δ = 27.7 (5), φ_m = 46.2 (3), ΔC_S(13′) = 4.4 (3), ΔC_S(14′) = 29.6 (3)° for molecule 2. The 3β-acetoxy group, which does not disturb the usual chair conformation of ring *A*, is planar and oriented equatorially in both molecules. For molecule 1, the dihedral angle between this group and the mean molecular plane is 49.61 (13)°. For molecule 2, the structure refinement reveals a disorder of the 3β-acetoxy group over two positions with occupancies of 0.72 (1) and 0.28 (1). The conformation of the 17β-methyl ketone group is characterized by a torsion angle C13—C17—C20—O20 of −52.4 (5)° for molecule 1 and of 100.0 (4)° for molecule 2. This is curious as it represents the main difference between the two almost isostructural molecules. The conformation of this group in molecule 2 is close to those reported by Weeks *et al.* (1973) and Andrade, Paixão, de Almeida, Martins, Soares, Moreno *et al.* (2001), but in molecule 1, the conformation is closer to that found in the 16α,17α-epoxy steroid molecule, with a torsion angle of −7.1 (4)° (Andrade, Paixão, de Almeida, Martins, Soares, Morais *et al.*, 2001). The pseudo-torsion angle C19—C10—C13—C18 is rather large for both molecules [1: 7.35 (18)°; 2: 12.8 (2)°], indicating that both are highly twisted.

Experimental

Stereoselective epoxidation of the C16 double bond on the commercially available 20-oxopregna-5,16-dien-3β-yl acetate with hydrogen peroxide in alkaline conditions, and subsequent sonochemical reductive opening of the corresponding 16α,17α-epoxide with aluminium amalgam were performed according to the literature (Moreno *et al.*, 1993, 1998). The 3β,16α-dihydroxy-20-oxopregn-5-ene (600 mg, 1.81 mmol) obtained by this two-step procedure was then acetylated with acetic anhydride (3 ml, 31.8 mmol) in pyridine (15 ml) at room temperature for 24 h. The reaction mixture was poured into cooled water (250 ml) under magnetic stirring and the suspension was filtered to isolate the title compound (684 mg, 90.9%) as pure white solid (m.p. 441–445 K). IR: ν_{max} 1726 (3-OAc and 16-OAc), 1703 (20-CO), 1436, 1372, 1242 cm^{-1}. NMR, δ_H (300 MHz, $CDCl_3$, Me_4Si, p.p.m.): 0.67 (3H, *s*, 18-Me), 1.02 (3H, *s*, 19-Me), 2.00 (3H, *s*, 3-Ac), 2.03 (3H, *s*, 16-OAc), 2.17 (3H, *s*, 21-Me), 2.68 (1H, *d*, $J_{17\alpha,16\beta}$ = 6.36 Hz, 17α-H), 4.61 (1H, *m*, 3α-H), 5.37 (1H, *m*, 6-H), 5.49 (1H, *m*, 16β-H); δ_C (75.47 MHz, $CDCl_3$, Me_4Si, p.p.m.): 206.5 (C-20), 170.6 (3-$OCOCH_3$) and 16-$OCOCH_3$), 139.7 (C-5), 122.0 (C-6), 75.7 (C-3), 73.6 (C-16), 70.0 (C17). Crystals suitable for X-ray analysis were obtained by slow evaporation of a solution of the steroid in acetone/*n*-heptane.

Crystal data

$C_{25}H_{36}O_5$
M_r = 416.54
Monoclinic, $P2_1$
a = 14.892 (2) Å
b = 9.375 (3) Å
c = 17.119 (7) Å
β = 99.18 (2)°
V = 2359.3 (13) Å^3
Z = 4
D_x = 1.173 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 10.2–29.2°
μ = 0.64 mm^{-1}
T = 293 (2) K
Prism, colourless
0.55 × 0.24 × 0.22 mm

Data collection

Enraf–Nonius MACH3 diffractometer
Profile data from ω–2θ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.831, T_{max} = 0.868
7913 measured reflections
4918 independent reflections
4607 reflections with $I > 2\sigma(I)$
R_{int} = 0.034
θ_{max} = 71.9°
$h = -18 \rightarrow 18$
$k = -11 \rightarrow 11$
$l = -21 \rightarrow 5$
3 standard reflections
frequency: 180 min
intensity decay: 5.7%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.043
$wR(F^2)$ = 0.124
S = 1.05
4918 reflections
559 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0752P)^2 + 0.3449P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.27 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0014 (2)

The 3β-acetoxy group of molecule 2 is disordered over two positions with refined occupancies of 0.72 (1) and 0.28 (1). The bond lengths within the disordered group were restrained to standard values to regularize the refinement. All H atoms were refined as riding on their parent atoms using *SHELXL*97 defaults. Owing to the

absence of significant anomalous dispersion, Friedel pairs were merged and the absolute structure assigned on the basis of the known configuration of the molecules from the synthetic route. Examination of the crystal structure with *PLATON* (Spek, 2001) shows that there are no voids in the structure that might be occupied by solvent molecules.

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, 1997); 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.

This work was supported by Fundação para a Ciência e Tecnologia.

References

Allen, F. H., Kennard, O., Watson, D. G., Brammer, L., Orpen, A. G. & Taylor, R. (1987). *J. Chem. Soc. Perkin Trans.* 2, pp. S1–19.
Altona, C., Geize, H. J. & Romers, C. (1968). *Tetrahedron*, **24**, 13–32.
Andrade, L. C. R., Paixão, J. A., de Almeida, M. J. M., Martins, R. M. L. M., Soares, H. I. M., Morais, G. J. R., Moreno, M. J. S. M., Sá e Melo, M. L. & Campos Neves, A. S. (2001). *Acta Cryst.* C**57**, 587–589.
Andrade, L. C. R., Paixão, J. A., de Almeida, M. J. M., Martins, R. M. L. M., Soares, H. I. M., Moreno, M. J. S. M., Sá e Melo, M. L. & Campos Neves, A. S. (2001). *Acta Cryst.* E**57**, o571–o573.
Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.
Duax, W. L. & Norton, D. A. (1975). *Atlas of Steroid Structure*, Vol. 1. New York: Plenum.
Enraf–Nonius (1989). *CAD*-4 *Software*. Version 5.0. Enraf–Nonius, Delft, The Netherlands.
Johnson, C. K. (1976). *ORTEP*II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.
Kálmán, A., Argay, G., Scharfenberg-Pfeiffer, D., Höhne, E. & Ribár, B. (1991). *Acta Cryst.* B**47**, 68–77.
Moreno, M. J. M., Sá e Melo, M. L. & Campos Neves, A. S. (1993). *Tetrahedron Lett.* **34**, 353–356.
Moreno, M. J. S. M., Costa, S. C. P., Martins, R. M. L. M., Sá e Melo, M. L. & Campos Neves, A. S. (1998). *Tetrahedron*, **54**, 13877–13886.
North, A. C. T., Phillips, D. C. & Mathews, F. S. (1968). *Acta Cryst.* A**24**, 351–359.
Sheldrick, G. M. (1997). *SHELXS*97 and *SHELXL*97. University of Göttingen, Germany.
Spek, A. L. (1997). *HELENA.* University of Utrecht, The Netherlands.
Spek, A. L. (2001). *PLATON.* University of Utrecht, The Netherlands.
Weeks, C. M., Duax, W. L. & Wolff, M. E. (1973). *J. Am. Chem. Soc.* **95**, 2865–2868.