

Ethyl 3#-hydroxypregna-5,17(20)-dien-21-oate

Author

Quader, S, Boyd, SE, Houston, TA, Jenkins, ID, Healy, PC

Published

2006

Journal Title

Acta Crystallographica. Section E: Structure reports online

DOI

[10.1107/S1600536805040912](https://doi.org/10.1107/S1600536805040912)

Rights statement

© The Author(s) 2006. For information about this journal please refer to the journal's website. All articles published in Acta Crystallographica Section E are open access and distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. See <http://creativecommons.org/licenses/by/2.0/uk/legalcode>

Downloaded from

<http://hdl.handle.net/10072/14340>

Link to published version

<http://journals.iucr.org/e/journalhomepage.html>

Griffith Research Online

<https://research-repository.griffith.edu.au>

Sabina Quader, Sue E. Boyd,
Todd A. Houston, Ian D. Jenkins
and Peter C. Healy*Eskitis Institute, Chemical Biology, Griffith
University, Nathan, Brisbane 4111, Australia

Correspondence e-mail: p.healy@griffith.edu.au

Key indicators

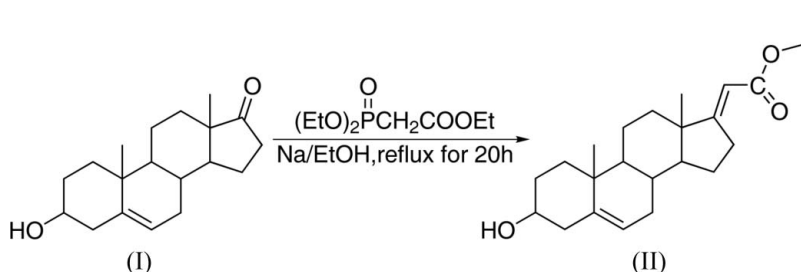
Single-crystal X-ray study
 $T = 295\text{ K}$
Mean $\sigma(\text{C}-\text{C}) = 0.005\text{ \AA}$
 R factor = 0.041
 wR factor = 0.111
Data-to-parameter ratio = 7.5For details of how these key indicators were
automatically derived from the article, see
<http://journals.iucr.org/e>.Ethyl 3 β -hydroxypregna-5,17(20)-dien-21-oateIn the structure of the title steroid, $\text{C}_{23}\text{H}_{34}\text{O}_3$, the molecules are linked in infinite chains through intermolecular $\text{C}_1(n)\text{O}-\text{H}\cdots\text{O}$ hydrogen bonds between the hydroxy proton and the ester carbonyl O atom.

Received 28 November 2005

Accepted 6 December 2005

Online 10 December 2005

Comment

Recent research suggests that steroids such as ergosterol and fusidic acid display antitubercular activity (Ruggutt & Ruggutt, 2001). In fact, the minimum inhibitory concentration (MIC) for these steroids is comparable to a number of clinically used anti-TB drugs. This, as well as the structural similarity of the title compound, (II), with fusidic acid and ergosterol has prompted us to consider conjugation of this compound with a number of well known anti-TB agents (Ballell *et al.*, 2005). Our aim is to increase the lipophilicity of the parent drug by attaching a steroid moiety which could have anti-TB activity in its own right. As part of this project, compound (II) was prepared from the commercially available ketone, dehydroandrosterone (I) (Verma *et al.*, 2004), by the Wittig–Horner reaction (Wicha *et al.*, 1977), and was recrystallized from methanol.Compound (II) crystallizes in the space group $P1$ with one molecule in the unit cell. The fused tetracyclic ring system adopts the expected conformations for the all-*trans* A/B/C/D junctions. The six-membered rings A and C adopt normal chair conformations. As previously observed in related structures (Thamotharan *et al.*, 2004; Verma *et al.*, 2004), the hydroxy group on C3 does not perturb the structure of ring A. The $\text{C}5=\text{C}6$ bond length of $1.326(5)\text{ \AA}$ confirms the presence of the double bond in this position and imposes an $8\beta,9\alpha$ -half-chair conformation on ring B. Ring D adopts the 14α -envelope conformation previously observed in the dehydroandrosterone parent (Verma *et al.*, 2004); this conformation minimizes steric interactions with the angular C18 methyl group (Fuchs, 1978).The $\text{C}17=\text{C}20$ bond length of $1.331(5)\text{ \AA}$ confirms the presence of the double bond in this position. The substituents on this bond adopt the thermodynamically favoured *E*

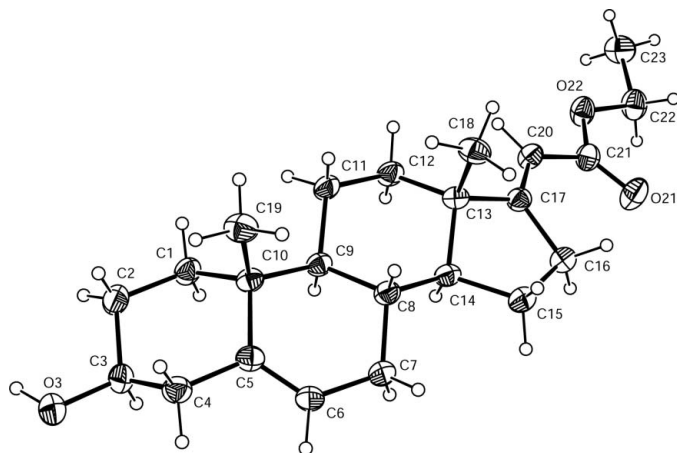


Figure 1

Representative view of (II), with the atom-numbering scheme. Displacement ellipsoids for non-H atoms are drawn at the 30% probability level.

configuration which, again, minimizes interactions with the angular methyl group. The C20–C21 bond length of 1.460 (5) Å suggests partial double-bond character, with the ester group adopting an *s-trans* configuration. The molecules in the crystal structure are linked through intermolecular $C_1^1(n)$ (Bernstein *et al.*, 1995) O–H...O hydrogen bonds between the O3 hydroxy proton and the O21 carbonyl O atom (Table 2), forming infinite chains along the body diagonal of the unit cell.

The ^1H and ^{13}C NMR spectra of the compound were fully assigned using two-dimensional gCOSY, gHSQC and gHMBC methods. The lowfield ^{13}C chemical shifts of the C17 (176.15 p.p.m.) and C21 (167.45 p.p.m.) C atoms were confirmed by the presence of unambiguous cross peaks in the gHMBC spectrum linking (i) the 176.15 p.p.m. resonance with the H18 and H16 resonances and (ii) the 167.45 p.p.m. resonance with the H20 and H22 resonances. The ^{13}C chemical shift of C20 (108.62 p.p.m.) was confirmed by direct correlation of the C20 and H20 resonances in the gHSQC matrix. The ^{13}C chemical shifts of the C17, C21 and C20 atoms can be compared with those previously observed for ^{13}C nuclei in the isolated D-ring analogue methyl 2-methylenecyclopentane acetate (Molander & Harris, 1997), *i.e.* 169.51, 167.31 and 111.18 p.p.m., respectively.

Experimental

A solution of sodium ethoxide (1.243 M, 5 ml) was added slowly to a stirred solution of dehydroisoandrosterone (600 mg, 2 mmol) and triethyl phosphonoacetate (1.6 ml, 6 mmol) in ethanol (5 ml) at room temperature, under an N_2 atmosphere. The reaction mixture was refluxed for 20 h, then cooled to room temperature and concentrated *in vacuo*. The residue was diluted with water and the resulting suspension acidified (acetic acid) and extracted with a mixture of ethyl acetate and tetrahydrofuran (3:1, 60 ml). The organic layer was washed with water and brine, dried (Na_2SO_4) and the solvent removed by evaporation at reduced pressure. Crystallization of the residue from methanol gave the product ethyl 3 β -hydroxypregna-5,17(20)-dien-21-oate (525 mg, 70%) as fine colourless crystals,

suitable for X-ray crystallographic analysis [m.p. 457–459 K; literature 457–458 K (Wicha *et al.*, 1977)]. ^1H NMR (400 MHz, CDCl_3 , 298 K): δ 5.51 (1H, *dd*, $J = 2.5, 2.5$ Hz, H2O), 5.32 (1H, *m*, H6), 4.11 (2H, *m*, CH2, H22), 3.49 (1H, *dddd*, $J = 4, 5, 11, 11$ Hz, H3), 2.88–2.72 (2H, *m*, H16*a,b*), 2.31–2.15 (2H, *m*, H4*a,b*), 2.03 (1H, *m*, H7*a*), 1.85–1.72 (4H, *br m*, H12*a*, H15*a*, H1*a*, H2*a*), 1.68–1.41 (5H, *br m*, H11*a,b*, H8, H2*b*, H7*b*), 1.38–1.20 (2H, *br m*, H15*b*, H12*b*), 1.22 (3H, *dd*, CH₃, H23), 1.10–0.91 (3H, *m*, H1*b*, H14, H9), 0.99 (3H, *s*, CH₃, H19), 0.80 (3H, *s*, CH₃, H18); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3 , 298 K): δ 176.15 (C17), 167.45 (C=O, C21), 140.82 (C5), 121.28 (C6), 108.62 (C20), 71.61 (C3), 59.50 (C22), 53.81 (C14), 50.21 (C9), 46.03 (C13), 42.20 (C4), 37.20 (C1), 36.56 (C10), 35.18 (C12), 31.64–31.55 (C7, C2, C8), 30.41 (C16), 24.45 (C15), 20.94 (C11), 19.39 (C19), 18.23 (C18), 14.36 (C23). ESMS (*m/z*): +ve ion, 381.15 [$M + \text{Na}$]⁺, 359.13, [$M + \text{H}$]⁺.

Crystal data

$\text{C}_{23}\text{H}_{34}\text{O}_3$

$M_r = 358.50$

Triclinic, *P1*

$a = 6.3179$ (17) Å

$b = 8.0901$ (16) Å

$c = 10.880$ (2) Å

$\alpha = 73.8$ (2)°

$\beta = 100.311$ (19)°

$\gamma = 109.285$ (16)°

$V = 501.7$ (5) Å³

$Z = 1$

$D_x = 1.187$ Mg m⁻³

Mo $K\alpha$ radiation

Cell parameters from 25

reflections

$\theta = 12.7$ – 17.3 °

$\mu = 0.08$ mm⁻¹

$T = 295$ (2) K

Prism, colourless

$0.40 \times 0.35 \times 0.20$ mm

Data collection

Rigaku AFC-7R diffractometer

ω - 2θ scans

Absorption correction: none

2086 measured reflections

1756 independent reflections

1506 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.033$

$\theta_{\text{max}} = 25.0$ °

$h = -7 \rightarrow 7$

$k = 0 \rightarrow 9$

$l = -11 \rightarrow 12$

3 standard reflections

every 150 reflections

intensity decay: 1.2%

Refinement

Refinement on F^2

$R[F^2 > 2\sigma(F^2)] = 0.041$

$wR(F^2) = 0.111$

$S = 1.04$

1756 reflections

235 parameters

H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0611P)^2$

$+ 0.0627P]$

where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\text{max}} = 0.023$

$\Delta\rho_{\text{max}} = 0.15$ e Å⁻³

$\Delta\rho_{\text{min}} = -0.19$ e Å⁻³

Table 1

Selected geometric parameters (Å, °).

O3–C3	1.436 (4)	C5–C6	1.326 (5)
O21–C21	1.208 (5)	C17–C20	1.331 (5)
O22–C21	1.340 (4)	C20–C21	1.460 (5)
O22–C22	1.445 (5)		
C21–O22–C22	117.1 (3)	O22–C21–C20	110.2 (4)
O3–C3–C2	112.6 (3)	O21–C21–C20	126.8 (4)
O3–C3–C4	107.8 (4)	O22–C22–C23	106.9 (4)
O21–C21–O22	123.0 (4)		

Table 2

Hydrogen-bond geometry (Å, °).

<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>
O3–H3...O21 ⁱ	0.91	2.07	2.964 (4)	167

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

C-bound H atoms were constrained as riding atoms, with C—H = 0.94–0.96 Å, and with $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{parent atom})$. The hydroxy H atom was located in a difference Fourier synthesis and constrained as a riding atom, with O—H = 0.91 Å. In the absence of significant anomalous scattering effects, Friedel pairs were merged. The absolute configuration was assigned on the basis of the known configuration of the starting material.

Data collection: *MSC/AF7 Diffractometer Control Software for Windows* (Molecular Structure Corporation, 1999); cell refinement: *MSC/AF7 Diffractometer Control Software for Windows*; data reduction: *TEXSAN for Windows* (Molecular Structure Corporation, 2001); program(s) used to solve structure: *TEXSAN for Windows*; program(s) used to refine structure: *TEXSAN for Windows* and *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP3* (Farrugia, 1997); software used to prepare material for publication: *TEXSAN for Windows* and *PLATON* (Spek, 2003).

We acknowledge financial support of this work by Griffith University and the Eskitis Institute for Cell and Molecular Therapies.

References

- Ballell, L., Field, R. A., Duncan, K. & Young, R. J. (2005). *Antimicrob. Agents Chemother.* **49**, 2153–2163.
- Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.
- Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
- Fuchs, B. (1978). *Top. Stereochem.* **10**, 1–94.
- Molander, G. A. & Harris, C. M. (1997). *J. Org. Chem.* **62**, 7418–7429.
- Molecular Structure Corporation (1999). *MSC/AF7 Diffractometer Control Software for Windows*. Version 1.02. MSC, 9009 New Trails Drive, The Woodlands, TX 77381, USA.
- Molecular Structure Corporation (2001). *TEXSAN for Windows*. Version 1.06. MSC, 9009 New Trails Drive, The Woodlands, TX 77381, USA.
- Ruggutt, J. K. & Ruggutt, K. J. (2001). *Nat. Prod. Lett.* **16**, 107–113.
- Sheldrick, G. M. (1997). *SHELXL97*. University of Göttingen, Germany.
- Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.
- Thamotharan, S., Parthasarathi, V., Gupta, R., Guleria, S., Jindal, D. P. & Linden, A. (2004). *Acta Cryst. C* **60**, o75–o78.
- Verma, R., Jasrotia, D., Sawheny, A., Bhat, M. & Gupta, B. D. (2004). *J. Chem. Crystallogr.* **34**, 523–528.
- Wicha, J., Bal, K. & Piekut, S. (1977). *Synth. Commun.* **7**, 215–222.