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

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Key indicators

Single-crystal X-ray study
T = 295 K
Mean σ(C–C) = 0.005 Å
R factor = 0.041
wR factor = 0.111
Data-to-parameter ratio = 7.5

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

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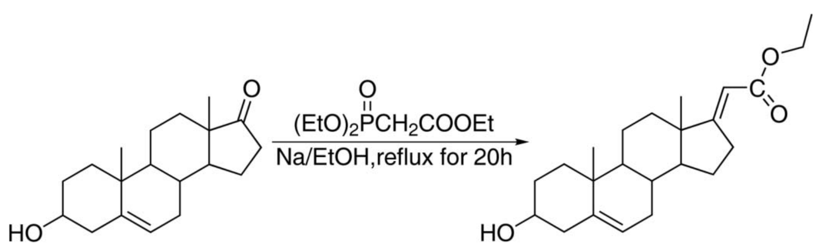
In the structure of the title steroid, $C_{23}H_{34}O_3$, the molecules are linked in infinite chains through intermolecular $C_1^1(n)$ O—H···O hydrogen bonds between the hydroxy proton and the ester carbonyl O atom.

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 *P*1 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 C5═C6 bond length of 1.326 (5) Å confirms the presence of the double bond in this position and imposes an 8β,9α-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 C17═C20 bond length of 1.331 (5) Å confirms the presence of the double bond in this position. The substituents on this bond adopt the thermodynamically favoured *E*

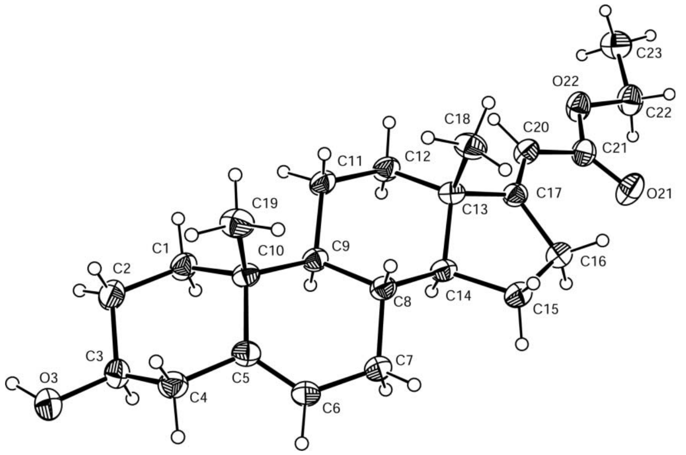


Figure 1
Representative view of (II), with the atom-numbering scheme. Displacement ellipsoids for non-H atoms are drawn at the 30% probability level.

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 ^{1}H 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 3β-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)]. ^{1}H 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*, CH_3, H23), 1.10–0.91 (3H, *m*, H1*b*, H14, H9), 0.99 (3H, *s*, CH_3, H19), 0.80 (3H, *s*, CH_3, H18); ^{13}C{^{1}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 $[M + Na]^+$, 359.13, $[M + H]^+$.

Crystal data

$C_{23}H_{34}O_3$	$Z = 1$
$M_r = 358.50$	$D_x = 1.187$ Mg m^{-3}
Triclinic, $P1$	Mo $K\alpha$ radiation
$a = 6.3179$ (17) Å	Cell parameters from 25 reflections
$b = 8.0901$ (16) Å	$\theta = 12.7$–$17.3°$
$c = 10.880$ (2) Å	$\mu = 0.08$ mm^{-1}
$\alpha = 73.8$ (2)°	$T = 295$ (2) K
$\beta = 100.311$ (19)°	Prism, colourless
$\gamma = 109.285$ (16)°	0.40 × 0.35 × 0.20 mm
$V = 501.7$ (5) Å^3	

Data collection

Rigaku AFC-7R diffractometer	$\theta_{max} = 25.0°$
ω–2θ scans	$h = -7 \rightarrow 7$
Absorption correction: none	$k = 0 \rightarrow 9$
2086 measured reflections	$l = -11 \rightarrow 12$
1756 independent reflections	3 standard reflections every 150 reflections intensity decay: 1.2%
1506 reflections with $I > 2\sigma(I)$	
$R_{int} = 0.033$	

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0611P)^2 + 0.0627P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.041$	$(\Delta/\sigma)_{max} = 0.023$
$wR(F^2) = 0.111$	$\Delta\rho_{max} = 0.15$ e Å^{-3}
$S = 1.04$	$\Delta\rho_{min} = -0.19$ e Å^{-3}
1756 reflections	
235 parameters	
H-atom parameters constrained	

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, °).

D—H···A	D—H	H···A	D···A	D—H···A
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 $U_{iso}(H) = 1.2U_{eq}$(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/AFC7 Diffractometer Control Software for Windows* (Molecular Structure Corporation, 1999); cell refinement: *MSC/AFC7 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).

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