Crystal Structure and Synthesis of Two Steroidal Derivatives: 3 β -Propanoyloxyandrost-5-en-17-one and 3 β -Pentanoyloxyandrost-5-en-17-one

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C₂₂H₃₂O₃ (**1**) and C₂₄H₃₆O₃ (**2**) are orthorhombic, *P*2₁2₁2₁. The unit-cell dimensions for **1** and **2** at 298(2)K are *a* = 8.9849(11), *b* = 12.5300(15), *c* = 17.441(2) Å, *V* = 1963.5(4) Å³, *D_x* = 1.165 g/cm³, and *Z* = 4; *a* = 8.9457(17), *b* = 12.447(2), *c* = 19.242(4) Å, *V* = 2142.6(7) Å³, *D_x* = 1.155 g/cm³, and *Z* = 4, respectively. The *R* values for molecules **1** and **2** are *R* = 0.0607 for 3598 reflections and *R* = 0.0445 for 3981 reflections, respectively. The A, B, C, and D rings for molecule **1** are chair, half-chair, chair, half-chair (for molecule **2**: chair, half-chair, chair, half-chair) conformations. In both structures, the molecules are linked by C-H...O interactions and van der Waals forces.

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Actually, prostate cancer and benign prostatic hyperplasia are two of the most common sufferings in the North American male population. Prostate cancer is the second leading cause of death, and prostatic hyperplasia the second most-common operation performed on males of age over 60 years. Both sufferings are directly related to androgen excess in the organism.¹

The principal androgen produced in the organism is testosterone, which under the influence of the enzyme 5 α -reductase is converted to dihydrotestosterone,^{2,3} an androgen that is more potent than testosterone or adrenal androgens. It has also been demonstrated that dihydrotestosterone interacts more efficiently with the androgens receptor than does testosterone.⁴ Androgen antagonists are a potentially useful treatment for these two diseases, because they can block the

androgen receptor, or cause inhibition of the enzyme 5 α -reductase, which prevents the conversion of testosterone to dihydrotestosterone.³

In this paper, we describe the synthesis and X-ray determination of two steroidal derivatives: 3 β -propanoyloxyandrost-5-en-17-one **1**, and 3 β -pentanoyloxyandrost-5-en-17-one **2**. These compounds were prepared from commercially available dehydroepiandrosterone (3 β -hydroxyandrost-5-en-17-one) **I**, as shown in Fig. 1. Crystals suitable for X-ray crystallography were grown from a mixture of a chloroform and methanol (1:1)

Fig. 1 Synthesis of compounds **1** and **2**.

Fig. 2 Molecular structures of **1** and **2**, with displacement ellipsoids at 50% probability.

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Table 1 Crystal and experimental data

	Compound 1	Compound 2
Chemical formula:	C ₂₂ H ₃₂ O ₃	C ₂₄ H ₃₆ O ₃
Formula weight	344.48	372.53
<i>T</i>	298 K	298 K
Crystal system	orthorhombic	orthorhombic
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 2 ₁ 2 ₁ 2 ₁
<i>a</i>	8.9849(11) Å	8.9457(17) Å
<i>b</i>	12.5300(15) Å	12.447(3) Å
<i>c</i>	17.441(2) Å	19.242(4) Å
<i>V</i> ; <i>Z</i>	1963.5(4) Å ³ ; <i>Z</i> = 4	2142.6(7) Å ³ ; <i>Z</i> = 4
<i>D</i> _x ; <i>D</i> _m (floatation)	1.165 g/cm ⁻³ ; 1.17 g/cm ⁻³	1.155 g/cm ⁻³ ; 1.16 g/cm ⁻³
Radiation	Mo <i>K</i> _α (<i>λ</i> = 0.71073 Å)	Mo <i>K</i> _α (<i>λ</i> = 0.71073 Å)
<i>μ</i> (Mo <i>K</i> _α); <i>F</i> (0 0 0)	0.075 mm ⁻¹ ; 752	0.074 mm ⁻¹ ; 816
Crystal size	0.32 × 0.15 × 0.10 mm ³	0.35 × 0.10 × 0.06 mm ³
No. of reflections collected	16308	23635
No. of independent reflections	3598	3981
<i>θ</i> range for data collection	2.00 to 25.38°	1.95 to 25.66°
Data/Restraints/Parameters	3598/0/229	3981/0/248
Goodness-of-fit on <i>F</i> ²	1.020	0.813
<i>R</i> indices [<i>I</i> > 2σ(<i>I</i>): <i>R</i> 1; <i>wR</i> 2	0.0607; 0.1282	0.0445; 0.0785
<i>R</i> indices (all data): <i>R</i> 1; <i>wR</i> 2	0.1193; 0.1520	0.1020; 0.0881
(Δ/ <i>σ</i>) _{max}	0.001	0.001
(Δ <i>ρ</i>) _{max} ; (Δ <i>ρ</i>) _{min}	0.109 eÅ ⁻³ ; -0.144 eÅ ⁻³	0.148 eÅ ⁻³ ; -0.186 eÅ ⁻³
Measurement	Bruker APEX2 CCD area detector	Bruker APEX2 CCD area detector
Programs system	SHELXTL	SHELXTL
Structure determination	SHELXTL-97	SHELXTL-97
CCDC deposition number	1026270	1026271

solution by slow evaporation of the solvent at room temperature. X-ray data for the crystals of the title compound were collected by graphite-monochromatized Mo *K*_α radiation at 298(2)K. An analytical absorption-correction was applied. The structure was solved by direct methods and refined by full-matrix least-squares with anisotropic temperature factors for the non-hydrogen atoms. The positions of all H atoms, except for those of the hydroxyl groups, were calculated geometrically, and a riding model was used in the refinement, with C-H distances in the range of 0.95 to 0.98 Å and *U*_{iso}(H) = 1.17*U*_{eq}(C) for molecule **1** (for molecule **2**, with a range of 0.93 to 0.98 Å and *U*_{iso}(H) = 1.05*U*_{eq}(C)). Those H atoms attached to the O atoms were found in a difference Fourier map at an advantage stage of the anisotropic refinement, and were included in the final cycles of refinement. The software used to prepare material for publication was PARST97.⁵ Table 1 summarizes the crystal and experimental data. The chemical and molecular structures for molecules **1** and **2** are shown in Fig. 2.

The absolute configurations of both compound **1** and **2** are C3S, C8R, C9S, C10R, C13S and C14S, which is inferred from the known stereochemistry of dehydroepiandrosterone (3β-hydroxyandrost-5-en-17-one).⁶ This observation agrees with results obtained in the structures of three antiandrogen derivatives: 3β-cyclobutyl carbonyloxy-5-androsten-17-one; 3β-cyclopentyl carbonyloxy-5-androsten-17-one; and 3β-cyclohexyl carbonyloxy-5-androsten-17-one.⁷ Both molecules consist of four six-membered rings and one five-membered ring. For the puckering-parameters values (*φ*₂, *θ*₂ and *Q*),⁸ the A, B, C, and D rings for both molecules **1** and **2** are chair (¹C₄), half-chair (⁵H₄), chair (¹C₄) and half-chair conformations. Rings B, C and D are all *trans* fused. All of the bond lengths and angles are normal. The absolute configurations of both title compounds for the chiral centers are 3S, 8R, 9S, 10R, 13S and 14S. The stereochemistry of both title

compounds is as follows: C8-βH is *trans* to C9-αH; C9-αH is *trans* to C10-βCH₃; C13-βCH₃ is *trans* to C14-αH; and C13-βCH₃ is *anti* to C17-CO. Molecules **1** in their crystal are linked by four C-H...O interactions, while in molecules **2** only two of these interactions occur, due to their length, and could be considered to be significant ones.⁹

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