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ORIGINAL PAPER

Crystal Structure and Synthesis of 17α-Acetoxy-pregn-4,6-diene-3,20-dione

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Abstract 17α-Acetoxy-pregn-4,6-diene-3,20-dione (**1**), $C_{23}H_{30}O_4$, was synthesized from the commercially available 17α-acetoxyprogesterone. X-ray diffraction analysis of (**1**) demonstrated that it consists of four rings, three six-membered rings (A, B and C) and one-five-membered ring (D). A, B, C and D rings occur in an envelope; half chair and chair; and half chair conformations, respectively. The crystal of 17α-acetoxy-pregn-4,6-diene-3,20-dione is in orthorhombic crystal system with space group $P2_12_12_1$, lattice constants: $a = 10.843(1)$, $b = 11.744(1)$, $c = 15.815(2)$Å, $V = 2013.9(4)$Å^3, $Dx = 1.222$ g/cm^3 and $Z = 4$. The molecules in the crystal are stabilized by C–H···O interactions and van der Waals forces.

Keywords Androgen receptor · 5-alpha-reductase inhibitors · Binding · Prostate

Introduction

Prostate cancer is now the most common malignancy and the second leading cause of cancer death in North American males. Androgen antagonists offer a potentially useful treatment for androgen mediated diseases such as: prostate cancer, hirsutism, acne, seborrhea, androgenic alopecia and benign prostatic hyperplasia [1]. Although surgery presently represents the usual treatment for prostate cancer, there are several other alternative modalities currently available for the treatment of these androgen-dependent afflictions [2, 3].

At the present time, the most common therapy for the treatment of prostate cancer and benign prostatic hyperplasia is blockage of the androgen receptor by androgen antagonists or inhibition of the conversion of testosterone to the more active androgen, dihydrotestosterone by the enzyme 5α-reductase [4–6].

In this article we describe the synthesis and X-ray determination of one steroidal derivative, 17α-acetoxypregn-4,6-diene-3, 20-dione **1**. This compound was prepared from the commercially available 17α-acetoxyprogesterone. Compound **1** exhibited a high antiandrogenic effect and could be considered as a potential drug for the treatment of prostate cancer.

Experimental

Synthesis

A solution of 17α-acetoxyprogesterone (1 g, 2.69 mmol), chloranil (0.7 g, 2.8 mmol) in toluene (2 ml) and glacial acetic acid (8 ml) was allowed to reflux for 4 h. The precipitated tetrachlorohydroquinone was filtered. The filtrate was washed with a 10% aqueous sodium hydroxide solution, water and dried over anhydrous sodium sulfate; the solvent was removed in vacuum. The crude product was recrystallized from ethyl acetate. Yield 0.7 g, (1.8 mmol), 70.4%, mp 224–226 °C. UV (nm) 282 (ε = 27,400). IR

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(KBr) cm^{-1}: 2978, 1730, 1700, 1675. ^{1}H-NMR ($CDCl_3$) δ: 0.7 (3H, s, H-18), 1.1 (3H, s, H-19), 2.0 (3H, s, acetoxy), 2.1 (3H, s, H-21), 5.7 (1H, q, $J = 2$ Hz and $J = 4$ Hz, H-6), 6.0 (1H, s, H-4), 6.2 (1H,d, $J = 10$ Hz, H-7). ^{13}C-NMR ($CDCl_3$) δ: 14.3 (C-18), 16.3 (C-19), 21.2 (C-21), 123.9 (C-4), 128.3 (C-6), 130.3 (C-7), 170.6 (ester carbonyl), 199.9 (C-3), 203.8 (C-20).

Crystal Structure Determination

X-ray data were collected on a Bruker Smart APEX AXS CCD area detector with a graphite monochromator and Mo Kα radiation ($\lambda = 0.71073$ Å) by the ω-scan method. The observed reflections were corrected for Lorentz and polarization effects, but not for X-ray absorption. The structure was solved using direct methods with SHELXTL software package [7] and refined on F^2 by full-matrix least-squares with anisotropic displacements parameters for all non-hydrogen atoms [8]. All hydrogen atoms were geometrically fixed and allowed to ride on the parent C atoms. The crystals data and pertinent details of the experimental conditions are summarized in Table 1.

Table 1 Crystal data, collection parameters and refinements for compound **1**

Compound	**1**
CCDC deposit no.	699041
Crystal size (mm)	0.28 × 0.24 × 0.22
Color/shape	Colorless/prism
Empirical formula	$C_{23}H_{30}O_4$
Formula weight	370.47
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	
a (Å)	10.843(1)
b (Å)	11.744(1)
c (Å)	15.815(2)
Volume (Å^3)	2013.9(4)
Z	4
Density (calculated) (mg/m^3)	1.222
Absorption coefficient (mm^{-1})	0.082
F(000)	800
θ range for data collection (°)	2.16–25.37
Index ranges	$-13 \leq h \leq 13, -14 \leq k \leq 14, -19 \leq l \leq 19$
Reflections collected/unique	16773/3692
Observed reflections ($I > 2\sigma(I)$)[a]	3692($R_{\text{int}} = 0.0449$)
Data/restraints/parameters	2748/0/248
Goodness-of-fit[a] on F^2	0.915
Final *R* indices [(I) > $2\sigma(I)$][a]	$R_1 = 0.0412$, $wR_2 = 0.0782$
R indices (all data)[a]	$R_1 = 0.0571$, $wR_2 = 0.0827$
Largest diff. peak and hole (e A^{-3})	0.167 and −0.125

[a] $R_{\text{int}} = \dfrac{\sum |F_o^2 - \langle F_o^2 \rangle|}{\sum F_o^2}$, $R_1 = \dfrac{\sum ||F_o| - |F_c||}{\sum |F_o|}$,

$$wR_2 = \sqrt{\frac{\sum w(F_o^2 - F_c^2)^2}{\sum w(F_o^2)^2}}, S = \sqrt{\frac{\sum w(F_o^2 - F_c^2)^2}{m - n}}$$

Table 2 Bond distances (Å) and angles (°) for compound **1**

Bond lengths (Å)			
O1–C3	1.222(3)	O2–C20	1.206(2)
O3–C22	1.347(2)	O3–C17	1.464(2)
O4–C22	1.193(2)	C1–C10	1.527(3)
C1–C2	1.531(3)	C2–C3	1.493(3)
C3–C4	1.438(3)	C4–C5	1.339(3)
C5–C6	1.442(3)	C5–C10	1.512(3)
C6–C7	1.322(3)	C7–C8	1.491(3)
C8–C14	1.528(2)	C8–C9	1.536(3)
C9–C11	1.527(3)	C9–C10	1.554(3)
C10–C19	1.533(3)	C11–C12	1.537(3)
C12–C13	1.531(3)	C13–C14	1.531(2)
C13–C18	1.539(3)	C13–C17	1.559(2)
C14–C15	1.524(3)	C15–C16	1.540(3)
C16–C17	1.534(3)	C17–C20	1.531(3)
C20–C21	1.497(3)	C22–C23	1.488(3)
Bond angles (°)			
C22–O3–C17	117.81(15)	C10–C1–C2	113.96(18)
C3–C2–C1	113.3(2)	O1–C3–C4	121.5(2)
O1–C3–C2	121.3(2)	C4–C3–C2	117.2(2)
C5–C4–C3	125.0(2)	C4–C5–C6	120.42(19)
C4–C5–C10	121.43(19)	C6–C5–C10	118.09(17)
C7–C6–C5	123.7(2)	C6–C7–C8	122.9(2)
C7–C8–C14	113.49(16)	C7–C8–C9	110.91(16)
C14–C8–C9	108.26(14)	C11–C9–C8	110.37(16)
C11–C9–C10	115.09(15)	C8–C9–C10	113.01(15)
C5–C10–C1	108.87(17)	C5–C10–C19	107.77(15)
C1–C10–C19	110.80(18)	C5–C10–C9	108.26(15)
C1–C10–C9	110.02(15)	C19–C10–C9	111.03(16)
C9–C11–C12	112.50(15)	C13–C12–C11	111.51(16)
C14–C13–C12	108.64(15)	C14–C13–C18	112.53(15)
C12–C13–C18	109.95(17)	C14–C13–C17	100.42(14)
C12–C13–C17	117.38(15)	C18–C13–C17	107.69(15)
C15–C14–C8	120.35(15)	C15–C14–C13	104.16(15)
C8–C14–C13	112.81(15)	C14–C15–C16	103.94(16)
C17–C16–C15	107.11(16)	O3–C17–C20	109.40(14)
O3–C17–C16	109.94(15)	C20–C17–C16	114.39(16)
O3–C17–C13	105.04(14)	C20–C17–C13	113.40(15)
C16–C17–C13	104.18(14)	O2–C20–C21	120.67(19)
O2–C20–C17	120.01(18)	C21–C20–C17	119.06(17)
O4–C22–O3	123.91(19)	O4–C22–C23	125.4(2)
O3–C22–C23	110.65(19)	–	–

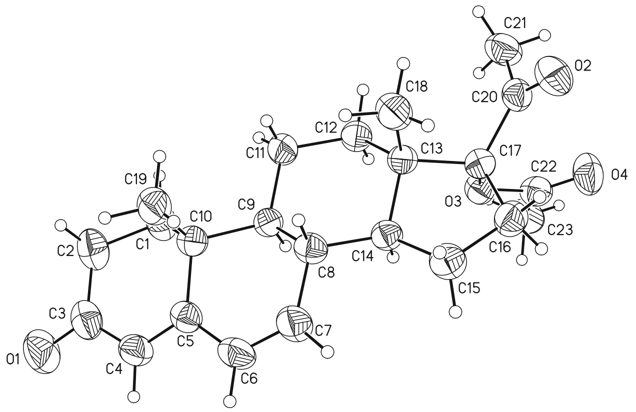


Fig. 1 Molecular structure of **1**, with displacement ellipsoids at the 50% probability level. Hydrogen atoms are drawn as circles with an arbitrary radius

Results and Discussion

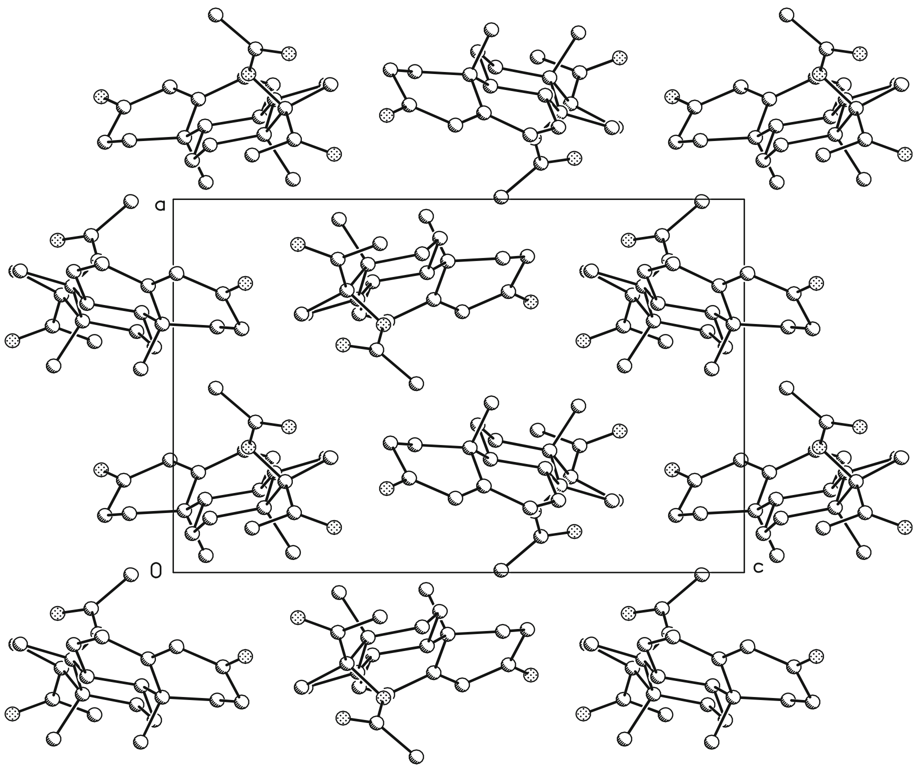
Table 2 gives the bond distances and bond angles of non-hydrogen atoms, respectively. ORTEP views of the title compounds with atomic labeling are shown in Figs. 1 and 2 [9]. The geometry of the molecule was calculated using the WinGX [10] and PARST [11, 12] softwares.

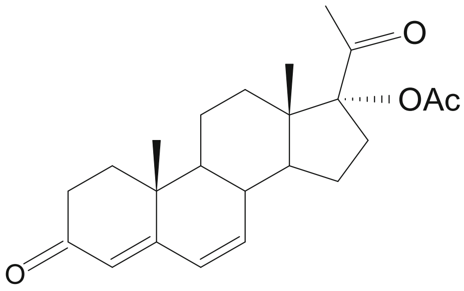
The bond distances and bond angles are in good agreement with the corresponding values obtained in case of 17α-acetoxy-6,7-epoxypregn-4-ene,3,20-dione [13]. Mean bond lengths [$C(sp^3)–C(sp^3)$, $C(sp^3)=O$ and $C(sp^2)=O$, for compound **1** are 1.518(3), 1.406(2), 1.207(2) Å, respectively. These bond lengths values are comparable to the theoretical values as reported by Allen et al. [14] although some bonds show significant deviation from the mean value.

In all essential details, the molecular geometry of (**1**) in terms of the bond lengths and angles are in good agreement with standard values. However, the C11–C9–C10 and C12–C13–C17 bond angles of 115.1(2) and 117.4(2)° have been increased to minimize the steric interactions between the double bond at C6–C7 and the methyl group at C10; and the interaction between the methyl group at C13 and the O atoms of the acetoxy group at C17, respectively. The molecule is comprised of a quadricyclic skeleton consisting of three-six-membered rings (A, B and C) and one-five-membered ring (D). The molecule consists of three-six-membered rings and one-five-membered ring, all *trans* fused. For the puckering-parameters values (ϕ_2, θ_2 and Q) [15]. The six-membered rings A, B, and C occur in an envelope (^{1}E), half chair ($^{5}H_{6}$), and chair ($^{1}C_{4}$) conformations, respectively. Ring D occurs in a half chair conformation.

Although the absolute configuration of **1** could not be determined from the diffraction data alone, it was established based on the structure of 17α-acetoxy-6,7-epoxypregn-4-ene, 3,20-dione compound [13]. The stereochemistry of the title compound is as follows: C8–βH is *trans* to C9–αH; C9–αH is *trans* to C10–βCH_3; C13–βCH_3 is *trans* to

Fig. 2 The packing diagram for **1** projected along the *b*-axis





1

Scheme 1 Structure of compound **1**

C14–αH; C13–βCH_3 is *cis* to C17–α($COCH_3$); and C13–βH is *trans* to C17–α($OCOCH_3$) group (Scheme 1).

Figure 2 shows the unit-cell packing arrangement for **1** along the *b*-axis. There are four intramolecular C–H···O interactions, which are due to their length, and could be considered as significant ones [16] [C2···O4, C7···O1, C19···O2, C23···O1 3.464(3), 3.368(3), 3.348(3), 3.443(3)Å; H2B···O4, H7···O1, H19C···O2, H23C···O1 2.693(2), 2.817(2), 2.801(2), 2.522(2)Å and C2–H2B···O4, C7–H7···O1, C19–H19C···O2, C23–H23C···O1 136.8(1), 119.1(1), 117.1(1), 161.0(1)°]. The molecules in the crystal are packed at normal van der Waals distances.

Supplementary Materials

CCDC-699041 contains the supplementary crystallographic data for this article. These data can be obtained free of charge via www.ccdc.cam.ac.uk/cgi-bin/catreq.cgi, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, fax; +44(0)1223-336033.

References

1. Cabeza M, Zambrano A, Heuze I, Carrizales E, Palacios A, Segura T, Valencia N, Bratoeff E (2009) Steroids 74:793
2. Bratoeff E, Segura T, Recillas S, Carrizales E, Palacios A, Heuze I, Cabeza M (2009) J Enzym Inhib Med Chem 2009(24):655
3. Bratoeff E, Cabeza M, Perez V, Recillas S, Heuze IJ (2008) Steroid Biochem Mol Biol 111:275
4. Cabeza M, Bratoeff E, Gómez G, Heuze I, Rojas A, Ochoa M, Palomino M, Revilla CJ (2008) Steroid Biochem Mol Biol 111:232
5. Cabeza M, Bratoeff E, Ramirez E, Heuze I, Recillas S, Berrios H, Cruz A, Cabrera O, Perez V (2008) Steroids 73:838
6. Cabeza M, Bratoeff E, Heuze I, Guzman A, Gómez G, Berrios H, Rosales A (2007) J Steroid Biochem Mol Biol 104:321
7. Siemens (1997) SHELXTL Version 5.10 Bruker AXS Inc. Madison, Wisconsin, USA
8. Sheldrick GM (1997) Program package for crystal structure solution and refinement. University of Gottingen, Germany
9. Farrugia LJ (1997) J Appl Cryst 30:565
10. Farrugia LJ (1997) J Appl Cryst 32:837
11. Nardelli M (1983) Compt Chem 7:95
12. Nardelli M (1995) J Appl Cryst 28:659
13. Soriano-García M, Zambrano A, Cabeza M, Bratoeff E (2009) Anal Sci 25:61
14. Allen FH, Kennard O, Watson DG, Brammer L, Orpen AG, Taylor R (1987) J Chem Soc [Perkin] 2:S1–S9
15. Cremer D, Pople JA (1975) J Am Chem Soc 97:1354
16. Desiraju GR, Kashino S, Cooms MM, Glusker JP (1993) Acta Cryst B49:880