Crystal Structure and Synthesis of 3 β -Acetoxy-4,16-pregnadiene-6,20-dione

Manuel SORIANO-GARCÍA,^{*†} Norma VALENCIA,^{**} Eugenio FLORES,^{**} Eugene BRATOEFF,^{**}
Elena RAMÍREZ,^{**} and Marisa CABEZA^{***}

^{*}*Departamento de Bioquímica, Instituto de Química, UNAM, Circuito Exterior, Ciudad Universitaria, Coyoacán, México D. F. 04510, México*

^{**}*Departamento de Farmacia, Facultad de Química, UNAM, Ciudad Universitaria, Coyoacán, México D. F. 04510, México*

^{***}*Departamento de Sistemas Biológicos y Producción Animal, Universidad Autónoma Metropolitana Unidad Xochimilco, México D. F. México.*

C₂₃H₃₀O₄ is orthorhombic, $P2_12_12_1$. The unit-cell dimensions at 293 K are $a = 6.0490(3)$, $b = 12.7788(7)$, $c = 26.8859(15)$ Å, $V = 2078.25(19)$ Å³, $D_x = 1.184$ g/cm³, and $Z = 4$. The R value is $R = 0.050$ for 3663 reflections. The A, B, C and D rings occur in distorted half chair, distorted chair, distorted chair, and distorted envelope conformations. The molecules in the crystal are packed at the normal van der Waals distances.

(Received July 22, 2003; Accepted October 24, 2003; Published on Web January 15, 2004)

Benign prostatic hyperplasia and prostate cancer are androgen-dependent diseases that afflict a large percentage of males over the age of fifty, and are usually treated by surgery.¹ Dihydrotestosterone, a 5- α -reductase metabolite of testosterone, has been implicated as a causative factor in the progression of these diseases.² It has also been determined that dihydrotestosterone interacts more efficiently with the androgen receptors than testosterone. This fact indicates that the logical step in treating these diseases should be an inhibition of the 5- α -reductase enzyme,³ or blockage of dihydrotestosterone-receptor complex formation.^{4,5}

In this paper, we describe the synthesis and X-ray structure determination of a new antiandrogen, 3 β -acetoxy-4,16-pregnadiene-6,20-dione **4**. This compound was prepared from the commercially available 3 β -acetoxypregna-5,16-diene-20-one **1** described in Scheme 1.

X-ray data for crystals of the title compound were collected by graphite-monochromatized Mo K α radiation at 293 K. No

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. O4 shows two atomic positions with occupancy factors for O4A and O4B of 0.50, respectively. The positions of all H atoms were calculated geometrically and a riding model was used in their refinement, with C-H distances in the range of 0.85–0.98 Å and $U_{iso}(H) = 1.2U_{eq}(C)$. The software used to prepare the material for publication was PARST97.⁶ Table 1 summarizes the crystal and experimental data. The molecular structure is shown in Fig. 1. The bond angles, the final atomic parameters for the hydrogen atoms, anisotropic thermal parameters for non-hydrogen atoms, and the observed and calculated structure factors may be obtained from the first author.

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),⁷ the six-membered rings A, B and C occur in distorted half chair (¹H₂), distorted chair (¹C₄)

Scheme 1

Fig. 1 Molecular structure of 3 β -Acetoxy-4,16-pregnadiene-6,20-dione with atom labeling. Thermal ellipsoids are drawn at the 50% probability level.

[†] To whom correspondence should be addressed.

Table 1 Crystal and experimental data

Formula: C ₂₃ H ₃₀ O ₄
Formula weight = 370.47
Crystal system: orthorhombic
Space group: P2 ₁ 2 ₁ 2 ₁ Z = 4
a = 6.0490(3) Å
b = 12.7788(7) Å
c = 26.8859(15) Å
V = 2078.25(19) Å ³
D _x = 1.184 g/cm ³
D _m = 1.180 g/cm ³ (measured by flotation)
μ(Mo Kα) = 0.080 mm ⁻¹
T = 293 K
Colorless
F(0 0 0) = 800
0.38 × 0.14 × 0.12 mm
Radiation: Mo Kα
2θ/θ scans with 2θ _{max} = 50°
R = 0.050 (on F ²)
wR = 0.097 (on F ²)
(Δ/σ) _{max} = 0.029
(Δρ) _{max} = 0.217 e Å ⁻³
(Δρ) _{min} = -0.127 e Å ⁻³
No. of reflections measured = 17124
No. of reflections used = 3663
No. of parameters = 247
Goodness-of-fit = 0.912
Measurement: Bruker Smart Apex CCD diffractometer
Program system: SMART V 5.625 and SAINT V 6.23C
Structure determination: direct methods (SHELXS-97)
Refinement: full matrix least-squares (SHELXL-97)

Table 2 Final atomic coordinates and equivalent isotropic temperature factors (Å²)

Atom	x	y	z	U _{eq} ^a
O1	0.8043(4)	0.3128(2)	0.78036(8)	0.0876(8)
O2	0.3375(4)	0.30042(17)	0.92935(8)	0.0788(7)
O3	1.2145(4)	0.6728(2)	1.14054(8)	0.0883(8)
O4A	1.0846(11)	0.1938(5)	0.7716(2)	0.0938(18)
O4B	0.9442(9)	0.1621(4)	0.78233(18)	0.0960(16)
C1	0.9909(5)	0.4929(3)	0.88011(10)	0.0644(9)
C2	0.9448(6)	0.4560(3)	0.82746(11)	0.0752(10)
C3	0.8865(6)	0.3414(3)	0.82886(11)	0.0743(11)
C4	0.7162(6)	0.3184(2)	0.86673(11)	0.0651(9)
C5	0.6721(5)	0.3817(2)	0.90499(11)	0.0515(8)
C6	0.5041(6)	0.3474(2)	0.94208(11)	0.0499(8)
C7	0.5506(5)	0.3685(2)	0.99562(10)	0.0530(8)
C8	0.6762(4)	0.4697(2)	1.00673(9)	0.0418(7)
C9	0.8674(5)	0.4858(2)	0.96995(9)	0.0450(7)
C10	0.7908(5)	0.4847(2)	0.91487(9)	0.0463(7)
C11	1.0071(5)	0.5812(2)	0.98338(10)	0.0559(8)
C12	1.0870(5)	0.5835(2)	1.03770(9)	0.0559(8)
C13	0.8954(5)	0.5695(2)	1.07320(9)	0.0445(7)
C14	0.7746(5)	0.4682(2)	1.05883(9)	0.0450(7)
C15	0.6402(5)	0.4400(2)	1.10501(10)	0.0593(9)
C16	0.7944(6)	0.4761(2)	1.14466(11)	0.0661(9)
C17	0.9442(5)	0.5453(2)	1.12762(10)	0.0538(8)
C18	0.7460(5)	0.6669(2)	1.07198(10)	0.0568(8)
C19	0.6281(5)	0.5733(2)	0.90401(10)	0.0606(8)
C20	1.1112(6)	0.5988(3)	1.15720(11)	0.0650(9)
C21	1.1599(7)	0.5617(3)	1.20936(12)	0.1080(14)
C22	0.8809(10)	0.2306(3)	0.75835(13)	0.1114(19)
C23	0.7897(10)	0.2147(3)	0.70856(12)	0.140(2)

$$U_{eq} = (1/3)\sum_i\sum_j U_{ij}(a_i^*a_j^*)(a_i\cdot a_j).$$

Table 3 Bond distances (Å)

C1 - C2	1.517(4)	C1 - C10	1.533(4)
C2 - C3	1.507(4)	C3 - O1	1.443(3)
C3 - C4	1.478(4)	C4 - C5	1.336(4)
C5 - C6	1.490(4)	C5 - C10	1.522(4)
C6 - O2	1.222(3)	C6 - C7	1.491(4)
C7 - C8	1.529(4)	C8 - C14	1.522(3)
C8 - C9	1.536(3)	C9 - C11	1.527(4)
C9 - C10	1.552(3)	C10 - C19	1.529(4)
C11 - C12	1.539(3)	C12 - C13	1.512(3)
C13 - C17	1.525(4)	C13 - C14	1.535(4)
C13 - C18	1.539(4)	C14 - C15	1.527(3)
C15 - C16	1.490(4)	C16 - C17	1.347(4)
C17 - C20	1.456(4)	C20 - O3	1.219(4)
C20 - C21	1.509(4)	C22 - O4B	1.153(5)
C22 - O1	1.291(4)	C22 - O4A	1.367(7)
C22 - C23	1.462(5)		

and distorted chair (¹C₄) conformations, respectively. Ring D occurs in a distorted envelope conformation. The bond lengths and angles are normal. The absolute configuration is inferred from the known stereochemistry of 3β-acetoxypregna-5,16-diene-20-one **1**. Compound **1** is commercially available. The stereochemistry of the title compound is as follows: C8-βH is *trans* to C9-αH; C9-αH is *trans* to C10-βCH₃; C13-βCH₃ is *trans* to C14-αH.

There are three intramolecular C-H...O interactions [C3...O4A, C3...O4B, C4...O2 2.714(7), 2.634(6), 2.852(4) Å; H3...O4A, H3...O4B, H4...O2, 2.244(6), 2.332(5), 2.583(2) Å; C3-H3...O4A, C3-H3...O4B, C4-H4...O2, 108.2(3), 96.8(2), 97.2(2)°]. In addition, there are three intermolecular C-H...O interactions <3.4 Å: C21...O4B (x + 1/2, -y + 1/2, -z + 2); C16...O4A, C16...O4B (x - 1, y, z), 3.345(7), 3.275(7) and 3.385(6) Å, respectively. Apart from the C...O intra- and intermolecular interactions, the molecules in the crystal are packed at normal van der Waals distances.

Acknowledgements

Contribution No. 2462 of the Instituto de Química, UNAM. E. Bratoeff thanks DGAPA, UNAM and CONACyT for the projects No. IN200301 and G33450-M for financial support.

References

1. E. Bratoeff, E. Ramirez, E. Murillo, and M. Cabeza, *Curr. Med. Chem.*, **1999**, 6, 501.
2. E. Flores, E. Bratoeff, M. Cabeza, E. Ramirez, A. Quiroz, and I. Heuze, *Mini-Rev. Med. Chem.*, **2003**, 3, 225.
3. M. Cabeza, E. Bratoeff, E. Flores, E. Ramirez, J. Calleros, D. Montes, A. Quiroz, and I. Heuze, *Chem. Pharm. Bull.*, **2002**, 50, 1447.
4. E. Bratoeff, H. Herrera, E. Ramirez, K. Solorzano, E. Murillo, A. Quiroz, and M. Cabeza, *Chem. Pharm. Bull.*, **2000**, 48, 1249.
5. M. Cabeza, I. Heuze, E. Bratoeff, E. Murillo, E. Ramirez, and A. Lira, *Chem. Pharm. Bull.*, **2001**, 49, 1081.
6. M. Nardelli, *J. Appl. Cryst.*, **1995**, 28, 659.
7. D. Cremer and J. A. Pople, *J. Am. Chem. Soc.*, **1975**, 97, 1354.