Crystal Structure and Synthesis of 17 α -(5-Bromovaleroyloxy)-16 β -methylpregna-4,6-diene-3,20-dione

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Benign prostatic hyperplasia and prostate cancer are androgen-dependent diseases, which 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 does. This fact indicates that the logical step in the treatment of these diseases should be the inhibition of the 5 α -reductase enzyme³ or the blockage of the dihydrotestosterone-receptor formation.³

In this paper, we describe the synthesis and x-ray structure determination of a new antiandrogen 17 α -(5-bromovaleroyloxy)-16 β -methylpregna-4,6-diene-3,20-dione **8**. All intermediate steroidal derivatives (**1**–**7**) involved in the synthesis of **8** have previously been published by our group;^{3–5} the preparation of the new antiandrogen **8** is described in Scheme 1.

The X-ray data for the crystals of the title compound were

collected by graphite-monochromatized Mo K α radiation at 293 K. No absorption correction was applied. The crystal is not sufficiently stable to X-ray beams and diffracts poorly. The structure was solved by direct methods and refined by full-matrix least-squares with anisotropic temperature factors for the non-hydrogen atoms. The hydrogen atoms bonded to the carbon atoms were assigned based on the expected bonding geometry, and those bonded to the nitrogen atoms were found in

Table 1 Crystal and experimental data

Formula:	C ₂₇ H ₃₇ O ₄ Br
Formula weight:	505.49
Crystal system:	monoclinic
Space group:	P2 ₁ 2 ₁ 2 ₁ Z = 4
a =	7.150(1) Å
b =	12.857(1) Å
c =	27.001(3) Å
V =	2482.2(5) Å ³
D _x =	1.353 g/cm ³
D _m =	1.360 g/cm ³ (measured by flotation)
μ (Mo K α) =	1.69 mm ⁻¹
T =	293 K
Colorless	
F(0 0 0) =	1064
0.45 × 0.40 × 0.20 mm	
Radiation:	Mo K α
2 θ / θ scans with 2 θ _{max} =	45°
R =	0.075 (on F ²)
Rw =	0.167 (on F ²)
($\Delta\rho$) _{max} =	0.268
($\Delta\rho$) _{max} =	0.250 e Å ⁻³
($\Delta\rho$) _{min} =	-0.293 e Å ⁻³
No. of reflections measured =	3284
No. of reflections used =	1895
No. of parameters =	284
Goodness-of-fit =	1.001
Measurement:	Siemens P4 diffractometer
Program system:	SHELXL-Plus
Structure determination:	direct methods (SHELXS-97)
Refinement:	full matrix least-squares (SHELXL-97)

Scheme 1

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Table 2 Final atomic coordinates and equivalent isotropic temperature factors ($\text{\AA}^2$)

Atom	x	y	z	U_{eq}
Br1	0.5829(5)	0.7835(2)	0.96633(9)	0.1346(14)
O1	1.184(2)	-0.0098(11)	1.0772(5)	0.097(5)
O2	1.234(2)	0.5182(10)	0.7245(4)	0.087(5)
O3	1.0975(18)	0.5413(9)	0.8507(4)	0.057(3)
O4	0.981(2)	0.6758(8)	0.8045(4)	0.074(4)
C1	1.383(2)	0.1441(13)	0.9805(5)	0.054(5)
C2	1.401(3)	0.0512(14)	1.0164(5)	0.056(5)
C3	1.214(4)	0.0233(14)	1.0354(7)	0.069(6)
C4	1.049(3)	0.0400(13)	1.0018(7)	0.065(6)
C5	1.067(3)	0.0870(12)	0.9567(7)	0.052(5)
C6	0.906(2)	0.0972(12)	0.9252(6)	0.046(5)
C7	0.909(3)	0.1545(11)	0.8835(6)	0.046(5)
C8	1.071(2)	0.2111(12)	0.8658(5)	0.037(4)
C9	1.215(2)	0.2251(11)	0.9075(5)	0.033(4)
C10	1.256(3)	0.1229(14)	0.9366(6)	0.050(5)
C11	1.397(3)	0.2791(12)	0.8890(6)	0.056(5)
C12	1.353(2)	0.3841(12)	0.8649(5)	0.040(5)
C13	1.206(3)	0.3760(14)	0.8238(6)	0.053(5)
C14	1.031(2)	0.3186(11)	0.8444(5)	0.037(5)
C15	0.886(3)	0.3317(14)	0.8040(6)	0.063(6)
C16	0.916(3)	0.4473(14)	0.7880(5)	0.063(5)
C17	1.114(2)	0.4788(12)	0.8048(6)	0.042(4)
C18	1.289(2)	0.3155(12)	0.7804(5)	0.053(5)
C19	1.334(2)	0.0375(11)	0.9020(5)	0.051(5)
C20	0.850(3)	0.4651(14)	0.7332(6)	0.079(7)
C21	1.246(3)	0.5355(15)	0.7681(7)	0.060(6)
C22	1.394(3)	0.6041(13)	0.7891(7)	0.077(6)
C23	1.027(3)	0.6369(15)	0.8436(7)	0.064(6)
C24	1.009(3)	0.6899(12)	0.8939(6)	0.070(6)
C25	0.944(3)	0.8061(13)	0.8907(7)	0.079(7)
C26	0.744(4)	0.8220(15)	0.8724(7)	0.092(8)
C27	0.596(3)	0.7614(15)	0.8972(6)	0.086(7)

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

a difference-Fourier map. The hydrogen atoms were refined isotropically in the final least-squares cycles. Software used to prepare material for publication was PARST97.⁶ Table 1 summarizes the crystal and experimental data.

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 a distorted envelope (^1E), a distorted half chair ($^5H_6$) and a chair ($^1C_4$) conformations, respectively. Ring D occurs in a conformation between an envelope and a half chair. The bond lengths and angles are normal. The stereochemistry of the title compound is as follows: C8- β H is *trans* to C9- α H; C9- α H is *trans* to C10- β CH₃; C13- β CH₃ is *trans* to C14- α H; C13- β CH₃ is *cis* to C17- α (COCH₃); and C16- β (CH₃) is *trans* to C17- α (OCO(CH₂)₃CH₂Br]. The molecular structure is shown in Fig. 1. The molecules in the crystal are packed at normal van der Waals distances. There are two intramolecular C-H...O interactions [C12...O3, C14...O3, 2.75(2), 2.91(2), H12B...O3, H14...O3, 2.32(1), 2.52(1) $\text{\AA}$ and C12-H12B...O3, C14-H14...O3, 106.1(9), 103.4(9)°]. In addition, there are three intermolecular C-H...O interactions <3.4 $\text{\AA}$, C12...O1 ($x + 1/2$, $-y + 1/2$, $-z + 2$); C24...O1, C27...O1 ($x - 1/2$, $-y + 1/2$, $-z + 2$), 3.27(2), 3.37(2) and 3.37(2) $\text{\AA}$, respectively.

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Table 3 Bond distances ($\text{\AA}$) and angles (°)

Br1 - C27	1.890(17)	O1 - C3	1.23(2)
O2 - C21	1.203(18)	O3 - C23	1.341(19)
O3 - C17	1.482(16)	O4 - C23	1.214(18)
C1 - C10	1.521(19)	C1 - C2	1.54(2)
C2 - C3	1.48(3)	C3 - C4	1.50(2)
C4 - C5	1.37(2)	C5 - C6	1.44(2)
C5 - C10	1.53(2)	C6 - C7	1.346(18)
C7 - C8	1.45(2)	C8 - C14	1.525(19)
C8 - C9	1.536(18)	C9 - C11	1.55(2)
C9 - C10	1.56(2)	C10 - C19	1.546(19)
C11 - C12	1.532(19)	C12 - C13	1.531(19)
C13 - C18	1.53(2)	C13 - C14	1.55(2)
C13 - C17	1.56(2)	C14 - C15	1.52(2)
C15 - C16	1.56(2)	C16 - C17	1.54(2)
C16 - C20	1.57(2)	C17 - C21	1.55(2)
C21 - C22	1.49(2)	C23 - C24	1.53(2)
C24 - C25	1.57(2)	C25 - C26	1.53(3)
C26 - C27	1.47(3)		

Fig. 1 Molecular structure of the title compound with atom labeling. Thermal ellipsoids are drawn at the 50% probability level.

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