Crystal Structure of 17- β -Benzoyloxy-16- β -methylpregna-4,6-diene-3,20-dione

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Prostate cancer is now the most common malignancy and the second leading cause of cancer deaths in North American men. Androgen antagonists offer a potentially useful treatment for androgen-mediated diseases, such as: prostatic cancer, hirsutism, acne, seborrhea, androgenic alopecia and benign prostatic hyperplasia.¹ Although surgery presently represents an alternative treatment for prostatic cancer, there are several modalities available.² Currently, the most common therapy for the treatment of androgen-dependent diseases is blockage of the androgen receptors by androgen antagonists³, or inhibition of the conversion of testosterone to the more active androgen dihydrotestosterone by the enzyme 5 α -reductase.⁴

In this paper we describe the synthesis and the X-ray structure determination of a new antiandrogen, 17- β -Benzoyloxy-16- β -methylpregna-4,6-diene-3,20-dione, **8**. All of the steps involved in this synthesis are well-known reactions⁵, and the preparation of **8** is summarized in Scheme 1. In this synthesis, the most intriguing

step is the transformation of **7** to the benzoate ester **8**, which occurs with an inversion of the configuration of the ester moiety. Probably, the bulky ester chain at C17 effects the conformation of the ring D, and acquires a β configuration. The X-ray data were collected by a graphite-monochromatized Mo K α radiation. No absorption correction was applied. Table 1 summarizes the crystal and experimental data. The molecular structure of the title compound is shown in Fig. 1. 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), the six-membered rings (A and B) both occur in a distorted envelope conformation, while ring C and D (ϕ_2 and Q) occur in a distorted chair and a half chair conforma-

Table 1 Crystal and experimental data

Formula: C ₂₉ H ₃₄ O ₄
Formula weight = 446.6
Crystal system: monoclinic
Space group: P2 ₁ Z = 2
a = 9.178(1) Å
b = 12.483(2) Å
c = 11.183(2) Å
β = 106.72(1)°
V = 1227.1(3) Å ³
D _x = 1.209 g/cm ³
D _m = 1.213 g/cm ³ (measured by flotation in bromoform/benzene)
μ (MoK α) = 0.079 mm ⁻¹
T = 293 K
colorless
F(000) = 480
0.40 x 0.24 x 0.24 mm
Radiation = MoK α
$\omega/2\theta$ scans with $2\theta_{max}$ = 45°
R = 0.058 (on I)
R _w = 0.131 (on I)
No. of reflections measured = 2279
No. of reflections used = 1857
No. of parameters = 407
Goodness-of-fit = 1.19
Minimum residual density = -0.15 e/Å ³
Maximum residual density = 0.40 e/Å ³
Measurement: Siemens P4 diffractometer
Program system: SHELXL-Plus
Structure determination: direct methods (SHELXS-86)
Refinement: full matrix (SHELXL-93)

Scheme 1

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

Fig. 2 Perspective drawing of the packing arrangement of the title compound in the crystal.

tions, respectively.⁵ 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 C17- α (COCH₃); and C16- α H is *cis* to C17- α (COCH₃). The bond lengths and angles are normal. The molecular packing is shown in Fig. 2. The molecules in the crystal are packed at normal van der Waals distances. There are three intramolecular C-H...O interactions [C21...O3, C21...O2, C29...O3, 2.99(1), 2.84(1), 2.81(1), H21A...O3, H21C...O2, H29...O3, 2.45(14), 2.48(9), 2.49(5) Å and C21-H21A...O3, C21-H21C...O2, C29-H29...O3, 114(9), 107(6), 106(5)°] which stabilize the molecule internally. In addition, there are five intermolecular C-H...O interactions <3.4 Å, which help to stabilize the molecules in the crystal: C25...O4, C11...O3 ($-x, +y-1/2, -z$); C28...O1, C27...O1 ($x+2, +y, +z+1$) and C1...O4 ($-x-1, +y-1/2, -z$), 3.34(1),

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

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{eq}
O1	-1.1089(7)	0.2654	-0.5123(7)	0.127(3)
O2	0.0831(5)	0.4030(4)	0.0142(5)	0.055(1)
O3	0.1801(6)	0.5417(5)	0.1409(6)	0.073(2)
O4	-0.1928(7)	0.5768(5)	0.0669(5)	0.072(2)
C1	-0.7341(9)	0.2219(9)	-0.2929(8)	0.062(2)
C2	-0.8816(11)	0.1836(9)	-0.3840(11)	0.076(3)
C3	-0.9732(11)	0.2728(10)	-0.4583(8)	0.083(3)
C4	-0.8945(10)	0.3739(8)	-0.4638(7)	0.071(3)
C5	-0.7401(10)	0.3846(7)	-0.4165(7)	0.060(2)
C6	-0.6709(11)	0.4856(7)	-0.4308(7)	0.071(3)
C7	-0.5207(13)	0.5012(8)	-0.3819(8)	0.074(3)
C8	-0.4133(9)	0.4221(7)	-0.3048(7)	0.049(2)
C9	-0.5033(9)	0.3425(6)	-0.2491(7)	0.044(2)
C10	-0.6405(8)	0.2940(6)	-0.3512(6)	0.050(2)
C11	-0.4006(9)	0.2603(6)	-0.1630(8)	0.046(2)
C12	-0.2702(9)	0.3120(7)	-0.0654(7)	0.049(2)
C13	-0.1769(8)	0.3862(6)	-0.1228(6)	0.043(2)
C14	-0.2848(9)	0.4717(6)	-0.2020(7)	0.048(2)
C15	-0.1807(10)	0.5515(8)	-0.2362(8)	0.062(2)
C16	-0.0399(9)	0.5599(7)	-0.1190(7)	0.058(2)
C17	-0.0556(8)	0.4636(6)	-0.0344(6)	0.047(2)
C18	-0.0983(10)	0.3179(8)	-0.1978(10)	0.059(2)
C19	-0.5847(12)	0.2319(10)	-0.4490(9)	0.067(3)
C20	-0.1143(10)	0.4970(7)	0.0756(7)	0.057(2)
C21	-0.0842(14)	0.4284(10)	0.1905(9)	0.071(3)
C22	0.1076(9)	0.5658(8)	-0.1543(8)	0.076(3)
C23	0.1958(9)	0.4528(7)	0.1042(8)	0.060(2)
C24	0.3324(9)	0.3869(6)	0.1493(7)	0.052(2)
C25	0.3523(8)	0.2916(7)	0.0961(8)	0.062(2)
C26	0.4835(10)	0.2311(8)	0.1437(9)	0.066(2)
C27	0.5934(10)	0.2687(9)	0.2479(9)	0.072(3)
C28	0.5758(11)	0.3622(9)	0.3023(9)	0.076(3)
C29	0.4456(11)	0.4238(9)	0.2509(9)	0.068(3)

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

3.36(1), 3.27(1), 3.23(1) and 3.33(1) Å, respectively. All of the H-atoms were located *via* an inspection of the difference-Fourier maps, and were refined using isotropic temperature factors, except for the H-atom positions at C4, C6, C22, C25 and C27, which were calculated based on the geometry of the C-atom skeleton, and refined with isotropic terms, $U = 0.06$ Å².

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