Acta Cryst. (1998). C**54**, 2022–2024

17α-Acetoxy-6-bromo-16β-methylpregna-4,6-diene-3,20-dione

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(*Received 26 September 1997; accepted 3 February 1998*)

Abstract

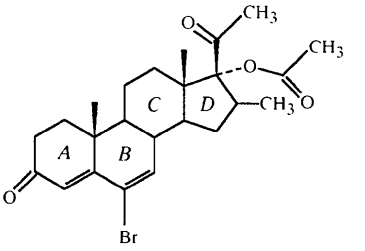
In the title compound, $C_{24}H_{31}BrO_4$, rings *A* and *C* adopt envelope and chair conformations, respectively, and rings *B* and *D* both adopt a conformation intermediate between half-chair and envelope. The *A*/*B*, *B*/*C* and *C*/*D* ring junctions are all *trans*. The molecules in the crystal are held together by van der Waals, C—H···Br and C—H···O interactions.

Comment

Androgen antagonists offer a potentially useful treatment for androgen-mediated diseases such as hirsutism, acne, seborrhea, androgenic alopecia, precocious puberty, benign prostatic hyperplasia and prostate cancer (Mallano *et al.*, 1992). The most important therapeutic application of antiandrogens is in the treatment of prostate cancer and benign prostatic hyperplasia, which are major medical problems in the aging male. Although surgery presently represents the most accepted treatment for prostate cancer (about 400 000 prostectomies performed each year in the USA), there are several other modalities available for the treatment of this disease, such as inhibition of androgen production by LHRH agonists, inhibition of the conversion of testosterone to dihydrotestosterone by 5α-reductase inhibitors (Brooks *et al.*, 1991; Labrie *et al.*, 1991; Rittmaster *et al.*, 1992), inhibition of androgen action by androgen receptor antagonists (Murphy, 1977; Wakeling, 1987; Santen, 1989) and several other less common therapies. The antiandrogens flutamide (Morris *et al.*, 1991), cyproterone acetate (Traish *et al.*, 1985) and proscar (finasteride) (Thigpen & Russel, 1992), and the androgen biosynthesis inhibitor ketoconazol (Eil, 1992), are effective drugs for the treatment of prostate cancer and benign prostatic hyperplasia. However, the various side effects of these compounds reduce their therapeutic use.

Testosterone is converted by the enzyme 5α-reductase into the more active androgen 5α-dihydrotestosterone, which interacts more efficiently with the androgen receptor. This fact indicates very clearly that the logical site of therapeutic intervention should be this last step (Anderson & Liao, 1986).

In this paper, we report the crystal structure of a new steroidal derivative, 17α-acetoxy-6-bromo-16β-methylpregna-4,6-diene-3,20-dione, (I). This compound showed high antiandrogenic activity *in vitro*, as well as *in vivo*, and its synthesis has been described recently (Bratoeff *et al.*, 1998).



(I)

The molecule consists of three six-membered rings and one five-membered ring, all *trans* fused. According to the torsion angles (Table 1) and the puckering-parameter values (φ_2, θ_2 and Q), the six-membered *A* and *C* rings occur in envelope and chair conformations, respectively, while rings *B* and *D* (φ_2 and Q) both occur in a conformation intermediate between half-chair and envelope (Cremer & Pople, 1975). It is interesting to note that the 4,6-dien-3-one formation causes flattening of the *A* and *B* rings relative to the rest of the steroid backbone. The distance of O1 (at C3) from the C5–C17 mean plane is only 1.1 Å, slightly different from the values of 2.2 and 2.1 Å for the *A* and *B* molecules in 6-methyl-3,20-dioxopregna-4,6-dien-17α-yl acetate (Wawrzak *et al.*, 1992).

The stereochemistry of the title compound is as follows: C9-αH is *trans* to C10-βCH$_3$, C13-βCH$_3$ is

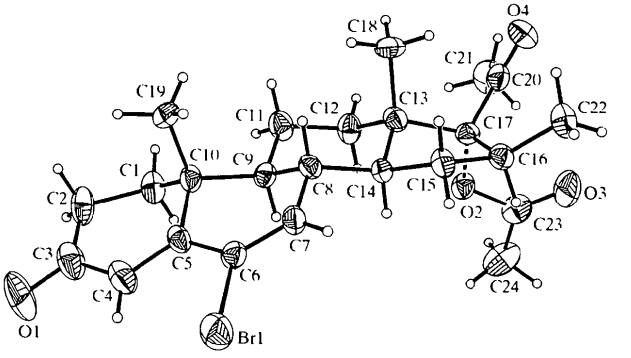


Fig. 1. The molecular structure of the title compound shown with 50% probability displacement ellipsoids.

cis to C17-β($COCH_3$), and C16-αH is *trans* to C17-β($COCH_3$). Bond lengths and angles are normal.

The molecules in the crystal are packed at normal van der Waals distances. There are two intramolecular C—H···O and C—H···Br interactions [C12···O2 2.755 (9), H12*A*···O2 2.36 Å and C12—H12*A*···O2 103.9 (8)°; C4···Br1 3.133 (7), H4···Br1 2.65 Å and C4—H4···Br1 113.1 (6)°]. In addition, there are two intermolecular C—H···O and C—H···Br interactions which help stabilize the molecules in the crystal; C19···O1^{i} and C24···Br1^{ii} of 3.343 (10) and 3.969 (8) Å, respectively [symmetry codes: (i) $-x, y-\frac{1}{2}, -z+2$; (ii) $x, y, z+1$].

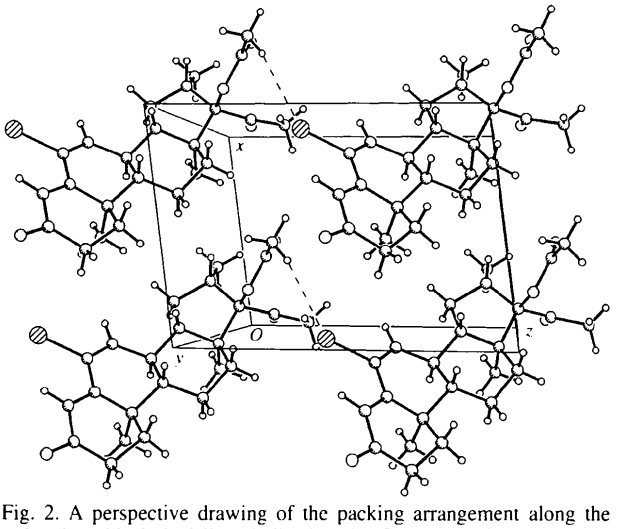


Fig. 2. A perspective drawing of the packing arrangement along the *b* axis, with dashed lines indicating the C—H···Br intermolecular interaction.

Experimental

The title compound has been synthesized as part of a study of new pregnane derivatives with antiandrogenic activity. It was crystallized from ethyl acetate solution by slow evaporation of the solvent at room temperature.

Crystal data

$C_{24}H_{31}BrO_4$
M_r = 463.41
Monoclinic
$P2_1$
a = 7.185 (1) Å
b = 15.460 (1) Å
c = 10.254 (1) Å
β = 97.410 (7)°
V = 1129.5 (2) Å^3
Z = 2
D_x = 1.363 Mg m^{-3}
D_m = 1.350 Mg m^{-3}
D_m measured by flotation in benzene/bromoform
Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 25 reflections
θ = 15–45°
μ = 1.846 mm^{-1}
T = 293 (2) K
Prism
0.32 × 0.22 × 0.22 mm
Colourless

Data collection

Siemens *P*4 diffractometer
$\theta/2\theta$ scans
Absorption correction: analytical (Siemens, 1994), based on faced-indexed numerical
T_{min} = 0.590, T_{max} = 0.687
4349 measured reflections
4349 independent reflections
3579 reflections with $F > 2\sigma(F)$
θ_{max} = 30°
h = 0 → 10
k = 0 → 21
l = −14 → 14
3 standard reflections
every 97 reflections
intensity decay: 2.0%

Refinement

Refinement on F
R = 0.048
wR = 0.095
S = 1.001
3579 reflections
261 parameters
H atoms not refined
$w = 1/[\sigma^2(F) + 0.0008(F^2)]$
$(\Delta/\sigma)_{max}$ = −0.001
$\Delta\rho_{max}$ = 0.49 e Å^{-3}
$\Delta\rho_{min}$ = −0.36 e Å^{-3}
Extinction correction: Larson (1970)
Extinction coefficient: 0.014 (13)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected torsion angles (°)*

C10—C1—C2—C3	−48.9 (6)	C10—C9—C11—C12	−176.3 (4)
C1—C2—C3—C4	20.9 (7)	C9—C11—C12—C13	168.3 (4)
C2—C3—C4—C5	5 (7)	C11—C12—C13—C14	56.4 (5)
C3—C4—C5—C6	176.0 (4)	C12—C13—C14—C8	−59.4 (5)
C4—C5—C6—C7	175.2 (4)	C17—C13—C14—C15	47.6 (4)
C4—C5—C10—C1	−25.3 (6)	C12—C13—C17—C16	−150.0 (4)
C6—C5—C10—C9	37.2 (5)	C14—C13—C17—C16	−32.7 (4)
C5—C6—C7—C8	−3.2 (7)	C8—C14—C15—C16	−169.6 (4)
C6—C7—C8—C9	−19.1 (6)	C13—C14—C15—C16	−44.6 (4)
C7—C8—C9—C10	51.1 (4)	C14—C15—C16—C17	23.0 (4)
C14—C8—C9—C11	−56.4 (4)	C15—C16—C17—C13	6.2 (4)
C8—C9—C11—C12	56.2 (5)		

H atoms were placed in ideal positions and allowed to ride on the attached atom with a fixed isotropic displacement parameter U of 0.06 Å^2. The absolute configuration was inferred according to the known stereochemistry at C9, C10 and C13 of (9*S*,10*R*,13*S*)-cyproterone acetate (Chandross & Bordner, 1974).

Data collection: *XSCANS* (Siemens, 1994). Cell refinement: *XSCANS*. Data reduction: *XSCANS*. Program(s) used to solve structure: *SHELXTL/PC* (Sheldrick, 1990). Program(s) used to refine structure: *SHELXTL/PC*. Molecular graphics: *XP* in *SHELXTL/PC*. Software used to prepare material for publication: *PARST* (Nardelli, 1983, 1995) and *PARSTCIF* (Nardelli, 1991).

MS-G and EB thank the DGAPA, UNAM, Mexico (project Nos. IN201395 and IN205295), for financial support. This is contribution No. 1674 of the Departamento de Bioestructura, Instituto de Química, UNAM, Mexico.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: DA1005). Services for accessing these data are described at the back of the journal.

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