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Note

17α-acetoxy-17β-methyl-16β-phenyl-D-homo-4,6-pregnadiene-3,17a-dione: synthesis and crystal structure determination of a new rearranged pregnane derivative

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The title compound is $C_{29}H_{34}O_4$, tetragonal, $P4_3$, $a = b = 10.310(1)$, $c = 23.871(2)$Å. The A, B, C, and D rings adopt envelope, half-chair, chair, and distorted chair conformations, respectively. The phenyl ring is planar. The methyl substituents at the A/B, C/D, and at C(17) are *axial*; and the $-OCOCH_3$ group at C(17) and phenyl ring at C(16) are *equatorial*. The molecules in the crystal are held together by van der Waals forces and several C−H···O hydrogen bond interactions.

KEY WORDS: Steroid; pregnadiene; x-ray diffraction; crystal structure.

Introduction

Prostate cancer is now the most common malignancy and the second leading cause of cancer deaths in North American men.[1] Androgen antagonists offer a potentially useful treatment for androgen mediated diseases such as: prostatic cancer, hirsutism, acne, seborrhea, androgenic alopecia and benign prostatic hyperplasia.[2] Although surgery presently represents an alternative treatment for prostatic cancer, there are several other modalities available for the treatment of this disease.[3] Currently the most common therapy for the treatment of androgen dependent diseases is the blockage of androgen receptors by androgen antagonists[4,5] or inhibition of the conversion of testosterone to dihydrotestosterone by the enzyme 5α-reductase.[6,7] This fact indicates very clearly that in this case the logical site of therapeutic intervention should be the inhibition of this enzyme. In this paper we describe the synthesis and structure determination by X-rays of 17α-acetoxy-17β-methyl-16β-phenyl-D-homo-4,6-pregnadiene-3,17a-dione. The synthesis of this compound is shown in Scheme 1. All of the synthetic steps involved in the synthesis of **9** are well-known reactions. Probably the most intriguing step in this synthesis is the hydrolysis of the ketal **5**; this reaction did not afford the expected intermediate **6**, but yielded the D-homo steroid 7. This D-ring expansion could be explained by protonation of the C-20 carbonyl group (perchloric acid) to form the carbonium ion **7a**. A subsequent Wagner Meerwein shift of the 16,17 bond afforded compound **7** with the D-homo ring (Fig. 1).

Experimental

Suitable crystals were formed directly from the synthesis of the compound and recrystallized from ethyl acetate solution by slow evaporation of the solvent at room temperature.

The structure of the title compound was solved by the program SHELXS-86[8] and refined on F^2 with SHEXTL[9] with scattering factors from International

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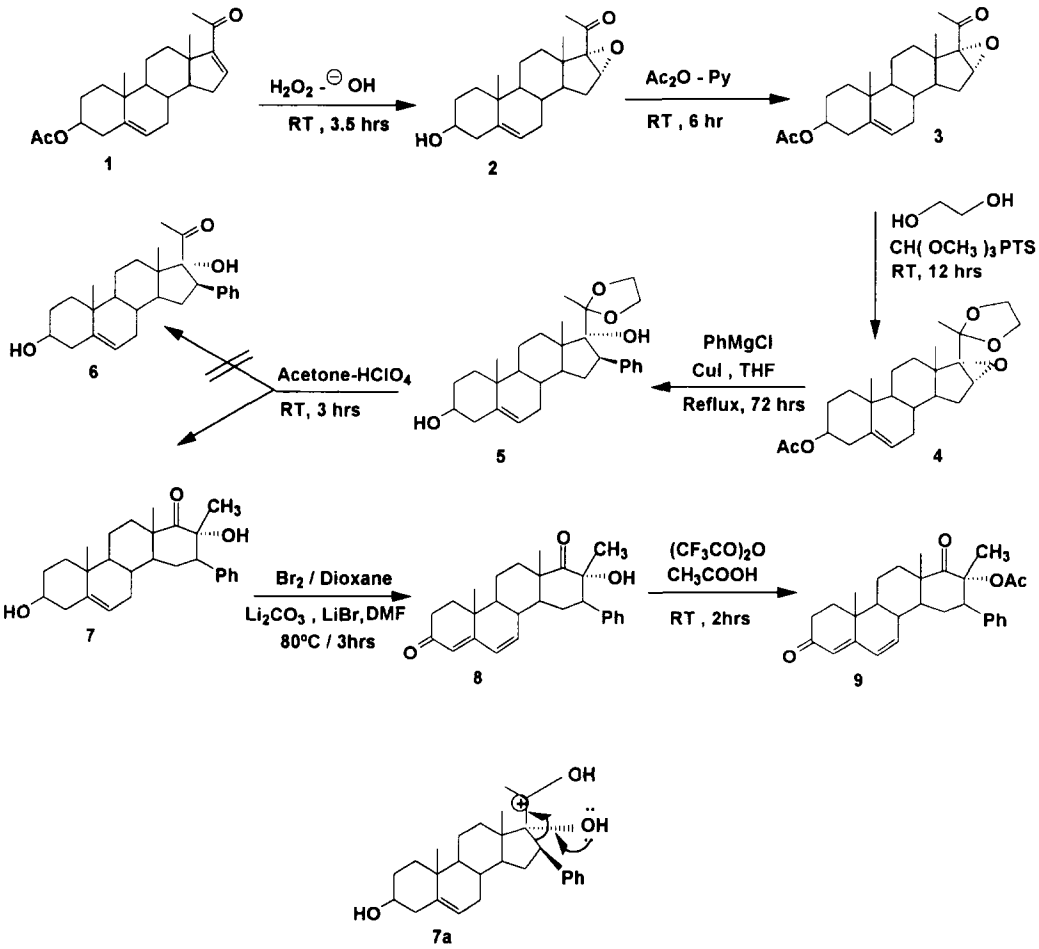

Scheme 1.

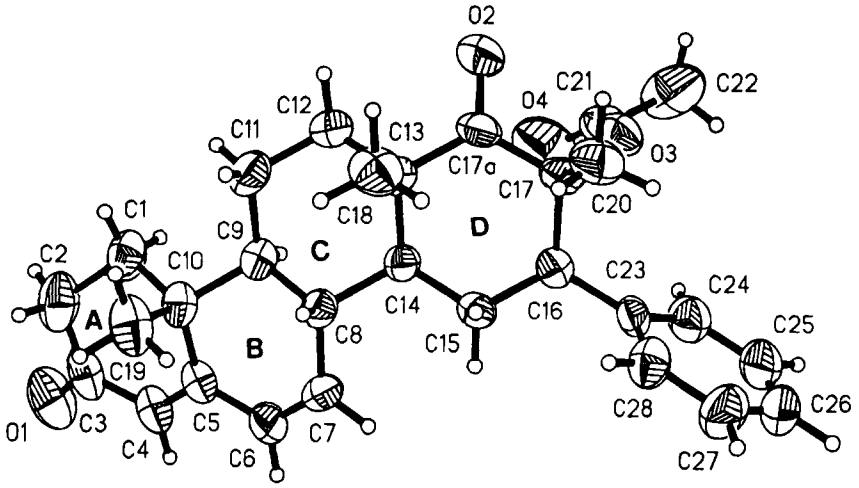

Fig. 1. A thermal ellipsoid plot of the molecular structure of 17α-Acetoxy-17β-methyl-16β-phenyl-D-homo-4,6-pregnadiene-3,17a-dione.

Tables.[10] Other programs include PARST97[11,12] and PARSTCIF.[13] Hydrogen atoms were located geometrically to the related carbon atoms with isotropic and fixed temperature parameters and not refined. Final R and weighted R values and data collection parameters are in Table 1, the final geometrical parameters are in Table 2, and bond lengths and angles are in Table 3. The molecule with numbering is shown in Fig. 1.

Discussion

Figure 1 shows the structure of the molecule. The molecule consists of four rings, three methyl groups at C(10), C(13), and C(17), an $OCOCH_3$ group at C(17), and a phenyl ring at C(16). The A/B, B/C, and C/D junctions are *trans* fused. Rings A, B,C, and D adopt envelope ^1E, half/chair $^5H_6$, chair $^1C_4$, and distorted chair $^4C_1$ conformations, respectively. The phenyl ring is planar. The methyl substituents at C(10), C(13) and C(17) are *axial*; and the $-OCOCH_3$ and phenyl ring at C(16) are *equatorial*.

Table 1. Crystal data, summary data collection, and structure refinement for 17α-acetoxy-17β-methyl-16β-phenyl-D-homo-4,6-pregnadiene-3,17a-dione

Empirical formula	$C_{29}H_{34}O_4$
Formula weight	446.6
Temperature	293(2)K
Wavelength	Cu$K\alpha$, λ = 1.54178 Å
Crystal system, lattice	Tetragonal, primitive
Space group	$P4_3$
a,b, Å	10.310(1)
c, Å	23.871(2)
Volume, Å^3	2537(1)
Formula units per cell	4
Density (calculated)	1.169 mg/m^3
Absorption coefficient	0.606 mm^{-1}
$F(000)$	960
Crystal size	0.08 × 0.10 × 0.40 mm
Theta range for data collection	55°
Index range, h, k, l	+10, +10, +25
Reflections collected	2472
Independent reflections	1735 (R_{int} = 0.016)
Observed reflections ($F > 3.0\sigma$ (F))	1513
Refinement method	Full-matrix least-squares on F
Data/restraints/parameters	1513/0/298
Goodness-of-fit on F	1.10
Final R indices ($F > 3.0\sigma$ (F))	R_1 = 0.0442, wR_2 = 0.0505
R indices (all data)	R_1 = 0.0521, wR_2 = 0.0526
Weighting scheme	σ^2 (F) + 0.0005F^2
Largest difference map residuals	+0.14 and −0.17 e/Å^{-3}

Table 2. Atomic coordinates (× 10^4) and equivalent isotropic displacements parameters (Å^2 × 10^4) for the non-H-atoms of 17α-acetoxy-17β-methyl-16β-phenyl-D-homo-4,6-pregnadiene-3,17a-dione

Atom	x/a	y/b	z/c	U(eq)
O(1)	1429(5)	13508(5)	1502	92(2)
O(2)	5732(5)	4797(5)	471(3)	97(2)
O(3)	8007(4)	5269(4)	−52(3)	58(1)
O(4)	7936(6)	6542(5)	711(3)	103(2)
C(1)	1714(6)	10079(6)	1245(3)	63(2)
C(2)	931(6)	11291(7)	1384(3)	78(3)
C(3)	1632(5)	12500(7)	1244(3)	65(2)
C(4)	2544(5)	12430(6)	782(3)	58(2)
C(5)	2841(5)	11341(5)	505(3)	45(2)
C(6)	3773(5)	11360(5)	55(3)	57(2)
C(7)	4212(5)	10297(5)	−193(3)	55(2)
C(8)	3858(5)	8957(5)	−18(3)	43(2)
C(9)	3262(5)	8981(5)	573(3)	46(2)
C(10)	2211(5)	10053(5)	642(3)	47(2)
C(11)	2813(6)	7634(6)	749(3)	61(2)
C(12)	3922(6)	6643(5)	710(3)	62(2)
C(13)	4557(5)	6604(5)	129(3)	45(2)
C(14)	5003(4)	7987(5)	−28(3)	39(2)
C(15)	5818(5)	7975(5)	−566(3)	42(2)
C(16)	7086(5)	7235(5)	−470(3)	41(2)
C(17)	6813(5)	5825(4)	−280(3)	44(2)
C(17A)	5721(6)	5699(5)	147(3)	53(2)
C(18)	3591(6)	6021(5)	−298(3)	64(2)
C(19)	1068(6)	9850(7)	229(3)	69(2)
C(20)	6526(6)	4905(5)	−762(3)	64(2)
C(21)	8477(7)	5732(7)	431(4)	75(3)
C(22)	9742(7)	5102(10)	558(4)	121(4)
C(23)	8044(5)	7328(5)	−951(3)	43(2)
C(24)	9355(5)	7475(6)	−846(3)	61(2)
C(25)	10233(7)	7576(7)	−1284(4)	85(3)
C(26)	9817(8)	7536(6)	−1824(4)	82(3)
C(27)	8521(7)	7399(6)	−1938(3)	73(3)
C(28)	7642(6)	7289(5)	−1505(3)	56(2)

The stereochemistry of the title compound is as follows: C(9)−αH is *trans* to both C(19)−βCH_3 and C(8)−βH; C(14)−αH is *trans* to both C(18)−βCH_3 and C(8)−βH; C(16)−αH is *trans* to C(17)−βCH_3 and *cis* to C(17)−α(−$OCOCH_3$), and C(17)−βCH_3 is *cis* to C(16)−β(phenyl ring).

The molecules in the crystal are packed at normal van der Waals distances. There is only one C−H···O intramolecular interaction [C(16)···O(4), 3.037(10), H(16)···O(4), 2.434(9) and C(16)−H(16)···O(4) 120.6(7)°] which stabilizes the molecule internally. In addition, there are three intermolecular interactions C−H···O < 3.3Å, which help stabilize the molecules in the crystal; C(7)−H(7) ··· O(1) (− y + 2, + x +

Table 3. Bond lengths and selected angles (Å, °) in 17α-acetoxy-17β-methyl-16β-phenyl-D-homo-4,6-pregnadiene-3,17a-dione

O(1)−C(3)	1.226(9)	O(2)−C(17A)	1.210(9)
O(3)−C(17)	1.462(7)	O(3)−C(21)	1.340(11)
O(4)−C(21)	1.205(10)	C(1)−C(2)	1.524(9)
C(1)−C(10)	1.527(10)	C(2)−C(3)	1.479(10)
C(3)−C(4)	1.451(10)	C(4)−C(5)	1.339(9)
C(5)−C(6)	1.441(9)	C(5)−C(10)	1.514(7)
C(6)−C(7)	1.325(8)	C(7)−C(8)	1.489(7)
C(8)−C(9)	1.538(10)	C(8)−C(14)	1.548(7)
C(9)−C(10)	1.557(7)	C(9)−C(11)	1.523(8)
C(10)−C(19)	1.551(9)	C(11)−C(12)	1.536(8)
C(12)−C(13)	1.534(10)	C(13)−C(14)	1.545(7)
C(13)−C(18)	1.546(9)	C(13)−C(17A)	1.521(8)
C(14)−C(15)	1.534(9)	C(15)−C(16)	1.531(7)
C(16)−C(17)	1.549(7)	C(16)−C(23)	1.516(9)
C(17)−C(17A)	1.523(9)	C(17)−C(20)	1.521(9)
C(21)−C(22)	1.489(11)	C(23)−C(24)	1.383(8)
C(23)−C(28)	1.387(10)	C(24)−C(25)	1.388(12)
C(25)−C(26)	1.358(14)	C(26)−C(27)	1.371(11)
C(27)−C(28)	1.380(10)		
C(2)−C1−C(10)	113.5(6)	C(1)−C(2)−C(3)	112.5(6)
C(2)−C(3)−C(4)	116.5(6)	C(3)−C(4)−C(5)	124.5(6)
C(4)−C(5)−C(6)	120.6(5)	C(4)−C(5)−C(10)	122.0(6)
C(6)−C(5)−C(10)	117.4(5)	C(5)−C(6)−C(7)	123.3(5)
C(6)−C(7)−C(8)	124.0(6)	C(7)−C(8)−C(9)	109.9(5)
C(7)−C(8)−C(14)	114.1(4)	C(9)−C(8)−C(14)	109.3(5)
C(8)−C(9)−C(10)	112.8(5)	C(8)−C(9)−C(11)	111.0(5)
C(10)−C(9)−C(11)	114.0(4)	C(1)−C(10)−C(5)	109.4(5)
C(1)−C(10)−C(9)	110.3(5)	C(5)−C(10)−C(9)	107.5(4)
C(9)−C(11)−C(12)	111.3(5)	C(11)−C(12)−C(13)	112.9(6)
C(12)−C(13)−C(14)	108.9(5)	C(12)−C(13)−C(17A)	109.2(5)
C(14)−C(13)−C(17A)	109.7(4)	C(18)−C(13)−C(17A)	106.7(5)
C(8)−C(14)−C(13)	111.4(4)	C(8)−C(14)−C(15)	115.9(5)
C(13)−C(14)−C(15)	111.1(4)	C(14)−C(15)−C(16)	110.3(5)
C(15)−C(16)−C(17)	110.9(4)	C(16)−C(17)−C(17A)	114.3(4)
C(13)−C(17A)−C(17)	120.8(5)		

1, + $z - \frac{1}{4}$); C(28)−H(28) ··· O(2) ($-y$ + 1, + x, + $z - \frac{1}{4}$) and C(22)−H(22A) ··· O(1) (x + 1, + y − 1, + z). The D···A lengths are, respectively 3.253(7), 3.236(8), and 3.287(10) Å, H···A 2.364(7), 2.419(8) and 2.816(10) Å and the corresponding D−H···A angles are 153.8(6), 142.7(6) and 111.2(8)°.

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