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ORIGINAL PAPER

Analysis of C–H···O Intermolecular Interactions in 4-Androstene-3,17-dione

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Abstract 4-Androstene-3,17-dione was synthesized for its crystallographic analysis and to investigate the role of intra- and intermolecular interactions in steroids. It crystallizes in the orthorhombic space group $P2_12_12_1$ with unit cell parameters, $a = 7.330(2)$ Å, $b = 13.095(11)$ Å, $c = 16.856(17)$ Å, $V = 1{,}618(5)$ Å^3 and $Z = 4$. The structure has been solved by direct methods using X-ray diffraction techniques and the refined final reliability index for the computed structure is 0.033 for 1,655 observed reflections. Two six-membered rings B and C exist in *chair* conformation while ring A occupies a *sofa* conformation. The five-membered ring D depicts *envelope* conformation. The C–H···O intermolecular hydrogen interaction results into a ring like configuration which makes the dimers.

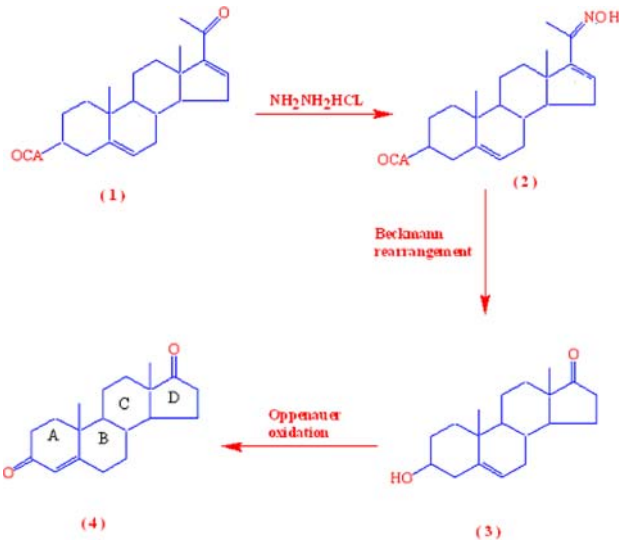
Keywords Androstane · Crystal structure · Conformations · Hydrogen bonding · Dimer

Introduction

Androgen is the generic term for any natural or synthetic compound, usually a steroid hormone, that stimulates or controls the development and maintenance of masculine characteristics in vertebrates by binding to androgen receptors [1]. Androgens have been used in breast cancer when excision or radiotherapy have failed to control the progress of local recurrent disease. They are also used in case where the primary tumour is inoperable or is unsuited for, or resistant to, radiotherapy. Androgens are also believed to be responsible for linear bone growth in both males and females, probably in conjunction with somatotrophin [2]. In continuation to our work on the single crystal growth of X-ray diffraction quality crystals and crystallographic analysis of steroidal molecules [3–7], synthesis and crystallographic study 4-androstene-3,17-dione is reported in this paper.

Experimental

4-Androstene-3,17-dione was synthesized from 16-dehydropregnenolone acetate **(1)**. 16-Dehydropregnenolone acetate **(1)** was converted to oxime **(2)** by treatment with hydroxylamine hydrochloride in anhydrous pyridine which underwent Beckmann rearrangement when treated with phosphorous oxychloride in pyridine at −5 °C to yield an enamide, hydrolysis of which produced dehydroepiandrosterone **(3)**



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Dehydroepiandrosterone was subjected to Oppenauer oxidation with aluminium isopropoxide in toluene and cyclohexanone to yield the desired compound 4-androstene-3,17-dione **(4)**. The material was dissolved in acetone and a few drops of methanol were added to the solution to achieve quality crystallization. The chemical structure has been assigned on the basis of IR, UV, NMR and mass spectral data [8].

The three-dimensional data were collected by using Mo Kα radiation ($\lambda = 0.71073$ Å) [9]. $\omega/2\theta$ scan mode in the θ-range of 2.42–24.98°. The cell parameters were refined from accurately determined 25 reflections in the θ-range of 12.4–14.8°. A total number of 1,653 reflections were collected and the same number were found to be unique ($0 \leq h \leq 8$, $0 \leq k \leq 15$, $0 \leq l \leq 20$) whereas 1,307 were treated as observed reflections [$F_o > 4\sigma(F_o)$]. The reflection data were corrected for Lorentz and polarization effects. The absorption (0.074 mm^{-1}) and extinction [0.012(2)] corrections were not applied.

The structure has been solved by direct methods using SHELXS97 program [10]. All non-hydrogen atoms of the molecule were located from the E-map. Using SHELXL97 program [11] carried out full-matrix least-squares refinement of the structure. Final refinement with anisotropic thermal parameters of non-hydrogen atoms and fixing the hydrogen atoms stereochemically resulted $R = 0.0331$, $wR = 0.0876$. The hydrogen atoms were fixed at chemically acceptable positions and were allowed to ride on their parent atoms. Atomic scattering factors can be obtained from International Tables for Crystallography (1992, Vol. C Tables 4.2.6.8 and 6.1.1.4). The crystallographic data are listed in Table 1.

Table 1 Crystal data and other experimental details

Empirical formula	$C_{19}H_{26}O_2$
Formula weight	286.40
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions	$a = 7.330(2)$ Å, $\alpha = 90°$ $b = 13.095(11)$ Å, $\beta = 90°$ $c = 16.856(17)$ Å, $\gamma = 90°$
Volume, Z	1,618(5) $Å^3$, 4
Calculated density	1.176 Mg/m^3
Absorption coefficient	0.074 mm
$F(000)$	624
Crystal size	0.5 × 0.45 × 0.3 mm
Theta range for data collection	2.42–24.98°
Limiting indices	$0 \leq h \leq 8$, $0 \leq k \leq 15$, $0 \leq l \leq 20$
Reflections collected/unique	1,655/1,655 [R(int) = 0.0000]
Maximum and minimum transmission	0.978 and 0.964
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1,655/0/191
Goodness-of-fit on F^2	1.036
Final R indices [$F_o > 4\sigma(F_o)$]	$R = 0.0331$, $wR = 0.0876$
R indices (all data)	$R = 0.0500$, $wR = 0.0966$
Extinction coefficient	0.012(2)
Largest diff. peak and hole	0.114 and −0.106 e $Å^{-3}$

Results and Discussion

Bond distances and bond angles for non-hydrogen atoms are listed in Table 2. An ORTEP view of the molecules indicating atomic-numbering scheme (thermal ellipsoids drawn at 50% probability) is shown in Fig. 1 [12]. The geometrical calculations were performed using PARST program [13].

The bond distances and bond angles were found to be in good agreement with some analogous structures [7, 14–17]. The mean bond lengths, [$C(sp^3)$–C (sp^3)] = 1.523(4), [$C(sp^3)$–$C(sp^2)$] = 1.486(4), [$C(sp^2)$–C (sp^2)] = 1.330(3), [$C(sp^3)$–O] = 1.216(3) Å, are quite close to the standard values [18, 19]. The values of bond distances C3(sp^2)–C2(sp^3) = 1.503(4) Å [1.499 Å] and C3(sp^2)–C4(sp^2) = 1.447(5) Å [1.459 Å] are found quite close, when compared with the average values of 60 analogous androstane derivatives. The endocyclic bond angles in the steroid nucleus comprising three six-membered rings fall in the range 108.8(1)–124.7(3)° [average value being 112.8(2)°] for the five-membered ring bond angles fall in the range 101.6(2)–108.4(2)° [average value being 104.5(2)°]. The C2(sp^3)–C3(sp^2)–C4(sp^2) bond angle is exactly equal [116.4(2)°] to the average value of this bond angle of 60 androstane derivatives.

Ring A adopts *sofa* conformation [asymmetry parameter ΔC_s (C1–C4) = 7.96] [20]. Ring B and C depicts *chair* conformation [asymmetry parameter ΔC_2 (C5–C10) = 5.60, ΔC_s (C5–C8) = 1.06 and ΔC_2 (C9–C11) = 3.40, ΔC_s (C9–C13) = 3.26] [23]. The five-membered ring D occurs in *envelope* conformation [ΔC_s (C14–C16) = 3.05] [23] with a phase angle of pseudorotation $\Delta = -4.35°$ and maximum angle of torsion $\phi_m = 40.8°$ [21].

The hydrogen bonding network is shown in Fig. 2. In orthorhombic space group $P2_12_12_1$, the molecules of 4-androstene-3,17-dione are linked by paired C–H···O hydrogen bonds into $R_2^2(6)$ graph set, where R refers to Ring [22]. The C(16)–H(16B)···O(1) intermolecular hydrogen interaction results into a ring like configuration which makes the dimers. The molecules are linked by another C(2)–H(2A)···O(2) which connects the dimers and it shows that the crystal could be pictorially described as supramolecular structure which is being formed by chains of dimers diagonally along the bc-plane as shown in Fig. 3.

Table 2 Bond distances (Å) and bond angles (°) for non-hydrogen atoms (e.s.d.'s are given in parentheses)

C(1)–C(2)	1.524(3)	C(1)–C(10)	1.542(5)
C(2)–C(3)	1.503(4)	C(3)–O(1)	1.222(3)
C(3)–C(4)	1.447(5)	C(4)–C(5)	1.330(3)
C(5)–C(6)	1.498(5)	C(5)–C(10)	1.525(4)
C(6)–C(7)	1.524(4)	C(7)–C(8)	1.521(3)
C(8)–C(14)	1.516(3)	C(8)–C(9)	1.549(5)
C(9)–C(11)	1.542(4)	C(9)–C(10)	1.562(3)
C(10)–C(19)	1.546(3)	C(11)–C(12)	1.532(3)
C(12)–C(13)	1.514(5)	C(13)–C(17)	1.513(3)
C(13)–C(14)	1.528(3)	C(13)–C(18)	1.540(3)
C(14)–C(15)	1.526(5)	C(15)–C(16)	1.541(4)
C(16)–C(17)	1.510(5)	C(17)–O(2)	1.211(3)
C(2)–C(1)–C(10)	113.60(2)	C(3)–C(2)–C(1)	111.80(2)
O(1)–C(3)–C(4)	121.50(3)	O(1)–C(3)–C(2)	121.90(3)
C(4)–C(3)–C(2)	116.40(2)	C(5)–C(4)–C(3)	124.70(3)
C(4)–C(5)–C(6)	120.60(2)	C(4)–C(5)–C(10)	122.60(3)
C(6)–C(5)–C(10)	116.70(2)	C(5)–C(6)–C(7)	113.20(2)
C(8)–C(7)–C(6)	110.70(2)	C(14)–C(8)–C(7)	112.67(2)
C(14)–C(8)–C(9)	109.50(1)	C(7)–C(8)–C(9)	109.20(2)
C(11)–C(9)–C(8)	113.30(2)	C(11)–C(9)–C(10)	112.53(2)
C(8)–C(9)–C(10)	112.21(2)	C(5)–C(10)–C(1)	109.30(2)
C(5)–C(10)–C(19)	108.20(2)	C(1)–C(10)–C(19)	109.80(2)
C(5)–C(10)–C(9)	108.78(2)	C(1)–C(10)–C(9)	108.95(2)
C(19)–C(10)–C(9)	111.78(2)	C(12)–C(11)–C(9)	114.40(2)
C(13)–C(12)–C(11)	109.80(2)	C(17)–C(13)–C(12)	117.40(2)
C(17)–C(13)–C(14)	101.60(2)	C(12)–C(13)–C(14)	109.00(2)
C(17)–C(13)–C(18)	104.33(2)	C(12)–C(13)–C(18)	111.40(2)
C(14)–C(13)–C(18)	112.80(2)	C(8)–C(14)–C(15)	119.50(2)
C(8)–C(14)–C(13)	112.79(2)	C(15)–C(14)–C(13)	104.20(2)
C(14)–C(15)–C(16)	102.60(2)	C(17)–C(16)–C(15)	105.80(2)
O(2)–C(17)–C(16)	125.30(3)	O(2)–C(17)–C(13)	126.30(3)
C(16)–C(17)–C(13)	108.40(2)		

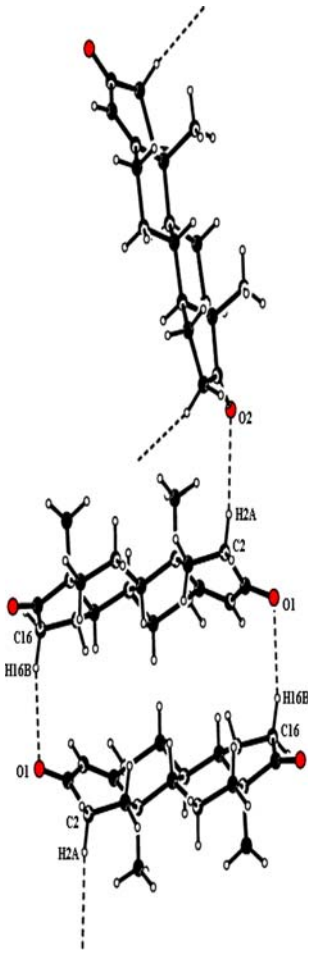

Fig. 2 Dimer view of molecules by C–H···O hydrogen bonding network

As evident from literature, [23] the C–H···O hydrogen bonding is most predominant in androstane derivatives and observed mostly in molecules having a keto group (>C=O) as substituents in which oxygen atom of the keto group acts

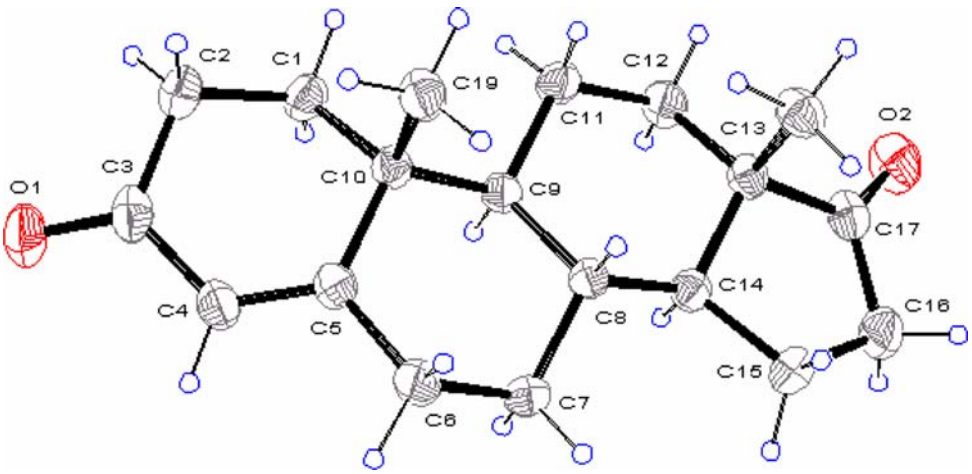

Fig. 1 ORTEP view of the molecule indicating atomic-numbering scheme

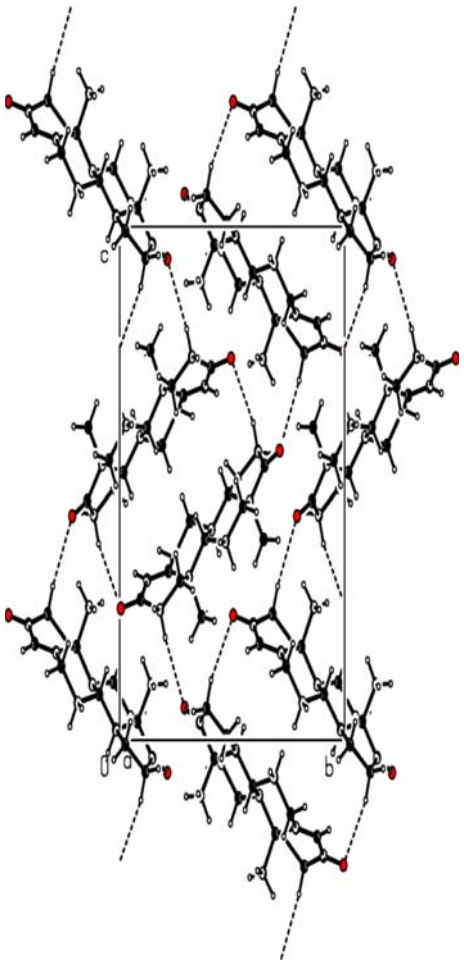

Fig. 3 Unit cell packing along *bc-plane* depicting the pictorial view of dimers connected through chains

as a proton acceptor. The geometry of the C–H···O hydrogen bonds are presented below

X–H···A	H···A (Å)	X···A (Å)	X–H···A (°)
C(2)–H(2A)···O(2)[a]	2.60	3.560(5)	171.8
C(16)–H(16B)···O(1)[b]	2.51	3.446(5)	163.5

Symmetry code: [a] $-x + 3/2$, $-y$, $z + 1/2$; [b] $2x - 1/2$, $-y + 1/2$, $-z + 1$

Supplementary Material

CCDC-622967 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.an.uk/uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, United Kingdom; Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk.

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