Synthesis and X-ray crystallographic analysis of 17α-hydroxy-17-methylandrost-4-ene-17-one

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17α-Hydroxy-17-methylandrost-4-ene-17-one is a complex of two steroid molecules with water and its crystal structure has been determined by X-ray crystallographic techniques. The transparent plate-like crystals of this compound crystallized in the orthorhombic space group $P2_12_12_1$, with unit cell parameters: a = 6.382(2), b = 12.841(5), c = 43.350(2) Å, λ (Mo K α) = 0.71073 Å, Z = 8. The structure has been solved by direct methods and refined to R = 0.047, wR = 0.086. There are two crystallographically independent molecules, I and II, in the asymmetric unit. In both the molecules, rings A and D adopt a *distorted half-chair conformation* while rings B and C exist in *chair conformation*. The crystal structure is stabilized by intermolecular O-H···O and C-H···O hydrogen bonds.

KEY WORDS: X-ray crystallography; crystal structure; ring conformations; hydrogen bonds.

Introduction

Selected by the evolutionary process to perform some of the most fundamental biological functions,^{1,2} the steroid system not only has inspired the endocrinologists, but has also become the basis for some of the most phenomenal development in organic chemistry. The substituents at C3 position of the steroid moiety are either linked by intra or intermolecular hydrogen bonds that help in understanding the stacking interactions.³

The study being reported in this paper is a part of our ongoing work on synthesis, structure analysis, and role of hydrogen bonding in steroidal molecules.^{3–10}

Experimental

A solution of 10 g of pregnenolone in a mixture of 50 mL of tetrahydrofuran and 140 mL of t-butanol containing potassium t-butoxide (from 6.4 g of potassium metal) is oxygenated at 5- 7° until 1.1 molar equivalents of oxygen have been consumed. Nitrogen is passed through the solution for several minutes and the reaction mixture is then heated to 60-70°C for 20 min. Precipitation with water and crystallization gives 7.4 g of 3β -hydroxyandrost-5-ene-17-one which on treatment with methylmagnesium iodide gives the 17 α -methyl compound, which is then oxidized to yield 17α -hydroxy-17-methylandrost-4ene-17-one. Solvent loss technique was then employed for the growth of transparent plate shaped crystals (mp 434 K) using methanol as the solvent system.

Three-dimensional intensity data of a single crystal of the title compound were collected

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(17α-Hydroxy-17-methylandrost-4-en-3-one)

on an Enraf-Nonius CAD-4 diffractometer using MoK α radiation ($\lambda = 0.71073$ Å) and ω -2 θ scan mode was employed for data collection. The unit cell parameters were refined from accurately determined 25 reflections in the range (6.16 $< \theta <$ 10.32°). A total number of 3681 reflections were recorded in the range $2.12 < \theta < 24.95^{\circ}$. From the number of reflections as recorded, 3602 were found unique (with index range: $0 \le h \le 7, 0$ $\leq k \leq 15, 0 \leq l \leq 51$) and 1537 were treated as observed $[F_0 > 4\sigma(F_0)]$. Two standard reflections $(\bar{2} \, 3 \, 1 \text{ and } \bar{1} \, 1 \, \bar{3})$ were monitored every 100 reflections to check for crystal deterioration, if any, during beam exposure to the sample. The data were corrected for Lorentz and polarization effects. Absorption ($\mu = 0.074 \text{ mm}^{-1}$) and extinction (0.001) corrections were not applied.

The crystal structure has been solved by direct methods using SHELXS97 software.¹¹ Two crystallographically independent molecules (I and II) were found in the asymmetric unit cell. All non-hydrogen atoms of both the molecules were located from the E-map.

Refinement was carried out by using fullmatrix method on F^2 using SHELXL97 software.¹² Initially, the isotropic refinement of all the non-hydrogen atoms brought the reliability index down to 0.156. All hydrogens were fixed stereochemically. Finally, the *R*-factor converged to 0.047 [$wR(F^2) = 0.086$] after few cycles of refinement. The maximum positive and negative electron density ($\Delta \rho$) in final difference Fourier map ranges from 0.13 to -0.13 e Å⁻³, respectively. The goodness-of-fit on F^2 is 0.812. Atomic scattering factors were taken 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.

17α-hydroxy-17-methylandrost-4-ene-17-one

Table 1. Crystal Data and Structure Refinement Details

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Crystal description	Transparent rectangular plates
CCDC reference no	CCDC 217672
Chemical formula	$C_{20}H_{30}O_2 \cdot H_2O$
Molecular weight	319.46
Crystal system	Orthorhombic
Space group	P212121
Unit cell dimensions	
<i>a</i> (Å)	6.382(2)
<i>b</i> (Å)	12.841(5)
<i>c</i> (Å)	43.350(17)
Volume (Å ³)	3552(2)
Ζ	8
Calculated density (Mg/m ³)	1.165
Radiation, wavelength (λ)	Mo Kα, 0.71073 Å
F(000)	1368
Crystal size (mm)	$0.30 \times 0.25 \times 0.20$
θ range for data collection (°)	2.12-24.96
Limiting indices	$0 \le h \le 7, 0 \le k \le 15, 0 \le l$
	≤ 51
Reflections collected/unique	3681/3602
Data/restraints/parameters	3602/0/413
Absorption coefficient (mm^{-1})	0.074
Goodness-of-fit on F^2	0.812
Final R-factor	0.0479
wR	0.0860
Largest diff. peak and hole (e \AA^{-3})	$-0.13 < \Delta \rho < 0.13$

Results and discussion

The bond lengths and bond angles for nonhydrogen atoms are given in Table 2. A general view of the molecule indicating atomic numbering scheme (thermal ellipsoid drawn at 50% probability) is shown in Fig. 1.¹³ In both the molecules, the bond distances and angles agree well with the values reported in the literature for some analogous structures.^{4–10} The bond lengths C3–C4 [1.464(7)] and C3'–C4' [1.481(7)] are greater than the standard C(sp²)–C(sp²) value [1.447] and this could be due to large deviation of the oxygen atoms attached to C3 and C3' [deviation being -0.175 for O1 and 0.327 for O1').

In molecule I, the ring A adopts a *distorted* half-chair conformation [asymmetry parameter, $\Delta C_2(C1-C2) = 8.48$; $\Delta C_s(C1) = 14.34$].¹⁴ Ring B exists in normal chair conformation [$\Delta C_2(C5-C10) = 1.20$; $\Delta C_s(C7) = 3.60$]. Ring C also depicts a normal chair conformation [$\Delta C_2(C9-C11) = 3.89$; $\Delta C_s(C9) = 2.64$].¹⁴ The

 Table 2.
 Bond Distances (Å) and Bond Angles (°) for Non-Hydrogen Atoms (ESDs are Given in Parentheses)

Molecule I		Molecule II	
Bond distances (Å)			
C1-C2	1.521(6)	C1'-C2'	1.495(6)
C1-C10	1.547(7)	C1'-C10'	1.543(6)
C2–C3	1.501(7)	C2'-C3'	1.495(7)
C3-O1	1.218(6)	C3'-O1'	1.193(6)
C3–C4	1.464(7)	C3'-C4'	1.485(7)
C4–C5	1.324(6)	C4'-C5'	1.354(6)
C5–C6	1.507(6)	C5'-C6'	1.519(7)
C5-C10	1.509(6)	C5'-C10'	1.507(6)
C6–C7	1.513(6)	C6'-C7'	1.526(6)
C7–C8	1.528(6)	C7'–C8'	1.536(5)
C8-C14	1.504(6)	C8'-C14'	1.534(6)
C8–C9	1.544(5)	C8'-C9'	1.558(6)
C9-C10	1.529(6)	C9'-C10'	1.553(6)
C9-C11	1.546(6)	C9'-C11'	1.532(6)
C10-C19	1.568(7)	C10'-C19'	1.537(6)
C11-C12	1.521(6)	C11'-C12'	1.557(6)
C12–C13	1.514(6)	C12'-C13'	1.522(6)
C13-C14	1.513(6)	C13'-C14'	1.536(6)
C13–C17	1.536(7)	C13'-C17'	1.548(6)
C13-C18	1.549(7)	C13'-C18'	1.533(6)
C14–C15	1.521(6)	C14′–C15′	1.522(6)
C15-C16	1.527(7)	C15'-C16'	1.537(7)
C16-C17	1.555(7)	C16'-C17'	1.533(7)
C17–O2	1.435(7)	C17′–O2′	1.437(6)
C17–C20	1.525(7)	C17'-C20'	1.514(7)
Bond angles (°)			
C2-C1-C10	114.7(4)	C2'-C1'-C10'	114.8(4)
C3-C2-C1	110.7(5)	C3'-C2'-C1'	111.7(4)
O1–C3–C4	122.7(6)	O1'-C3'-C4'	122.4(5)
O1–C3–C2	121.4(6)	O1'-C3'-C2'	123.7(5)
C4–C3–C2	115.5(5)	C4'-C3'-C2'	113.9(5)
C5–C4–C3	124.3(5)	C5'-C4'-C3'	124.0(5)
C4–C5–C6	120.3(5)	C4′–C5′–C6′	119.9(5)
C4-C5-C10	123.9(5)	C4′–C5′–C10′	123.2(5)
C6-C5-C10	115.8(5)	C6′-C5′-C10′	116.9(5)
C5–C6–C7	112.6(4)	C5′–C6′–C7′	111.1(4)
C6–C7–C8	111.5(5)	C6'-C7'-C8'	112.1(4)
C14–C8–C7	112.5(4)	C14′–C8′–C7′	110.8(4)
C14-C8-C9	110.6(4)	C14'-C8'-C9'	108.8(4)
C7–C8–C9	108.7(4)	C7′–C8′–C9′	109.5(4)
C10-C9-C8	113.9(4)	C10'-C9'-C8'	113.9(4)
C10-C9-C11	115.1(4)	C10'-C9'-C11'	113.5(3)
C8-C9-C11	110.7(4)	C8′-C9′-C11′	109.4(4)
C5-C10-C9	111.2(4)	C5'-C10'-C9'	108.7(4)
C5-C10-C1	109.1(4)	C5'-C10'-C1'	108.8(4)
C9-C10-C1	109.3(4)	C9'-C10'-C1'	108.9(4)
C5-C10-C19	107.9(5)	C5'-C10'-C19'	109.1(4)
C9-C10-C19	110.3(4)	C9'-C10'-C19'	111./(4)
CI-CI0-CI9	108.9(5)	CT - C10' - C19'	109.6(4)
C12-C11-C9	114.5(4)	C12' - C11' - C9'	112.7(4)
	110.9(4)	C13 - C12 - C11'	111.5(4)
C14-C13-C12	108.2(4)	C14'-C13'-C12'	107.6(4)

Table 2. Continued.

Molecul	e I	Molecule	II
C14-C13-C17 C12-C13-C17 C14-C13-C18 C12-C13-C18 C17-C13-C18 C8-C14-C13 C8-C14-C15 C13-C14-C15 C14-C15-C16 C15-C16-C17 O2-C17-C13 C20-C17-C13 O2-C17-C16	102.5(4) 116.9(5) 112.0(5) 109.8(5) 107.3(5) 114.8(4) 119.4(4) 104.1(4) 104.7(4) 106.9(5) 107.5(4) 115.0(5) 115.4(5) 105.9(5)	C14'-C13'-C17' C12'-C13'-C17' C14'-C13'-C18' C12'-C13'-C18' C17'-C13'-C18' C8'-C14'-C13' C8'-C14'-C15' C13'-C14'-C15' C13'-C14'-C15' C14'-C15'-C16' C15'-C16'-C17' O2'-C17'-C13' C20'-C17'-C13' O2'-C17'-C16'	$\begin{array}{c} 100.5(3)\\ 117.6(4)\\ 111.2(4)\\ 109.6(3)\\ 109.9(4)\\ 114.1(4)\\ 119.5(4)\\ 104.1(4)\\ 103.9(4)\\ 107.4(4)\\ 106.8(4)\\ 112.2(4)\\ 114.1(4)\\ 107.9(4) \end{array}$
C20-C17-C16 C13-C17-C16	109.4(6) 103.1(5)	C20'-C17'-C16' C13'-C17'-C16'	112.2(4) 103.6(4)

five-membered ring D occurs in a *distorted half-chair conformation* [ΔC_2 (C13–C14) = 7.15], with phase angle of pseudorotation, $\Delta = -3.65^{\circ}$ and maximum angle of torsion, $\varphi_m = -43.7^{\circ}$.¹⁵

In molecule II, ring A exists in *dis*torted half-chair conformation [asymmetry parameter, $\Delta C_2(C1'-C2') = 8.25$; $\Delta C_s(C1') =$ 17.22]. Ring B adopts a symmetrical chair conformation [$\Delta C_2(C5'-C10') = 1.66$; $\Delta C_s(C5') =$ 1.57]. Ring C also occurs in symmetrical chair conformation $[\Delta C_2(C11'-C12') = 2.69;$ $\Delta C_s(C11') = 0.83]$. The five-membered ring D depicts a distorted half-chair conformation $[\Delta C_2(C13'-C14') = 9.36]$, with phase angle of pseudorotation, $\Delta = -4.66^\circ$ and maximum angle of torsion, $\varphi_m = -45.4^\circ$.

In orthorhombic space group $P2_12_12_1$, the molecules of 17α -hydroxy-17-methylandrost-4ene-17-one are linked by paired O-H···O hydrogen bonds into $C_2^2(6)$ graph set,¹⁶ where C refers for chain. The crystal structure is stabilized by $O-H \cdots O$ and $C-H \cdots O$ hydrogen bonds and the hydrogen-bonding network is shown in Fig. 2. Both the crystallographic independent molecules I and II are linked to one another through $O-H \cdots O$ hydrogen bonds. The long linear chains bonded through O2–H2···O1' and O2'–H2'···O1 intermolecular hydrogen interactions have been observed. For both the molecules, the O2 atom acts as hydrogen donor whereas the O1 acts as acceptor atom. In molecule I, the atom C16 at (x, y, z)acts as hydrogen bond donor to the O3 atom of the water at (x-1/2-1, -y+1/2+1, -z+1), and thus makes C-H···O intermolecular interaction. The $H \cdots A$ distance (d) in both the O-H $\cdots O$ intermolecular interactions is almost equal and it leads that the crystal can be pictorially described as



Fig. 1. General view of the molecules (thermal ellipsoids drawn at 50% probability).



Fig. 2. Depiction of intermolecular hydrogen bonding interactions.

being formed by chains of molecules. The geometry of O–H···O and C–H···O hydrogen bonds is presented below:

D–H· · · A	$ \begin{array}{c} \operatorname{H} \cdots \operatorname{A} \left(\operatorname{\mathring{A}} \right) \\ (d) \end{array} $	$ \begin{array}{c} \mathbf{D} \cdots \mathbf{A} (\mathbf{\mathring{A}}) \\ (D) \end{array} $	$\begin{array}{c} D\!\!-\!\!H\!\!\cdot\!\!\cdot\!\!\cdot\!A\left(^{\circ}\right)\\ (\theta) \end{array}$
$\begin{array}{c} O2-H2\cdots O1'^{(i)}\\ O2'-H2'\cdots O1^{(ii)}\\ C16-H16A\cdots O3^{(iii)} \end{array}$	2.07(5)	2.884(6)	158(5)
	2.08(5)	2.901(6)	169(5)
	2.57(1)	3.406(10)	144(5)

Symmetry codes: (i) 2-x, 1/2+y, 1/2-z; (ii) 2-x, -1/2+y, 1/2-z; (iii) 1/2+x, 1/2-y, -z.

Supplementary material CCDC-217672 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(O) 1223-336033; e-mail: deposit@ccdc.cam.ac.uk.

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References

- 1. Williams-ashman, H.G.; Reddi, A.H. Annu. Rev. Physiol. 1971, 33, 31.
- Jensen, E.V.; Desombre, E.R. Annu. Rev. Biochem. 1972, 41, 203.
- Verma, Rajnikant; Jasrotia, Dinesh; Bhavnaish, C. Acta Crystallogr. A 2006, A62, 10.
- Singh, A.; Gupta, V.K.; Goswami, K.N.; Verma, Rajnikant; Gupta, B.D.; Banerjee, S.K. *Mol. Mat.* **1996**, *6*, 53.
- Verma, Rajnikant; Gupta, V.K.; Firoz, J.; Shafiullah; Gupta, R. Crystallogr. Rep. 2000, 5, 857.
- Verma, Rajnikant; Gupta, V.K.; Khan, E.H.; Shafi, S.; Hashmi, S.; Shafiullah; Varghese, V.; Jasrotia, D.; *Crystallogr. Rep.* 2001, 46(6), 1045.
- Verma, Rajnikant; Gupta, V.K.; Firoz, J.; Shafiullah; Khan, E.H.; Shafi, S.; Gupta, R. Cryst. Res. Technol. 2001, 2, 215.
- Verma, Rajnikant; Gupta, V.K.; Firoz, J.; Shafiullah; Khan, E.H.; Shafi, S.; Gupta, R. Cryst. Res. Technol. 2001, 4/5, 471.
- Verma, Rajnikant; Gupta, V.K.; Khan, E.H.; Shafi, S.; Shafiullah; Jasrotia, Dinesh. J. Chem. Crystallogr. 2002, 32(9), 325.
- Verma, Rajnikant; Jasrotia, Dinesh; Anshu, S.; Bhvnaish; Gupta, B.D.J Chem. Crystallogr. 2004, 34(8), 523.
- 11. Sheldrick, G.M. SHELXS97: Program for the Solution of Crystal Structure; University of Gottingen: Germany, 1997.
- 12. Sheldrick, G.M. SHELXS97: Program for Refinement of Crystal Structure; University of Gottingen: Germany, 1997.
- 13. Farrugia, L.J. J. Appl. Cryst. 1997, 30, 565.
- Duax, W.L.; Norton, D.A. Atlas of Steroid Structure; Plenum: New York, 1975; p. 1.
- 15. Altona, C.; Geise, H.J.; Romers, C. Tetrahedron 1968, 24, 13.
- Bernstein, J.; Davis, R.E.; Shimoni, L.; Chang, N.-L. Patterns in hydrogen bonding: functionality and graph set analysis in crystals. *Angewandte Chemie*, *International Edition in English*, 1995, 34, 1555.