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3 β -Hydroxy-17-oxo-5-androsten-19-al, a Steroid Pertinent to Estrogen Biosynthesis

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Abstract. C₁₉H₂₆O₃, orthorhombic, $P2_12_12_1$, $a = 11.311$ (5), $b = 22.197$ (5), $c = 6.686$ (8) Å, $V = 1678$ Å³, $Z = 4$, $M = 302.42$, $D_c = 1.19$ g cm⁻³, $D_m = 1.21$ g cm⁻³, m.p. 140–143°C. The C(19)=O(19) bond eclipses the C(1)–C(10) bond.

Introduction. The crystal structure of 3 β -hydroxy-17-oxo-5-androsten-19-al was determined as part of a study of the conformation of 19-oxygenated androstenes. A crystal with dimensions 0.1 × 0.4 × 0.6 mm was used for the X-ray measurements of the lattice parameters and intensities. The systematic absences indicated the space group to be $P2_12_12_1$ (D_2^2 , No. 19), and the cell

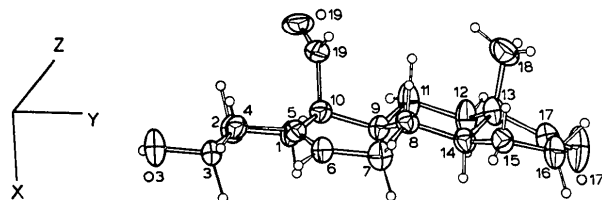


Fig. 1. Observed conformation of 3 β -hydroxy-17-oxo-5-androsten-19-al. The atomic numbering and thermal vibration ellipsoids, scaled to 50% probability, of the non-hydrogen atoms are illustrated.

constants were determined by a least-squares analysis of the 2θ values for 20 reflections with 2θ in the range 60–80° [at 20°C; $\lambda(\text{Cu } K\alpha) = 1.54178$ Å]. Integrated intensities for 1761 independent reflections with $2\theta < 140^\circ$ were measured on an Enraf–Nonius CAD-4 diffractometer using Cu $K\alpha$ radiation. After the Lorentz and polarization corrections $[(1 + \cos^2 2\theta)/2 \sin 2\theta]$ had been applied, normalized structure-factor amplitudes were computed, and the phases were found by the *MULTAN* program (Germain, Main & Woolfson, 1971).

The atomic parameters of 3 β -hydroxy-17-oxo-5-androsten-19-al were refined by block-diagonal least-squares calculations. After three cycles of anisotropic refinement, two successive difference maps were computed, and the hydrogen atoms were located. The parameters for all the atoms including the hydrogens were then refined for three final cycles. Data for which $|F_c|/|F_o|$ was less than 0.5 (57 reflections during the final cycle) were excluded from the refinement, and the quantities $(1/\sigma_f^2)$ were used as weights where σ_f is as defined by Stout & Jensen (1968, equation H. 14) and the instability correction was 0.06 rather than 0.01. The R index was defined as $\sum(|F_o| - |F_c|)/\sum|F_o|$, and its final value was 5.4% for the 1524 reflections with $I > 2\sigma_I$

Table 1. Positional and thermal parameters

(a) Final atomic coordinates and anisotropic thermal parameters for the non-hydrogen atoms. The thermal parameters are of the form $\exp[-2\pi^2(U_{11}h^2a^{*2} + 2U_{12}hka^*b^* + \dots)]$. The standard deviations of the last two figures are given in parentheses.

	X/A	Y/B	Z/C	U ₁₁	U ₂₂	U ₃₃	U ₁₂	U ₁₃	U ₂₃
C(1)	-0.03460(25)	-0.03653(12)	-0.24855(40)	0.0405(14)	0.0329(12)	0.0317(13)	-0.0028(11)	-0.0028(12)	-0.0010(10)
C(2)	-0.05353(26)	-0.10282(13)	-0.29463(46)	0.0493(16)	0.0374(13)	0.0359(14)	-0.0024(13)	-0.0054(14)	-0.0055(12)
C(3)	0.03643(29)	-0.14132(13)	-0.18666(48)	0.0474(16)	0.0330(13)	0.0434(16)	0.0009(12)	-0.0009(15)	-0.0032(13)
C(4)	0.02927(29)	-0.13041(13)	0.03628(48)	0.0491(17)	0.0326(13)	0.0426(15)	-0.0049(12)	0.0006(15)	0.0034(12)
C(5)	0.04716(25)	-0.06467(12)	0.08952(42)	0.0381(14)	0.0319(12)	0.0301(12)	0.0022(11)	0.0017(12)	0.0030(11)
C(6)	0.12611(26)	-0.04759(13)	0.22476(43)	0.0423(14)	0.0365(13)	0.0350(13)	0.0021(12)	-0.0039(13)	0.0038(12)
C(7)	0.14824(26)	0.01629(13)	0.28345(45)	0.0443(15)	0.0371(13)	0.0360(14)	0.0024(12)	-0.0090(14)	-0.0005(12)
C(8)	0.04928(24)	0.05871(11)	0.22351(40)	0.0342(13)	0.0325(12)	0.0295(12)	0.0002(10)	0.0010(11)	-0.0002(10)
C(9)	0.01034(25)	0.04574(11)	0.00717(39)	0.0377(13)	0.0300(12)	0.0298(12)	-0.0006(11)	-0.0024(12)	0.0011(11)
C(10)	-0.03220(23)	-0.02057(11)	-0.02248(39)	0.0334(13)	0.0290(11)	0.0301(12)	-0.0006(10)	-0.0000(11)	0.0004(10)
C(11)	-0.07991(34)	0.09186(14)	-0.06939(54)	0.0724(22)	0.0344(14)	0.0508(17)	0.0006(14)	-0.0268(19)	-0.0039(14)
C(12)	-0.03546(39)	0.15750(14)	-0.04995(53)	0.0864(27)	0.0332(14)	0.0458(18)	0.0041(16)	-0.0231(20)	0.0004(13)
C(13)	-0.00168(31)	0.17035(12)	0.16550(47)	0.0520(17)	0.0342(13)	0.0363(14)	0.0045(12)	-0.0066(14)	-0.0014(12)
C(14)	0.09135(25)	0.12414(12)	0.23399(41)	0.0402(14)	0.0340(12)	0.0297(13)	0.0013(11)	0.0018(13)	-0.0038(11)
C(15)	0.13917(29)	0.15018(14)	0.43012(46)	0.0451(16)	0.0445(15)	0.0365(14)	0.0010(13)	-0.0046(14)	-0.0068(13)
C(16)	0.14819(34)	0.21730(14)	0.38184(54)	0.0703(22)	0.0392(16)	0.0517(19)	-0.0049(15)	-0.0064(20)	-0.0115(15)
C(17)	0.07044(33)	0.22770(14)	0.20362(53)	0.0669(21)	0.0351(13)	0.0443(16)	0.0027(15)	0.0002(16)	-0.0055(14)
C(18)	-0.10991(32)	0.17511(17)	0.30589(69)	0.0488(19)	0.0607(21)	0.0715(24)	0.0173(16)	0.0013(20)	-0.0099(21)
C(19)	-0.15377(26)	-0.02768(13)	0.07051(51)	0.0330(15)	0.0446(15)	0.0429(15)	-0.0001(12)	0.0052(14)	-0.0047(13)
O(1)	0.02066(26)	-0.20434(9)	-0.21709(41)	0.0934(19)	0.0321(10)	0.0585(14)	0.0001(12)	-0.0096(17)	-0.0096(11)
O(19)	0.06576(32)	0.27342(11)	0.10678(40)	0.1234(25)	0.0362(11)	0.0561(15)	-0.0006(14)	-0.0160(19)	0.0002(11)
O(18)	-0.24298(20)	-0.03989(11)	-0.01610(38)	0.0011(99)	0.0016(99)	0.0015(99)	0.0011(51)	0.0012(8)	0.0014(99)

Table 1 (cont.)

(b) Final atomic coordinates for the hydrogen atoms. The average standard deviations of the x , y and z coordinates and the isotropic thermal parameters were 0.004, 0.002, 0.006 and 0.9 respectively.

	x/a	y/b	z/c	B_{iso}
H(1A)	0.044	-0.026	-0.306	1.5
H(1B)	-0.083	-0.012	-0.310	0.6
H(2A)	-0.035	-0.105	-0.416	1.5
H(2B)	-0.143	-0.116	-0.244	1.2
H(3A)	0.132	-0.125	-0.225	4.0
H(4A)	0.100	-0.158	-0.105	3.9
H(4B)	-0.022	-0.139	0.075	1.5
H(6A)	0.176	-0.081	0.277	1.1
H(7A)	0.229	0.032	0.224	0.9
H(7B)	0.155	0.019	0.410	4.8
H(8B)	-0.019	0.057	0.302	2.0
H(9A)	0.076	0.046	-0.073	0.9
H(11A)	-0.114	0.082	-0.191	2.8
H(11B)	-0.159	0.092	0.017	1.8
H(12A)	0.026	0.161	-0.123	3.8
H(12B)	-0.099	0.185	-0.084	3.2
H(14A)	0.157	0.128	0.139	1.2
H(15A)	0.200	0.132	0.480	1.1
H(15B)	0.086	0.147	0.531	3.7
H(16A)	0.239	0.229	0.357	2.5
H(16B)	0.107	0.246	0.498	3.6
H(18A)	-0.077	0.194	0.440	3.4
H(18B)	-0.157	0.139	0.340	3.5
H(18C)	-0.144	0.198	0.253	6.6
H(19)	-0.156	-0.025	0.207	4.7
H(30)	0.005	-0.208	-0.302	5.0

and 6.4% for all data. One hydrogen atom was removed and a final difference Fourier map was calculated. The peak corresponding to this hydrogen was twice as large as any other peak on the map. The final refined positional and thermal parameters are given in Table 1.*

Discussion. The crystallographically observed conformation of 3β -hydroxy-17-oxo-5-androsten-19-al is shown in Fig. 1. This figure also illustrates the atomic numbering and the non-hydrogen thermal vibration ellipsoids scaled to 50% probability. The interatomic distances, bond angles and endocyclic torsion angles involving the nonhydrogen atoms are given in Fig. 2, and there are no unusual values. The standard deviations of the distance and angle measurements are in the ranges 0.003–0.005 Å and 0.18–0.27°, respectively. The endocyclic torsion angles show that the *A* and *C* rings have normal chair conformations, and the *B* ring conformation is close to a perfect 7α , 8β half-chair. The *D* ring conformation is intermediate between a 13β , 14α half-chair and a 14α envelope as shown by parameters $\Delta = -13.7$ and $\varphi_m = 45.4$ (Altona, Geise & Romers,

1968). There are no unusual intermolecular contacts between nonhydrogen atoms. The O(3) hydroxyl forms a 2.83 Å hydrogen bond with O(17).

Estrogens are synthesized *in vivo* by the enzymatic

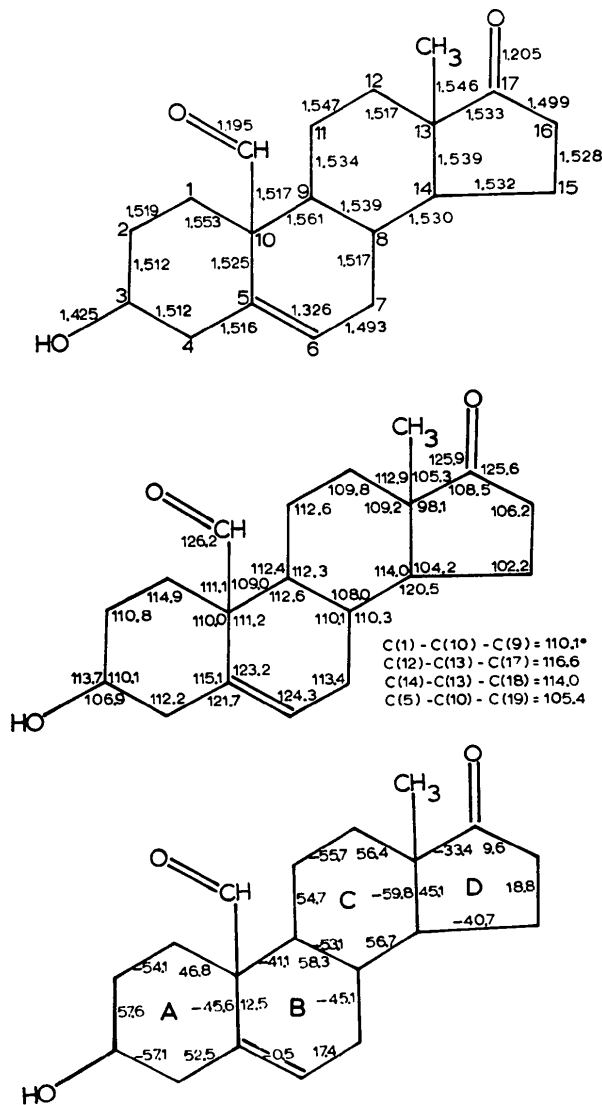


Fig. 2. Intramolecular geometry for 3β -hydroxy-17-oxo-5-androsten-19-al. (a) Interatomic distances. (b) Bond angles. (c) Endocyclic torsion angles.

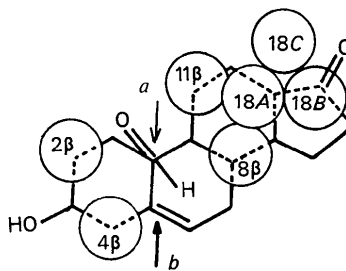


Fig. 3. Directions of probable access of reagents to the C(19) atom.

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31110 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England. A table containing the torsion angles involving non-hydrogen atoms not included in Fig. 2 has also been deposited.

aromatization of Δ^4 - and Δ^5 -androstene precursors. This reaction involves several successive oxidations and the formation of 19-hydroxy and 19,19-dihydroxy intermediates. There have been conflicting reports concerning the conformational stereochemistry of C(19) in these intermediates (Skinner & Akhtar, 1969; Osawa, 1972). This stereochemistry depends on the conformation of the 19-oxo moiety in the precursor as well as the steric hindrance involved in the various directions of approach to the carbonyl group. The present investigation shows that the conformer in which the oxo group eclipses the C(1)–C(10) bond is the minimum energy form in the solid state of 3 β -hydroxy-17-oxo-5-androsten-19-al [torsion angle C(1)–C(10)–C(19)–O(19) = 4.7°]. Comparative analysis of 165 steroids indicates that crystallographically observed conformations are primarily intramolecularly controlled and undistorted by packing forces (Duax, Weeks, Rohrer, Osawa & Wolff, 1975; Duax, Weeks & Rohrer, 1975). While Δ^5 -steroids have some flexibility in the B ring, substituents such as the 19-aldehyde restrict this flexibility, and the β -axial hydrogen atoms at C(2), C(4), C(8), and C(11) restrict the freedom of rotation of the 19-oxygen substituent. The O(19) atom in five of the six 19-mono-oxygenated steroids examined crystallographically lies between C(1), C(9), and C(11) with the C(19)–O(19) bond ranging from a position eclipsing the C(1)–C(10) bond in the present structure to a position *trans* to the C(5)–C(10) bond (Duax, Weeks & Rohrer, 1975). Consequently, the crystallographically observed conformation of 3 β -hydroxy-17-oxo-5-androsten-19-al is suggested as a suitable model

upon which to base the development of proposed reaction mechanisms. On the basis of steric considerations alone, the β -hydrogens at C(2), C(4), C(8), and C(11) hinder the approach of reagents to the 19-carbonyl from either the *A* or *C* ring sides. The distances between the β -axial hydrogens H(4 β) \cdots H(8) and H(2 β) \cdots H(11 β) are 4.9 Å and 4.6 Å respectively. Therefore, differentiation between the remaining directions of approach (Fig. 3) is not possible solely on the basis of this structure determination.

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Naphthalene–Octafluoronaphthalene, 1:1 Solid Compound

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Abstract. C₁₀H₈·C₁₀F₈, monoclinic, $P2_1/c$, $a = 7.457$ (5), $b = 8.503$ (2), $c = 12.710$ (2) Å, $\beta = 99.48$ (5)°, $Z = 2$, $D_o = 1.65$ (1), $D_c = 1.671$ g cm⁻³. The relative orientation of nearly parallel naphthalene and octafluoronaphthalene molecules within infinite columns closely resembles the stacking found in ordinary, hexagonal graphite. Within experimental error, both molecules exhibit D_{2h} symmetry and chemically equivalent C–C distances in naphthalene are equal to those in octafluoronaphthalene.

Introduction. White needle-like crystals of the title complex [m.p. 132 (1)°C] were prepared by evaporation of an acetone solution containing equimolar amounts of naphthalene and octafluoronaphthalene.

Elemental analysis (calculated for C₁₀H₈·C₁₀F₈: C 60.01, H 2.01%. Found: C 61.04, H 2.02%) was consistent with formulation of the compound as a 1:1 complex. A single crystal, 0.6 × 0.2 × 0.2 mm, mounted in a sealed glass capillary to prevent sublimation, was used. Preliminary Weissenberg photographs revealed systematic absences $h0l$, $l = 2n + 1$ and $0k0$, $k = 2n + 1$, fixing the space group as $P2_1/c$. With the assumption of a half formula unit per asymmetric unit, the observed (flotation) and calculated densities agreed well. Intensities were collected at 21 ± 2°C on a CAD-3 automated diffractometer (θ – 2θ scan) with Ni-filtered Cu $K\alpha$ radiation. Of the 1700 diffraction maxima recorded ($4 < 2\theta < 140^\circ$), 970 with $F^2 \geq 2\sigma$ (counting statistics) were considered observed, L_p corrected, and used in