2α-Hydroxytestosterone Diacetate

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Abstract. $C_{23}H_{32}O_5$, orthorhombic, $P2_12_12_1$, $a=22{\cdot}274$ (7), $b=7{\cdot}723$ (2), $c=12{\cdot}453$ (3) Å, $Z=4$, $M=388{\cdot}51$, $D_c=1{\cdot}20$, $D_m=1{\cdot}18$ g cm^{-3}, m.p. 200°C. The *A* ring has a normal half-chair conformation in contrast to the inverted half-chair conformation observed in 2β-hydroxytestosterone esters.

Introduction. The crystal structure of 2α-hydroxytestosterone diacetate (2α,17β-diacetoxy-4-androsten-3-one) was determined as part of an investigation of the solid and solution conformations of the *A* ring in 2-substituted Δ^4-3-keto steroids. 2α-Hydroxytestosterone diacetate was obtained by repeated recrystallization, from methanol, of the acetoxylation products of 6β-bromotestosterone acetate according to Clarke, Dobriner, Mooradian & Martini (1955), and suitable single crystals were also grown from methanol solution. X-ray diffraction measurements of the unit-cell parameters and intensities were carried out on a GE XRD-5 diffractometer. The systematic absences indicated the space group to be $P2_12_12_1$ (D_2^4, No. 19), and the cell constants were determined by a least-squares analysis of the 2θ values of 23 reflections having 2θ in the range 50–70° [at 20°C; λ(Cu *Kα*) = 1·54178 Å]. The intensities of the 2107 independent reflections with $2\theta < 130°$ were measured by the stationary-counter–stationary-crystal technique using Cu *Kα* radiation monochromated by balanced nickel and cobalt filters. Normalized structure-factor amplitudes were computed after the Lorentz and polarization corrections $[(1+\cos^2 2\theta)/2 \sin 2\theta]$ had been applied.

The structure was solved by direct methods. A set of 69 phases was found by manual analysis of the $\sum_2$ relationships after calculation of the cosine invariants by means of the triple product and MDKS formulas (Hauptman, 1972) had been used to eliminate unreliable relationships. Approximately 200 additional phases were found by the tangent formula, and an *E*-map calculated using these phases revealed a 23-atom molecular fragment. It was necessary to translate this fragment by 4·9 Å parallel to the *x* axis before the remaining nonhydrogen atoms could be located. The *Q* function (Tollin, 1966) was used to find the correct molecular position. The hydrogen atoms were found

Table 1. *Atomic coordinates and temperature factors*

(*a*) Final atomic coordinates (×10^5) and anisotropic thermal parameters (×10^4) for the non-hydrogen atoms. The thermal parameters are of the form $\exp[-2\pi^2(U_{11}h^2a^{*2}+2U_{12}hka^*b^*+\ldots)]$. The standard deviations of the last two figures are given in parentheses.

	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	55857 (40)	36105 (23)	−23480 (66)	648 (27)	581 (25)	564 (26)	−23 (23)	7 (25)	12 (23)
C(2)	66646 (44)	32933 (23)	−21726 (82)	728 (30)	552 (25)	788 (34)	10 (24)	13 (31)	−55 (27)
C(3)	70440 (46)	33102 (25)	−3228 (94)	689 (31)	631 (28)	943 (43)	38 (26)	−88 (34)	37 (31)
C(4)	62309 (45)	32150 (26)	9818 (86)	674 (31)	802 (34)	799 (36)	10 (29)	−70 (32)	106 (32)
C(5)	51685 (44)	32012 (21)	6188 (69)	722 (30)	549 (25)	594 (27)	−5 (23)	−16 (27)	122 (23)
C(6)	43721 (52)	30294 (29)	20049 (81)	840 (36)	978 (40)	625 (32)	4 (34)	−79 (32)	235 (32)
C(7)	34422 (47)	34851 (29)	21120 (75)	833 (35)	856 (36)	558 (29)	19 (31)	60 (31)	59 (29)
C(8)	29020 (39)	35746 (22)	3577 (62)	629 (26)	569 (23)	509 (25)	−138 (23)	−15 (23)	−16 (22)
C(9)	37564 (37)	37686 (20)	−10191 (59)	575 (24)	553 (23)	441 (21)	−101 (21)	−34 (22)	−41 (20)
C(10)	47220 (39)	33203 (21)	−11711 (65)	610 (26)	593 (25)	539 (25)	−116 (23)	−84 (24)	−26 (22)
C(11)	32411 (42)	38960 (25)	−27958 (67)	668 (28)	738 (30)	527 (27)	12 (25)	−26 (26)	20 (26)
C(12)	23062 (49)	43487 (25)	−26628 (71)	858 (36)	742 (32)	556 (29)	−18 (26)	−60 (30)	71 (26)
C(13)	14561 (38)	41405 (20)	−13573 (71)	590 (26)	465 (21)	708 (30)	−135 (21)	−35 (25)	27 (23)
C(14)	20313 (44)	40344 (21)	3954 (69)	733 (30)	555 (25)	634 (31)	−164 (24)	104 (28)	3 (24)
C(15)	10983 (49)	39654 (29)	16844 (83)	781 (35)	844 (35)	746 (35)	−149 (32)	97 (33)	1 (32)
C(16)	2142 (55)	43947 (29)	9779 (97)	854 (38)	814 (36)	902 (43)	−28 (33)	216 (39)	−82 (34)
C(17)	6406 (43)	46125 (21)	−8441 (77)	701 (29)	494 (23)	759 (32)	−105 (23)	117 (30)	−62 (24)
C(18)	8712 (49)	35666 (24)	−19473 (86)	826 (34)	542 (25)	899 (39)	20 (27)	−89 (36)	−81 (30)
C(19)	43812 (49)	27152 (23)	−19880 (84)	853 (35)	513 (24)	824 (35)	−59 (26)	−27 (35)	−69 (28)
C(20)	78216 (52)	32651 (25)	−46161 (91)	899 (39)	592 (27)	881 (42)	128 (29)	−89 (37)	−114 (30)
C(21)	86236 (49)	36019 (31)	−56173 (83)	787 (34)	940 (38)	726 (35)	3 (33)	169 (34)	−64 (33)
C(22)	−8655 (55)	51406 (28)	−19627 (99)	870 (39)	680 (33)	1151 (52)	−95 (31)	−12 (46)	30 (38)
C(23)	−17066 (65)	51372 (32)	−33399 (99)	992 (45)	869 (42)	1337 (64)	219 (38)	−66 (53)	56 (47)
O(2)	74359 (32)	35739 (17)	−32726 (54)	784 (22)	628 (18)	856 (25)	−30 (19)	255 (23)	−120 (20)
O(3)	79895 (33)	34089 (25)	341 (75)	667 (23)	1234 (36)	1052 (34)	34 (25)	−108 (26)	136 (30)
O(17)	−2026 (31)	46750 (16)	−20996 (56)	737 (21)	590 (19)	854 (25)	42 (17)	−53 (22)	−67 (19)
O(20)	75146 (70)	27638 (24)	−48627 (76)	2171 (65)	902 (30)	1063 (38)	−288 (41)	689 (48)	−262 (31)
O(22)	−7587 (50)	55131 (22)	−8580 (90)	1297 (39)	866 (30)	1496 (48)	256 (31)	−203 (45)	−333 (34)

Table 1 (*cont.*)

(*b*) Final atomic coordinates for the hydrogen atoms ($\times 10^3$). The average refined value for B_{iso} was 4·5 Å^2, and the average standard deviations of the *x*, *y*, and *z* coordinates and the isotropic thermal parameters were 0·005, 0·003, 0·009 Å, and 1·44 Å^2 respectively.

	x	*y*	*z*
H(1*A*)	562	402	−215
H(1*B*)	534	376	−347
H(2*B*)	655	288	−233
H(4)	644	312	245
H(6*A*)	473	294	318
H(6*B*)	409	255	186
H(7*A*)	348	388	236
H(7*B*)	286	336	288
H(8*B*)	256	323	3
H(9*A*)	403	414	−67
H(11*A*)	381	406	−335
H(11*B*)	299	350	−351
H(12*A*)	252	466	−220
H(12*B*)	195	436	−366
H(14*A*)	227	440	57
H(15*A*)	143	406	287
H(15*B*)	78	359	180
H(16*A*)	30	474	157
H(16*B*)	−51	413	57
H(17*A*)	92	505	−45
H(18*A*)	31	339	−90
H(18*B*)	140	326	−209
H(18*C*)	88	362	−266
H(19*A*)	380	256	−144
H(19*B*)	468	243	−197
H(19*C*)	406	277	−307
H(21*A*)	834	396	−602
H(21*B*)	926	365	−514
H(21*C*)	877	344	−672
H(23*A*)	−210	501	−286
H(23*B*)	−146	490	−429
H(23*C*)	−196	548	−368

on a Fourier difference map computed after the positional and anisotropic thermal parameters for the non-hydrogen atoms had been refined by four cycles of block-diagonal least-squares calculations. The parameters for all the atoms including the hydrogens were then refined for four final cycles using data (1665 reflections during the final cycle) for which $\sin\theta/\lambda > 0{\cdot}15$ and $|F_c|/|F_o| > 0{\cdot}7$. Weights were chosen so that $\langle w\Delta^2\rangle$ would be independent of $|F_o|$ where $w^{-1} = \{1+[(|F_o|-b)/a]^2\}$ and the constants *a* and *b* were taken to be 7 and 4 respectively. The *R* index was defined as $\sum(||F_o|-|F_c||)/\sum|F_o|$, and its final value was 6·0% for the 1273 reflections having $I > 3\sigma$ and 9·1% for all data. The final refined positional and thermal parameters are given in Table 1.*

Discussion. The crystallographically observed conformation of 2α-hydroxytestosterone diacetate 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 and bond 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 0·006–0·012 Å and

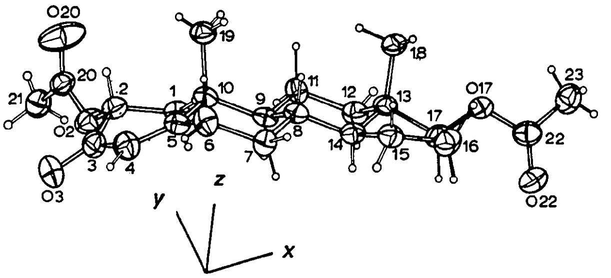

Fig. 1. Conformation of 2α-hydroxytestosterone diacetate. The atomic numbering and thermal vibration ellipsoids, scaled to 50% probability, of the nonhydrogen atoms are illustrated.

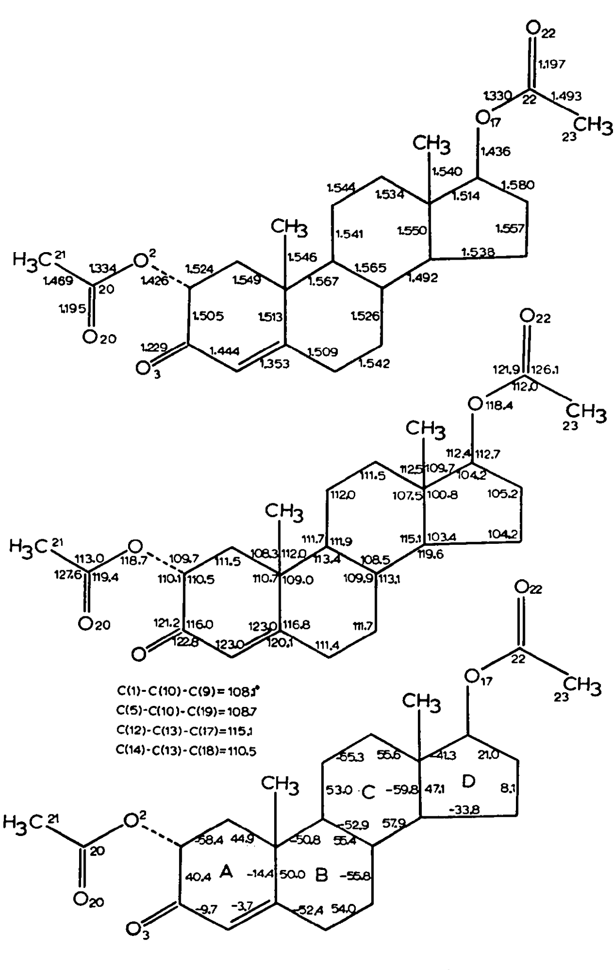

Fig. 2. Intramolecular geometry for 2α-hydroxytestosterone diacetate. (*a*) Interatomic distances (Å). (*b*) Bond angles (°). (*c*) Intraring torsional angles with sign convention of Klyne & Prelog (1960).

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* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30876 (11 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 2. *Torsional angles*

All torsional angles involving nonhydrogen atoms which are not included in Fig. 2(*c*) are listed here. φ is the torsional angle *i–j–k–l*. The sign convention of Klyne & Prelog (1960) is used.

i	*j*	*k*	*l*	φ	*i*	*j*	*k*	*l*	φ	*i*	*j*	*k*	*l*	φ
C(10)	C(1)	C(2)	O(2)	−180·0°	C(7)	C(8)	C(9)	C(10)	55·5°	C(18)	C(13)	C(14)	C(8)	63·4°
C(2)	C(1)	C(10)	C(9)	164·2	C(7)	C(8)	C(9)	C(11)	−177·1	C(18)	C(13)	C(14)	C(15)	−68·8
C(2)	C(1)	C(10)	C(19)	−74·2	C(14)	C(8)	C(9)	C(10)	180·0	C(12)	C(13)	C(17)	C(16)	−156·7
C(1)	C(2)	C(3)	O(3)	−138·5	C(7)	C(8)	C(14)	C(13)	−180·0	C(12)	C(13)	C(17)	O(17)	81·0
O(2)	C(2)	C(3)	C(4)	161·7	C(7)	C(8)	C(14)	C(15)	−55·9	C(14)	C(13)	C(17)	O(17)	−163·6
O(2)	C(2)	C(3)	O(3)	−17·2	C(9)	C(8)	C(14)	C(15)	−178·1	C(18)	C(13)	C(17)	C(16)	75·2
C(1)	C(2)	O(2)	C(20)	−113·2	C(8)	C(9)	C(10)	C(1)	−171·3	C(18)	C(13)	C(17)	O(17)	−47·1
C(3)	C(2)	O(2)	C(20)	125·1	C(8)	C(9)	C(10)	C(19)	69·5	C(8)	C(14)	C(15)	C(16)	−163·3
O(3)	C(3)	C(4)	C(5)	169·2	C(11)	C(9)	C(10)	C(1)	61·2	C(15)	C(16)	C(17)	O(17)	143·1
C(3)	C(4)	C(5)	O(6)	173·0	C(11)	C(9)	C(10)	C(5)	−178·4	C(13)	C(17)	O(17)	C(22)	−168·6
C(4)	C(5)	C(6)	C(7)	130·7	C(11)	C(9)	C(10)	C(19)	−58·1	C(16)	C(17)	O(17)	C(22)	74·0
C(4)	C(5)	C(10)	C(9)	−133·2	C(10)	C(9)	C(11)	C(12)	−178·7	C(21)	C(20)	O(2)	C(2)	−178·8
C(4)	C(5)	C(10)	C(19)	104·4	C(11)	C(12)	C(13)	C(17)	167·1	O(20)	C(20)	O(2)	C(2)	0·0
C(6)	C(5)	C(10)	C(1)	168·8	C(11)	C(12)	C(13)	C(18)	−66·3	C(23)	C(22)	O(17)	C(17)	−179·0
C(6)	C(5)	C(10)	C(19)	−72·3	C(12)	C(13)	C(14)	C(15)	168·1	O(22)	C(22)	O(17)	C(17)	2·0
C(6)	C(7)	C(8)	C(14)	−177·3	C(17)	C(13)	C(14)	C(8)	180·0					

0·35–0·55°, respectively. The intra-ring torsional angles given in Fig. 2(*c*) show that the *B* and *C* rings have normal chair conformations, and the *D* ring conformation is intermediate between a 13β,14α half-chair and a 13β envelope, as shown by the pseudorotation parameters $\Delta = 16·0$ and $\varphi_m = 47·6$ (Altona, Geise & Romers, 1968). The torsional angles not included in Fig. 2(*c*) are given in Table 2, and the intermolecular distances less than 3·5 Å are given in Table 3.

Table 3. *Intermolecular non-hydrogen distances less than* 3·5 Å

The equivalent positions are $1 = x,y,z$, $2 = \frac{1}{2}-x,\bar{y},\frac{1}{2}+z$, $3 = \frac{1}{2}+x,\frac{1}{2}-y,\bar{z}$, and $4 = \bar{x},\frac{1}{2}+y,\frac{1}{2}-z$.

	Distance	Position
C(1)—O(22)	3·348 Å	$2/01\bar{1}$
C(19)–O(3)	3·399	$3/\bar{1}00$
C(21)–O(3)	3·477	$1/00\bar{1}$

Several investigators found that the o.r.d. curves of 2β-substituted Δ^4-3-keto steroids such as 2β-hydroxytestosterone show inverted Cotton effects relative to the 2α-substituted and 2-unsubstituted compounds (Patashnik, Kimball & Burstein, 1963; Kuriyama, Kondo & Tori, 1963). It was proposed that these spectral differences resulted from differences in *A* ring conformation. X-ray analysis of testosterone (Roberts, Pettersen, Sheldrick, Isaacs & Kennard, 1973; Busetta, Courseille, Leroy & Hospital, 1972; Precigoux, Hospital & van den Bosche, 1973) showed the *A* ring conformation to be a 1α,2β half-chair, whereas 2β-hydroxytestosterone diacetate and 2β-hydroxytestosterone 2-acetate 17-chloroacetate were found to have inverted or 1β,2α half-chair conformations (Duax, Eger, Pokrywiecki & Osawa, 1971). The present structure determination shows that, in agreement with solution spectral data, the 2α-hydroxytestosterone diacetate *A* ring has the 1α,2β half-chair conformation observed in testosterone.

Atom C(2) is approximately coplanar with the atoms in the 2α-acetate, and C(17) lies in the plane of the 17β-acetate. The conformations about the O(2)–C(20) and O(17)–C(22) bonds are both *syn*-periplanar [torsional angles C(2)–O(2)–C(20)–O(20) = 0° and C(17)–O(17)–C(22)–O(22) = 2°]. The 17β-acetate is *anti*-periplanar to the C(13)–C(17) bond as shown by the torsional angle C(13)–C(17)–O(17)–C(22) of −168·6°. Analogous torsional angles in approximately 20 other steroid structures having 17β-acetates lie in the range −90° to −180° (Duax & Norton, 1975).

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