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Structure of 4-Hydroxy-4-androstene-3,17-dione

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Abstract. $C_{19}H_{26}O_3$, $P2_12_12_1$, $a = 18{\cdot}540\,(1)$, $b = 24{\cdot}348\,(4)$, $c = 7{\cdot}3237\,(6)$ Å, $V = 3306{\cdot}1$ Å^3, $M_r = 302{\cdot}41$, $Z = 8$, $D_c = 1{\cdot}22$ Mg m^{-3}; 3843 observations, $3114 > 2\sigma_F$. 4-Hydroxy-4-androstene-3,17-dione (4-OH-A) is an effective inhibitor of estrogen synthetase and has been shown to be effective in controlling estrogen-dependent reproductive and neoplastic processes [Brodie, Schwarzel, Shaikh & Brodie (1977). *Endocrinology*, **100**, 1684–1685]. The structure determination was undertaken as part of a study on the structural requirements for the aromatase system. The structure contains hydrogen-bonded dimers.

Introduction. Crystals of 4-hydroxy-4-androstene-3,17-dione were grown from ethyl acetate. A crystal approximately 0·20 × 0·22 × 0·80 mm was used for the collection of 3843 reflections on an Enraf–Nonius CAD-4 diffractometer. Cell constants were determined by least-squares analysis of the 2θ values for 22 independent reflections in the interval $72{\cdot}36° < 2\theta < 79{\cdot}52°$ with Cu $K\alpha$ radiation, $\lambda = 1{\cdot}5418$ Å.

The structure was solved through a routine application of *MULTAN* (Germain, Main & Woolfson, 1971) and NQEST (DeTitta, Edmonds, Langs & Hauptman, 1975). The E map generated from the solution with the highest absolute figure of merit and the most negative NQEST revealed 40 of a possible 44 skeletal atoms. The four remaining atoms were located in the Fourier synthesis based on this model. Full-matrix least-squares refinement of the 44 atoms, three cycles isotropically and two cycles anisotropically, reduced the R factor to 0·086. All 52 H atoms were found in the difference Fourier map computed at this point. Anisotropic refinement of skeletal atoms with isotropic refinement of H atoms resulted in a final R of 0·043 for 3114 data $>2\sigma_F$ and 0·066 for all 3843 data.† The function minimized in the least-squares procedure was $\sum w(|F_o| - |F_c|)^2$ where $w = 1/\sigma^2_{F_o}$ and σ_{F_o} is defined in Stout & Jensen (1968, equation $H14$) with an instability factor of 0·06. The scattering factors

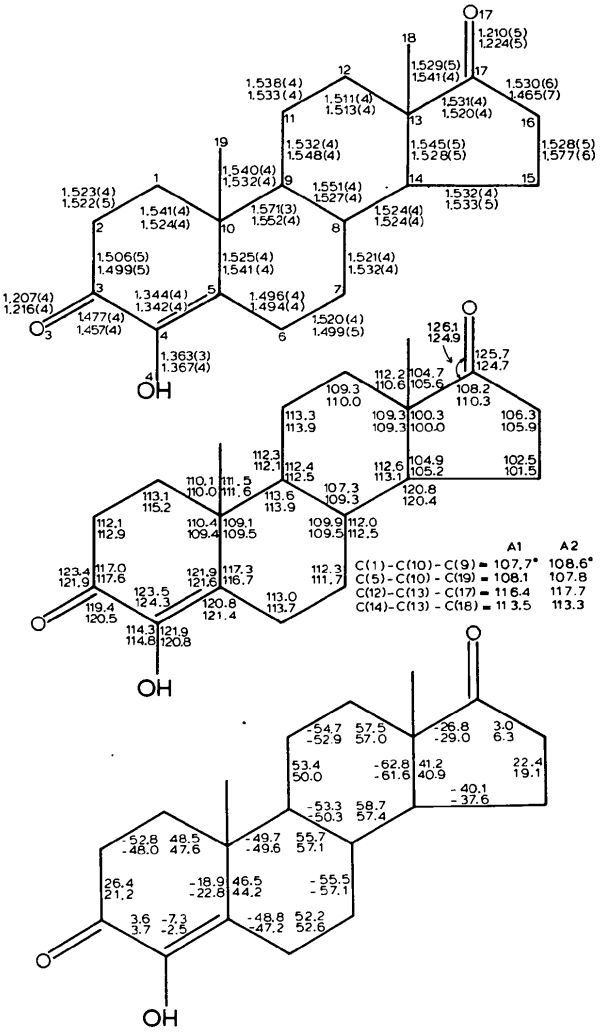

Fig. 1. Bond distances (Å), angles (°), and torsion angles (°) for the two independent molecules of 4-OH-A. The upper value of each pair of numbers is for the unprimed molecule, the bottom value for the primed. E.s.d.'s for bond angles are 0·2–0·3°, for torsion angles, 0·3–0·5°.

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† Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34747 (20 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Table 1. *Fractional atomic coordinates* ($\times 10^4$, *for* H $\times 10^3$)

	x	*y*	*z*		*x*	*y*	*z*
C(1)	9807 (2)	8599 (1)	6589 (4)	C(1′)	8101 (2)	5419 (1)	3434 (5)
C(2)	10614 (2)	8648 (2)	6942 (4)	C(2′)	7374 (2)	5686 (2)	3822 (5)
C(3)	10784 (2)	8689 (1)	8948 (4)	C(3′)	7267 (2)	5818 (1)	5802 (5)
C(4)	10262 (1)	8439 (1)	10225 (4)	C(4′)	7909 (2)	5866 (1)	6941 (4)
C(5)	9675 (1)	8159 (1)	9682 (4)	C(5′)	8587 (2)	5829 (1)	6315 (4)
C(6)	9240 (2)	7834 (1)	11019 (4)	C(6′)	9219 (2)	5959 (1)	7504 (4)
C(7)	8433 (1)	7922 (1)	10811 (4)	C(7′)	9837 (2)	5567 (2)	7286 (4)
C(8)	8179 (1)	7833 (1)	8858 (4)	C(8′)	10059 (1)	5506 (1)	5281 (4)
C(9)	8611 (1)	8209 (1)	7544 (3)	C(9′)	9411 (1)	5318 (1)	4157 (4)
C(10)	9450 (1)	8131 (1)	7681 (4)	C(10′)	8749 (2)	5706 (1)	4292 (4)
C(11)	8338 (2)	8173 (1)	5573 (4)	C(11′)	9613 (2)	5187 (1)	2153 (4)
C(12)	7523 (2)	8278 (1)	5393 (4)	C(12′)	10265 (2)	4805 (1)	1957 (5)
C(13)	7119 (1)	7891 (1)	6639 (5)	C(13′)	10897 (1)	5029 (1)	3030 (5)
C(14)	7383 (1)	7973 (1)	8621 (4)	C(14′)	10677 (2)	5100 (1)	5026 (5)
C(15)	6807 (2)	7698 (1)	9809 (5)	C(15′)	11386 (2)	5176 (2)	6072 (6)
C(16)	6108 (2)	7862 (1)	8850 (7)	C(16′)	11899 (2)	4766 (2)	5029 (7)
C(17)	6312 (2)	8001 (1)	6881 (6)	C(17′)	11554 (2)	4662 (1)	3262 (6)
C(18)	7162 (2)	7295 (1)	5989 (6)	C(18′)	11182 (2)	5562 (1)	2153 (5)
C(19)	9688 (2)	7571 (1)	6917 (5)	C(19′)	8888 (2)	6255 (1)	3330 (5)
O(3)	11338 (1)	8881 (1)	9536 (4)	O(3′)	6671 (1)	5899 (1)	6443 (3)
O(4)	10461 (1)	8467 (1)	12014 (3)	O(4′)	7776 (1)	5990 (1)	8730 (3)
O(17)	5903 (1)	8165 (1)	5715 (5)	O(17′)	11769 (1)	4331 (1)	2128 (6)
H(1*A*)	957 (2)	901 (1)	701 (5)	H(1*A*′)	807 (1)	502 (1)	403 (5)
H(1*B*)	974 (1)	858 (1)	533 (4)	H(1*B*′)	813 (1)	533 (1)	200 (4)
H(2*A*)	1088 (2)	885 (1)	602 (5)	H(2*A*′)	691 (2)	544 (1)	376 (5)
H(2*B*)	1083 (2)	832 (1)	662 (5)	H(2*B*′)	736 (2)	595 (1)	349 (4)
H(6*A*)	940 (2)	789 (1)	1206 (5)	H(6*A*′)	910 (2)	604 (1)	865 (5)
H(6*B*)	935 (1)	742 (1)	1067 (5)	H(6*B*′)	941 (2)	634 (1)	709 (5)
H(7*A*)	831 (1)	827 (1)	1125 (4)	H(7*A*′)	967 (1)	517 (1)	756 (5)
H(7*B*)	818 (1)	765 (1)	1168 (4)	H(7*B*′)	1025 (2)	572 (1)	787 (5)
H(8*B*)	824 (1)	743 (1)	839 (4)	H(8*B*′)	1025 (1)	588 (1)	489 (4)
H(9*A*)	855 (1)	859 (1)	810 (4)	H(9*A*′)	927 (1)	501 (1)	463 (4)
H(11*A*)	856 (2)	849 (1)	487 (5)	H(11*A*′)	921 (1)	499 (1)	173 (5)
H(11*B*)	848 (1)	784 (1)	507 (4)	H(11*B*′)	978 (2)	552 (1)	156 (5)
H(12*A*)	740 (2)	867 (1)	569 (4)	H(12*A*′)	1012 (2)	443 (1)	230 (5)
H(12*B*)	738 (2)	824 (1)	416 (5)	H(12*B*′)	1037 (2)	471 (1)	42 (5)
H(14*A*)	737 (2)	839 (1)	883 (5)	H(14*A*′)	1048 (1)	471 (1)	524 (4)
H(15*A*)	682 (2)	781 (1)	1111 (5)	H(15*A*′)	1137 (2)	510 (1)	734 (5)
H(15*B*)	690 (2)	726 (1)	965 (5)	H(15*B*′)	1156 (2)	556 (1)	596 (4)
H(16*A*)	595 (1)	815 (1)	927 (5)	H(16*A*′)	1198 (2)	443 (1)	611 (5)
H(16*B*)	572 (2)	760 (1)	880 (5)	H(16*B*′)	1233 (2)	498 (1)	466 (6)
H(18*A*)	769 (2)	715 (1)	607 (5)	H(18*A*′)	1084 (1)	582 (1)	210 (4)
H(18*B*)	690 (1)	705 (1)	677 (4)	H(18*B*′)	1158 (2)	571 (1)	266 (4)
H(18*C*)	700 (1)	722 (1)	495 (4)	H(18*C*′)	1132 (2)	547 (1)	93 (4)
H(19*A*)	1015 (1)	752 (1)	705 (4)	H(19*A*′)	847 (2)	653 (1)	354 (4)
H(19*B*)	949 (2)	728 (1)	736 (5)	H(19*B*′)	926 (2)	641 (1)	374 (5)
H(19*C*)	950 (2)	750 (1)	589 (5)	H(19*C*′)	893 (2)	626 (1)	190 (5)
H(4O)	1080 (2)	848 (1)	1210 (5)	H(4O′)	738 (2)	599 (1)	887 (5)

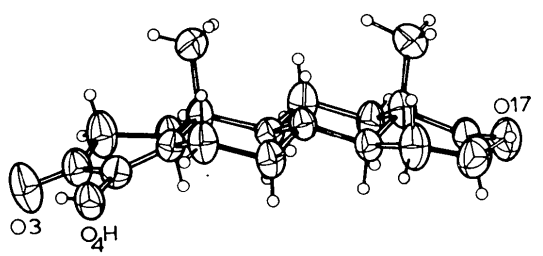

Fig. 2. Molecular structure of 4-OH-A (unprimed molecule). Thermal ellipsoids of non-hydrogen atoms are drawn at the 50% probability level and H atoms were given an arbitrary temperature parameter.

for C, O and H used in the least-squares refinement are from *International Tables for X-ray Crystallography* (1974). The final positional parameters are given in Table 1, and the bond distances, angles, and torsion angles computed from them are shown in Fig. 1. An *ORTEP* (Johnson, 1965) view of one molecule is depicted in Fig. 2.

Discussion. The structure consists of hydrogen-bonded dimers which have only van der Waals interactions with other dimers, *cf.* Fig. 3. The packing appears to be

Table 2. *Probability-plot comparisons of two independent molecules of* 4-OH-A

Values compared	Maximum Δ real	Slope	Intercept	Number of Δ real >4	Total number of points
(*a*) Distances <2·5 Å, all atoms	7·0	2·76	−0·0032	4	43
(*b*) Distances <4·6 Å, all atoms	8·0	2·95	+0·03	18	139
(*c*) Distances <4·65 Å, C(5)–C(15)	6·0	2·37	−0·04	3	49
(*d*) Distances <13 Å, all atoms	19·7	5·92	−0·8804	72	231

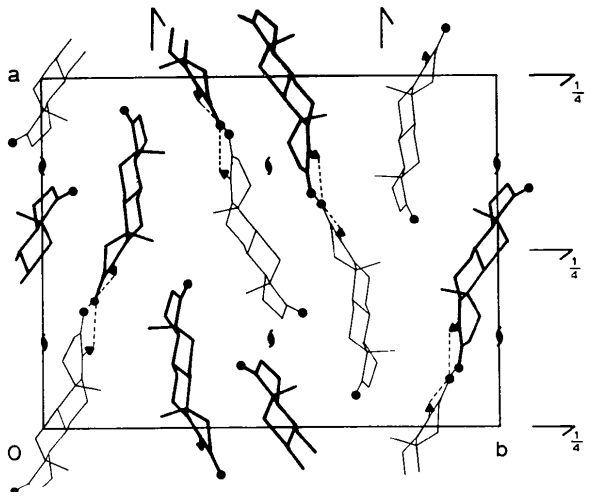

Fig. 3. [001] projection of 4-OH-A. Hydrogen-bonded dimers can be seen clearly in this projection.

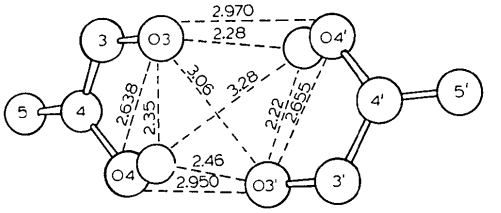

Fig. 4. Hydrogen bonding between two independent molecules of 4-OH-A.

controlled by the overall shape of the dimers. The geometry of the α-hydroxy region of the dimers, seen in detail in Fig. 4, indicates that O(3′) appears to interact both intermolecularly with H(O4), and intramolecularly with H(O4′): O(4′)–H(O4′)···O(3′) = 118°; O(4)–H(O4)···O(3′) = 136°.

Are the two molecules in the asymmetric unit identical within the limits of the accuracy of the experiment? The half-normal probability plot is a means of testing the hypothesis (Abrahams & Keve, 1971; De Camp, 1973). Random errors in interatomic distances should be normally distributed and result in a linear plot passing through the origin. Four half-normal probability plots were calculated and the results are given in Table 2; from the slopes of (*a*)–(*c*) it is clear that the standard deviations from the least-squares matrix have been underestimated by a factor of about 2·5. It is in looking at the long-range distances, however, that the fact that there are truly two different conformers is most evident. The regions of variance are ring *A*, due to the flexibility introduced by the C(4)–C(5) double bond, and ring *D*, a five-membered ring which has inherent flexibility.

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