

## Conformational Analysis of Synthetic Androgens. V. 17 $\beta$ -Hydroxy-9 $\alpha$ -methyl-4,14-estradien-3-one

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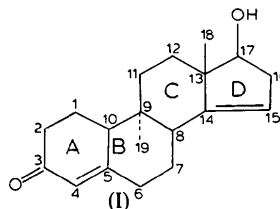
### Abstract

$C_{19}H_{26}O_2$ ,  $M_r = 286.4$ , is monoclinic,  $P2_1$ , with  $a = 17.608$  (1),  $b = 12.8805$  (7),  $c = 7.0992$  (5) Å,  $\beta = 91.329$  (6) $^\circ$  ( $\lambda = 1.5418$  Å,  $T = 291$  K),  $V = 1609.7$  Å<sup>3</sup>,  $Z = 4$ ,  $\rho_x = 1.18$  Mg m<sup>-3</sup>. The 9 $\alpha$ -methyl substituent causes the *A* ring to be closer to the least-squares plane of the *B* and *C* rings than it is in the parent compound. The two molecules in the asymmetric unit have significant differences in their *D* and *A* rings. The differences in the *D* ring are associated with differences in 17-hydroxyl H atom positions and allied hydrogen bonding. The different *A* rings may represent conformational isomers of comparable stability.

### Introduction

The 7 $\alpha$ -methylation of 19-nortestosterone produces a substantial increase in its systemic androgenicity as measured by the castrate rat ventral prostate and the introduction of a 14,15 double bond in this compound produces a further substantial increase in its androgenicity. In contrast, 9 $\alpha$ -methylation of 19-nortestosterone reduces the ventral prostate stimulating activity to approximately 10% that of testosterone. Although double-bond introduction at the 14,15 position of this compound restores much of this activity it still remains at 40% of the activity of testosterone (Segaloff & Gabbard, 1973). The structure determination of 17 $\beta$ -hydroxy-9 $\alpha$ -methyl-4,14-estradien-3-one (I) was undertaken in order to evaluate conformational-transmission effects and the dependence of androgenicity upon steroid conformation. Of particular interest in this structure is the influence of 9 $\alpha$ -methyl substitution on the *A* ring conformation and the overall shape of the steroid molecule. Crystallographic diffraction data were measured on a specimen crystal of dimensions 0.16 × 0.38 × 0.40 mm on an Enraf-Nonius CAD-4 automated diffractometer using Ni-filtered Cu  $K\alpha$  radiation. The condition  $k = 2n$  limiting the  $0k0$  reflections determined the space group to be  $P2_1$ . The lattice parameters were refined by a least-

squares fit to measured  $2\theta$  values for 38 reflections in the interval  $64^\circ < 2\theta < 69^\circ$ . Integrated relative intensities for 3445 independent reflections with  $2\theta < 150^\circ$  were measured as  $\omega$ - $2\theta$  scans; 2368 of these reflections were measured to be observed above background ( $I > 2\sigma$ ).



The intensities were reduced to structure factor amplitudes, and phase angles sufficient for location of the nonhydrogen atoms were derived using the direct-methods program *MULTAN* (Germain, Main & Woolfson, 1971) in conjunction with the negative-quartet figure of merit (DeTitta, Edmonds, Langs & Hauptman, 1975). All H atoms with the exception of H(O17) were located on a difference electron density map prepared at an intermediate stage of least-squares refinement of structural parameters. In the final cycles of full-matrix least-squares refinement, positional parameters for all the atoms, anisotropic thermal vibration parameters for the nonhydrogen atoms and isotropic thermal vibration parameters for the H atoms were varied. The quantities  $(1/\sigma_F^2)$ , where  $\sigma_F$  was as defined by Stout & Jensen (1968) but with an instrumental instability factor of 0.06, were used to weight the least-squares differences for the observed data; differences for data determined to be unobserved were given zero weight. The final values of the residual ( $R = \sum ||F_o| - |F_c|| / \sum |F_o|$ ) were 0.037 for the observed data and 0.086 for all the measured data. Final positional parameters are listed in Table 1.\*

\* Lists of structure factors and thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34865 (18 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. Atomic coordinates of 17 $\beta$ -hydroxy-9 $\alpha$ -methyl-4,14-estradien-3-one (nonhydrogens  $\times 10^4$ ; hydrogens  $\times 10^3$ )

Standard deviations are in parentheses.

	<i>x</i>	<i>y</i>	<i>z</i>		<i>x</i>	<i>y</i>	<i>z</i>
C(1)	4362 (2)	9828 (3)	2455 (4)	C(1')	1344 (2)	9422 (3)	9484 (6)
C(2)	3554 (2)	9751 (3)	3179 (5)	C(2')	1930 (2)	9442 (3)	7980 (5)
C(3)	3151 (2)	10771 (3)	2956 (5)	C(3')	2514 (2)	8619 (3)	8229 (4)
C(4)	3299 (2)	11339 (3)	1252 (5)	C(4')	2233 (2)	7625 (3)	8958 (5)
C(5)	3810 (2)	11053 (2)	-7 (4)	C(5')	1521 (2)	7470 (2)	9487 (4)
C(6)	3821 (2)	11543 (3)	-1930 (5)	C(6')	1238 (2)	6390 (2)	9833 (5)
C(7)	4608 (2)	11714 (2)	-2705 (4)	C(7')	797 (2)	6293 (2)	11644 (5)
C(8)	5104 (2)	10754 (-)	-2445 (4)	C(8')	183 (1)	7134 (2)	11744 (4)
C(9)	5171 (1)	10435 (2)	-312 (4)	C(9')	527 (1)	8243 (2)	11589 (4)
C(10)	4359 (1)	10168 (2)	365 (4)	C(10')	960 (2)	8343 (2)	9700 (4)
C(11)	5671 (2)	9444 (2)	-196 (4)	C(11')	-143 (2)	9021 (2)	11578 (5)
C(12)	6461 (2)	9590 (3)	-988 (4)	C(12')	-617 (2)	8947 (2)	13360 (5)
C(13)	6433 (2)	9955 (2)	-3051 (4)	C(13')	-933 (2)	7853 (2)	13724 (4)
C(14)	5884 (2)	10866 (2)	-3245 (4)	C(14')	-305 (1)	7064 (2)	13434 (4)
C(15)	6189 (2)	11661 (3)	-4111 (5)	C(15')	-268 (2)	6382 (2)	14844 (5)
C(16)	6977 (2)	11450 (3)	-4708 (6)	C(16')	-869 (2)	6561 (3)	16268 (5)
C(17)	7192 (2)	10486 (3)	-3646 (5)	C(17')	-1108 (2)	7676 (2)	15834 (5)
C(18)	6200 (2)	9067 (3)	-4362 (5)	C(18')	-1619 (2)	7613 (3)	12432 (5)
C(9AM)	5528 (2)	11321 (3)	852 (4)	C(9AM')	1067 (2)	8448 (2)	13255 (4)
O(3)	2708 (1)	11092 (3)	4132 (4)	O(3')	3175 (1)	8722 (2)	7759 (4)
O(17B)	7690 (2)	9898 (3)	-4736 (5)	O(17B')	-1854 (1)	7912 (2)	16409 (4)
H(1A)	465 (1)	1037 (2)	330 (4)	H(1'A)	171 (2)	958 (3)	1071 (5)
H(1B)	459 (2)	909 (3)	256 (5)	H(1'B)	97 (2)	992 (3)	939 (5)
H(2A)	358 (2)	955 (3)	434 (5)	H(2'A)	215 (2)	1015 (3)	787 (5)
H(2B)	322 (2)	921 (3)	248 (5)	H(2'B)	164 (2)	929 (3)	676 (5)
H(4)	300 (2)	1180 (2)	94 (4)	H(4')	256 (2)	707 (3)	892 (4)
H(6A)	354 (2)	1216 (3)	-183 (5)	H(6'A)	167 (2)	590 (3)	969 (5)
H(6B)	354 (2)	1108 (3)	-269 (5)	H(6'B)	89 (2)	629 (3)	872 (4)
H(7A)	483 (2)	1228 (3)	-209 (4)	H(7'A)	119 (2)	639 (3)	1274 (5)
H(7B)	459 (1)	1191 (2)	-399 (4)	H(7'B)	58 (2)	561 (3)	1173 (4)
H(8B)	485 (1)	1015 (2)	-316 (4)	H(8'B)	-12 (2)	706 (2)	1061 (4)
H(10B)	420 (1)	956 (2)	-52 (4)	H(10'B)	62 (2)	826 (3)	874 (4)
H(11A)	576 (2)	921 (3)	110 (4)	H(11'A)	8 (2)	972 (3)	1146 (4)
H(11B)	540 (2)	883 (2)	-88 (4)	H(11'B)	-51 (2)	884 (3)	1051 (4)
H(12A)	676 (2)	1012 (3)	-21 (5)	H(12'A)	-31 (2)	917 (3)	1446 (5)
H(12B)	677 (1)	895 (2)	-91 (4)	H(12'B)	-102 (2)	942 (3)	1339 (4)
H(15)	599 (2)	1227 (2)	-430 (4)	H(15')	10 (2)	579 (3)	1491 (6)
H(16A)	729 (2)	1187 (4)	-457 (6)	H(16'A)	-69 (2)	649 (3)	1765 (5)
H(16B)	715 (2)	1120 (4)	-613 (6)	H(16'B)	-130 (2)	610 (3)	1594 (5)
H(17A)	751 (2)	1065 (4)	-244 (5)	H(17'A)	-77 (2)	815 (3)	1656 (4)
H(18A)	562 (2)	883 (4)	-425 (6)	H(18'A)	-144 (2)	771 (3)	1113 (4)
H(18B)	613 (2)	930 (3)	-569 (4)	H(18'B)	-182 (2)	689 (3)	1282 (4)
H(18C)	653 (2)	852 (3)	-427 (5)	H(18'C)	-203 (2)	807 (4)	1273 (5)
H(9AMA)	513 (2)	1183 (3)	109 (5)	H(9'AMA)	157 (2)	814 (3)	1299 (4)
H(9AMB)	593 (2)	1162 (3)	25 (4)	H(9'AMB)	87 (2)	821 (3)	1450 (4)
H(9AMC)	579 (2)	1104 (3)	204 (4)	H(9'AMC)	115 (2)	920 (3)	1352 (5)
H(17O)	777 (2)	928 (4)	-396 (6)	H(17O')	-220 (2)	741 (4)	1622 (5)

### Discussion

The crystallographically observed structure of molecule (1) of the title compound is shown in Fig. 1. Fig. 2 compares the intramolecular dimensions involving the nonhydrogen atoms in the two molecules in the asymmetric unit; the largest estimated standard deviations are: for bond lengths 0.006 Å, for bond angles 0.2°, and for torsion angles 0.4°. The C—H bond distances range from 0.78 to 1.07 Å and average 0.98 Å. Only

two bond lengths [C(1)—C(2) and C(3)—C(4)] differ by more than three standard deviations in the crystallographically independent molecules. The geometry of the hydrogen bonds in the structure is given in Table 2.



Fig. 1. Stereo ORTEP (Johnson, 1965) drawing of molecule (1) of 17 $\beta$ -hydroxy-9 $\alpha$ -methyl-4,14-estradien-3-one.

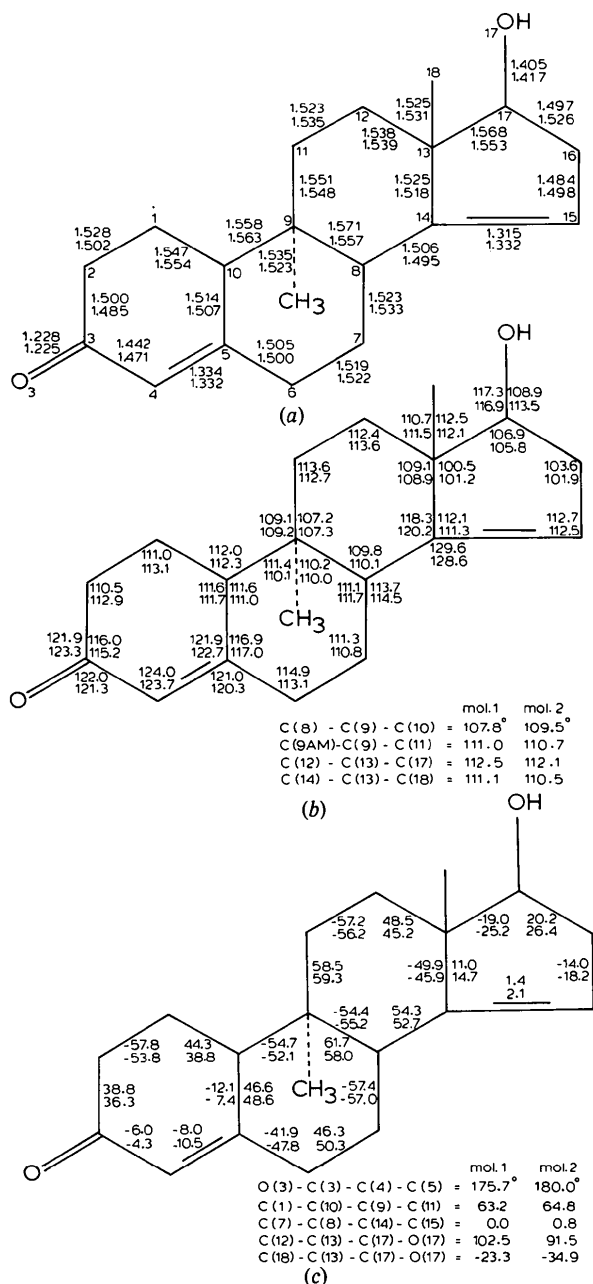


Fig. 2. Intramolecular dimensions of 17 $\beta$ -hydroxy-9 $\alpha$ -methyl-4,14-estradien-3-one. (a) Bond distances (Å);  $\sigma$  range = 0.008–0.010 Å. (b) Bond angles (°);  $\sigma$  range = 0.4–0.5°. (c) Endocyclic torsion angles (°). A torsion angle  $\alpha$ - $\beta$ - $\gamma$ - $\delta$  is positive if, when viewed down the  $\beta$ - $\gamma$  bond, the  $\alpha$ - $\beta$  bond will eclipse the  $\gamma$ - $\delta$  bond when rotated less than 180° in a clockwise direction.

To illustrate the influence of 9 $\alpha$ -methyl substitution on the overall conformation, the crystallographically independent molecules are superimposed on the parent molecule, 17 $\beta$ -hydroxy-4,14-estradien-3-one (Rohrer, Duax & Segaloff, 1978) in Fig. 3. Although the 9 $\alpha$ -methyl group is seen to bring the A ring closer to the plane of the rest of the steroid in both molecules, the molecules themselves are significantly different from one another.

Many biologically active steroids crystallize with two molecules in the asymmetric unit and in some cases only one of the co-crystallized conformers is active. This is true of vitamin D (Norman, Procsal, Okamura & Wing, 1975; Trinh-toan, DeLuca & Dahl, 1976) and the cardioactive steroids (Rohrer, Fullerton, From & Ahmed, 1979). For this reason it is of interest to determine the nature and cause of the differences between the molecules in a double asymmetric unit. Six intraring torsion angles differ between the two molecules by more than 4° as indicated on Fig. 2(c). The differences in the D ring are correlated with the differences in hydroxy H positions (torsion angles in Table 2). When the hydroxyl H is antiperiplanar to the C(17)–H bond, the ring puckers to tilt O(17) into a more axial orientation. The hydroxyl H position is correlated with hydrogen-bond formation and crystal packing. It is difficult to determine whether the packing is dictated by the H atom orientation or the H atom position is induced by the crystal packing.

The greatest overall difference between the two molecules is in the relative position of the A and B rings. The torsion-angle differences at the C(1)–C(10), C(5)–C(10), and C(5)–C(6) bonds appear to make a major contribution to these differences. The two observed overall conformations could represent: (1) minor distortions from a single minimum-energy conformation caused by crystal-packing forces, (2) a

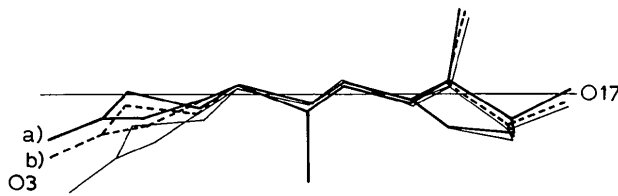


Fig. 3. Superposition of molecules (a) (1) and (b) (2) of 17 $\beta$ -hydroxy-9 $\alpha$ -methyl-4,14-estradien-3-one on 17 $\beta$ -hydroxy-4,14-estradien-3-one using the C and D rings as a reference element.

Table 2. Hydrogen-bond geometry in 17 $\beta$ -hydroxy-9 $\alpha$ -methyl-4,14-estradien-3-one with estimated standard deviations in parentheses

Donor (D)	Acceptor (A)	D...A	D–H	H...A	$\angle$ D–H...A	C(16)–C(17)–O(17)–H(O17) (D)
O(17)2*	O(3)1*	2.81 (1) Å	0.89 (4) Å	1.94 (5) Å	165 (2)°	–40 (3)°
O(17)1	O(17)2	2.80 (1)	0.97 (4)	1.90 (5)	152 (2)	–176 (3)

\* 2 = molecule (2), 1 = molecule (1).

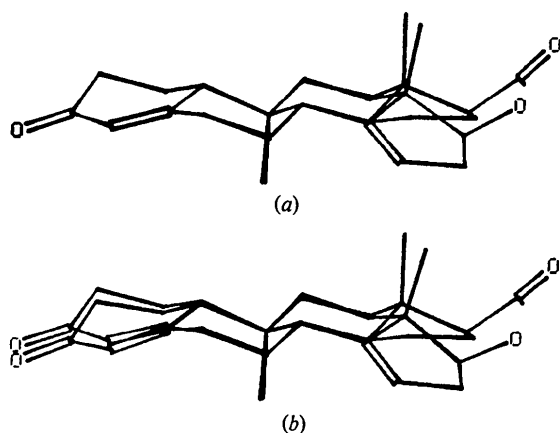


Fig. 4. A *PROPHET/FITMOL* (Rohrer *et al.*, 1979) overlay of the *B* and *C* rings of 9 $\alpha$ -methyl-19-nor-4-pregnen-3,20-dione on those of (a) molecule (1) and (b) molecule (2) of 17 $\beta$ -hydroxy-9 $\alpha$ -methyl-4,14-estradien-3-one.

minimum-energy form and a conformation distorted from the minimum-energy position, or (3) co-crystallization of conformational isomers that are at or very near local minimum-energy positions and between which there is a non-trivial barrier. Unambiguous examples of the third possibility occur in the vitamin D and cardenolide structures. Additional crystallographically independent observations of the title compound might suggest which of the three possibilities is most likely in this case. Unfortunately there are no other polymorphic or solvated forms of this molecule in the literature. The only other 9 $\alpha$ -methyl-19-nor-4-ene-3-one steroid previously reported is a pregnane having a saturated C(14)–C(15) bond. The conformations of the *A*, *B*, and *C* rings of this structure, 9 $\alpha$ -methyl-19-nor-4-pregnene-3,20-dione (Weber & Galantay, 1974), and the two molecules of 17 $\beta$ -hydroxy-9 $\alpha$ -methyl-4,14-estradien-3-one are compared in Fig. 4. In this figure a least-squares process (*FITMOL*) is used to optimize the overlap of the *B* and *C* rings in each pair of structures. The conformations of the *A*, *B* and *C* rings of molecule (1) are seen to be indistinguishable from those of 9 $\alpha$ -methyl-19-nor-4-pregnene-3,20-dione. It would

appear that molecule (1) has the minimum-energy conformation of *A*, *B* and *C* rings having this composition and the conformation of molecule (2) is either a local minimum or slightly higher-energy form stabilized by unsaturation of the C(14)–C(15) bond, by crystal-packing forces or both.

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