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# Conformational Analysis of Synthetic Androgens. VI. Structure and Crystal Packing of 17β-Hydroxy-7β-methyl-4,14-androstadien-3-one Monohydrate

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## Abstract

The X-ray crystal structure of 17β-hydroxy-7β-methyl-4,14-androstadien-3-one monohydrate was investigated to determine the influence of the 7β-methyl substituent on the overall conformation. The steroid hydrate ($C_{20}H_{28}O_2.H_2O$) crystallizes in the monoclinic space group $P2_1$ with $Z = 2$, $a = 10{\cdot}868$ (6), $b = 8{\cdot}472$ (4), $c = 9{\cdot}838$ (4) Å, $\beta = 98{\cdot}29$ (5)°, $\lambda = 1{\cdot}5418$ Å, $T = 291$ K, $V = 896{\cdot}3$ Å$^3$, $\rho_x = 1{\cdot}18$ Mg m$^{-3}$. $R = 4{\cdot}3\%$ for 1972 reflections. Subtle conformational differences between 17β-hydroxy-7β-methyl-4,14-androstadien-3-one, 17β-hydroxy-4,14-androstadien-3-one and 17β-hydroxy-7β-methyl-4,14-estradien-3-one are attributable to differences in methyl substitution. While the overall shapes of these molecules are very similar, the molecular packings in the crystals of these steroids are entirely different. In contrast to this, the crystal structure of 17β-hydroxy-7β-methyl-4,14-androstadien-3-one is isomorphous with those of the monohydrates of the most active endogenous androgens, testosterone and dihydrotestosterone. The order of hydrogen-bond lengths and their orientations are remarkably similar in these three structures. Since the hydrophobic surfaces of the molecule are significantly different, the crystal packing in these isomorphs appears to be a function of hydrate formation and the directionally specific hydrogen bonding mediated by the water molecules in the crystals.

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## Introduction

The structure determination was undertaken as part of a study of substituent influence on the conformations of modified androgenic steroids. The title compound has approximately 10% of the androgenicity of testosterone when administered parenterally in the castrate

rat or topically or parenterally in the day-old chick. In contrast the 7α-methyl analog has decreased activity when administered topically but enhanced activity when administered parenterally (Segaloff, 1963). Crystallographic diffraction data were measured on a specimen crystal of dimensions 0·25 × 0·50 × 0·60 mm with an Enraf–Nonius CAD-4 automated diffractometer using Ni-filtered Cu $K\alpha$ radiation. The lattice parameters were refined by a least-squares fit to measured $2\theta$ values for 25 reflections in the interval $30° < 2\theta < 40°$. Integrated relative intensities for 1972 independent reflections with $2\theta < 150°$ were measured as $\omega$–$2\theta$ scans; 1920 of these reflections were measured to be observed above background ($I > 2\sigma$).

Table 1. *Atomic coordinates* (× $10^4$, *for* H × $10^3$) *and isotropic thermal parameters* (Å$^2$ × 10) *for the title compound*

For non-hydrogen atoms $B_{eq} = \frac{4}{3}\sum_i\sum_j b_{ij}\mathbf{a}_i.\mathbf{a}_j$.

| | x | y | z | $B_{eq}/B$ |
|---|---|---|---|---|
| C(1) | 7379 (2) | 6656 (2) | 3379 (2) | 35 (1) |
| C(2) | 8775 (2) | 6584 (3) | 3991 (2) | 40 (1) |
| C(3) | 9004 (1) | 5363 (3) | 5113 (2) | 38 (1) |
| C(4) | 8206 (2) | 3977 (3) | 4966 (2) | 41 (1) |
| C(5) | 7275 (1) | 3764 (2) | 3907 (2) | 34 (1) |
| C(6) | 6646 (2) | 2193 (2) | 3673 (2) | 42 (1) |
| C(7) | 5226 (1) | 2235 (2) | 3412 (2) | 33 (1) |
| C(8) | 4725 (1) | 3536 (2) | 2374 (1) | 30 (1) |
| C(9) | 5407 (1) | 5136 (2) | 2695 (1) | 29 (1) |
| C(10) | 6855 (1) | 5043 | 2859 (1) | 31 (1) |
| C(11) | 4877 (2) | 6392 (2) | 1627 (2) | 36 (1) |
| C(12) | 3497 (2) | 6678 (2) | 1678 (2) | 37 (1) |
| C(13) | 2736 (1) | 5165 (2) | 1389 (1) | 31 (1) |
| C(14) | 3340 (1) | 3800 (2) | 2261 (1) | 31 (1) |
| C(15) | 2474 (2) | 2987 (3) | 2795 (2) | 41 (1) |
| C(16) | 1175 (2) | 3611 (3) | 2355 (2) | 45 (1) |
| C(17) | 1456 (2) | 5290 (2) | 1904 (2) | 35 (1) |
| C(18) | 2571 (2) | 4711 (3) | −136 (2) | 41 (1) |
| C(19) | 7322 (2) | 4620 (3) | 1493 (2) | 47 (1) |
| C(7*BM*) | 4780 (2) | 569 (2) | 2948 (3) | 47 (1) |
| O(3) | 9857 (1) | 5493 (2) | 6075 (2) | 52 (1) |
| O(17*B*) | 465 (1) | 5907 (2) | 950 (1) | 42 (1) |
| O(1*W*) | 668 (2) | 9110 (2) | 1325 (2) | 59 (1) |
| H(1*A*) | 686 (2) | 703 (3) | 408 (2) | 34 (4) |
| H(1*B*) | 724 (2) | 746 (4) | 271 (2) | 48 (5) |
| H(2*A*) | 908 (2) | 758 (4) | 433 (3) | 52 (5) |
| H(2*B*) | 930 (2) | 622 (3) | 330 (2) | 44 (5) |
| H(4) | 849 (2) | 304 (3) | 561 (3) | 49 (5) |
| H(6*A*) | 698 (2) | 139 (3) | 456 (3) | 47 (5) |
| H(6*B*) | 689 (2) | 165 (4) | 274 (3) | 65 (7) |
| H(7*A*) | 496 (2) | 249 (3) | 425 (2) | 33 (4) |
| H(8*B*) | 489 (2) | 316 (4) | 143 (2) | 49 (5) |
| H(9*A*) | 516 (2) | 551 (3) | 358 (2) | 33 (4) |
| H(11*A*) | 530 (2) | 744 (4) | 176 (3) | 50 (5) |
| H(11*B*) | 498 (2) | 592 (4) | 89 (2) | 44 (5) |
| H(12*A*) | 338 (3) | 709 (4) | 259 (2) | 53 (6) |
| H(12*B*) | 308 (2) | 757 (4) | 96 (3) | 51 (5) |
| H(15) | 265 (2) | 209 (3) | 326 (2) | 39 (4) |
| H(16*A*) | 63 (2) | 352 (4) | 315 (3) | 55 (6) |
| H(16*B*) | 74 (2) | 293 (4) | 155 (3) | 52 (6) |
| H(17*A*) | 157 (2) | 601 (3) | 263 (2) | 39 (4) |
| H(18*A*) | 342 (2) | 467 (4) | −37 (2) | 50 (6) |
| H(18*B*) | 211 (2) | 383 (3) | −33 (2) | 44 (5) |
| H(18*C*) | 202 (2) | 560 (3) | −66 (2) | 41 (4) |
| H(19*A*) | 822 (3) | 470 (5) | 163 (3) | 69 (7) |
| H(19*B*) | 688 (3) | 367 (5) | 112 (4) | 79 (8) |
| H(19*C*) | 705 (2) | 560 (4) | 79 (3) | 63 (6) |
| H(7*BMA*) | 510 (2) | −22 (4) | 359 (3) | 65 (7) |
| H(7*BMB*) | 387 (3) | 55 (6) | 295 (3) | 87 (8) |
| H(7*BMC*) | 506 (3) | 19 (4) | 196 (3) | 68 (7) |
| H(17O) | 45 (2) | 689 (4) | 107 (2) | 47 (5) |
| H(1*W*) | 32 (2) | 974 (4) | 71 (2) | 43 (5) |
| H(2*W*) | 23 (3) | 941 (6) | 198 (4) | 85 (8) |

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* (Main, Lessinger, Woolfson, Germain & Declercq, 1977). All H atoms were located on a difference electron density map prepared at an intermediate stage in the least-squares refinement of the 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, p. 457, equation *H*14) 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 for the residual ($R = \sum\|F_o| - |F_c\|/\sum|F_o|$) were 0·043 when unobserved data were omitted and 0·044 for all measured data. Final positional parameters are listed in Table 1.* The equivalent $B_{iso}$ for the nonhydrogen atoms were calculated as defined by equation (18) of Hamilton (1959).

## Discussion

The crystallographically observed structure of the title compound is shown in Fig. 1. The intramolecular dimensions involving the non-hydrogen atoms are given in Fig. 2. The C—H bond distances range from 0·85 to 1·12 Å and average 1·00 ± 0·07 Å. A comparison of the conformation of this structure with those of 17β-hydroxy-4,14-androstadien-3-one (Rohrer, Strong, Duax & Segaloff, 1978) and 17β-hydroxy-7β-methyl-4,14-estradien-3-one (Duax, Rohrer & Rao, 1979) provides information on the effect of specific methyl substituents on steroid conformation.

While the intraring torsion angles of the *A*, *C* and *D* rings of 17β-hydroxy-4,14-androstadien-3-one and its 7β-methyl derivative vary only slightly, the torsion angles in the *B* rings differ by as much as 12°. As

* Lists of structure factors and thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36279 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

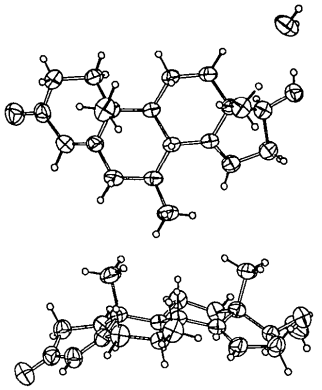

Fig. 1. *ORTEP* (Johnson, 1965) drawing of 17$\beta$-hydroxy-7$\beta$-methyl-4,14-androstadien-3-one monohydrate. Thermal ellipsoids for non-hydrogen atoms are scaled to 60% probability and H atoms are represented as spheres equivalent to $B = 1$ Å$^2$.

might be expected, the 7$\beta$ substituent flattens the ring at C(7) and this permits a puckering at C(10). When the distances between corresponding atoms in the *C* and *D* rings of these two structures are minimized (Fig. 3*a*) it becomes apparent that the changes in the *B* ring result in twisting of the molecule about its length. When viewed from C(10) to C(13) the *A* ring twists in a clockwise direction when compared to the androgen without a 7$\beta$-methyl substituent. When the intraring torsion angles of 17$\beta$-hydroxy-7$\beta$-methyl-4,14-androstadien-3-one and 17$\beta$-hydroxy-7$\beta$-methyl-4,14-estradien-3-one are compared, the *B* rings are found to have similar conformations and the *A*, *C* and *D* rings all change extensively. When the distances between corresponding atoms of the *B* ring of these two structures are minimized, it appears that the 19-methyl group causes a flattening of the *A* ring in the androstane relative to the estrane and a twist about the length of the steroid. When viewed from C(10) to C(13) the *A* ring of the title structure twists in a clockwise direction when compared to the estrogen having the same 7$\beta$ substituent.

In spite of the conformational similarities in the three molecules, their crystal-packing arrangements (Fig. 4*a*,*b*,*c*) are seen to be entirely different from one another. In contrast to this, the crystal structure of 17$\beta$-hydroxy-7$\beta$-methyl-4,14-androstadien-3-one monohydrate is nearly isomorphous with those of the monohydrates of the two most active endogenous androgens, testosterone (Busetta, Courseille, Leroy & Hospital, 1972) and dihydrotestosterone (Busetta, Courseille, Fornies-Marquina & Hospital, 1972) as illustrated in Fig. 4(*a*,*d*,*e*). In these nearly isomorphous structures the steroids are aligned so that there is a layer of hydrogen-bonded O atoms perpendicular to the $a^*$ axis. In the other structures (*b* and *c*) there is no solvent in the lattice and the steroid stacking is staggered. In the three isomorphous structures the

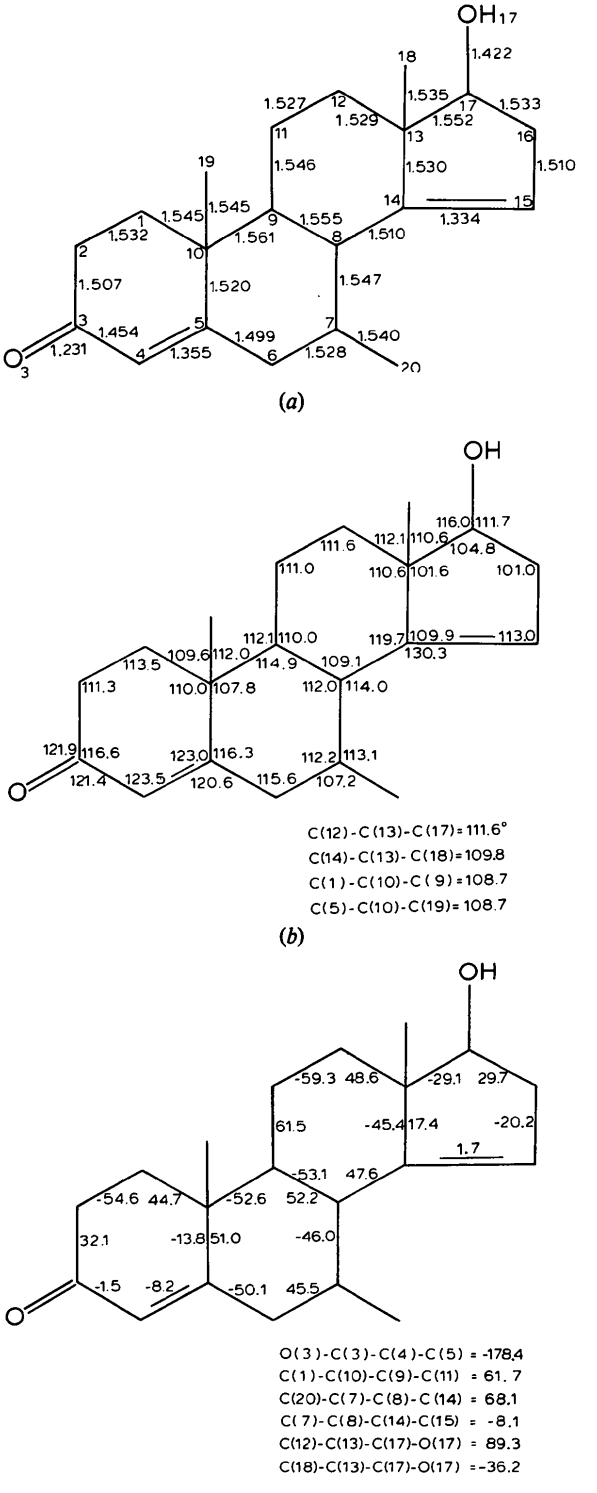


Fig. 2. Intramolecular dimensions of 17$\beta$-hydroxy-7$\beta$-methyl-4,14-androstadien-3-one. (*a*) Bond distances (Å); $\sigma$ range = 0·002–0·003 Å. (*b*) Bond angles (°); $\sigma$ range = 0·1–0·2°. (*c*) Endocyclic torsion angles (°); $\sigma = 2°$. A torsion angle $\alpha$–$\beta$–$\gamma$–$\delta$ 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.

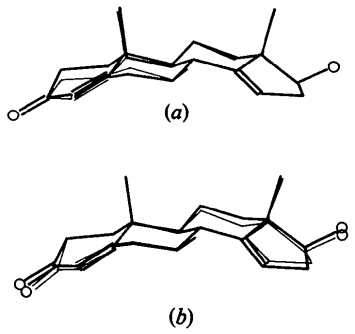


Fig. 3. (*a*) Least-squares fit of corresponding atoms of the *C* and *D* rings of 17$\beta$-hydroxy-7$\beta$-methyl-4,14-androstadien-3-one (dark lines) and the structure without the 7$\beta$-methyl substitution (light lines). (*b*) Least-squares fit of corresponding atoms of the *B* rings of 17$\beta$-hydroxy-7$\beta$-methyl-4,14-androstadien-3-one (dark lines) and the structure without the 19-methyl (light lines).

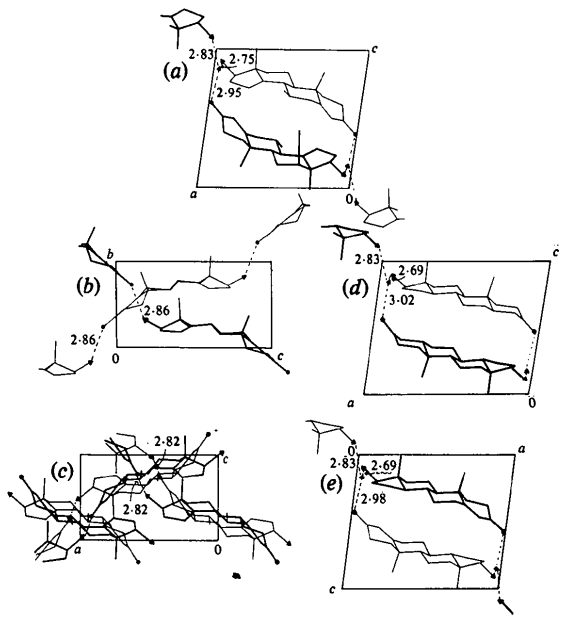


Fig. 4. Crystal packing and hydrogen bonding observed in (*a*) this structure (e.s.d.'s for hydrogen-bond length are 0·003 Å), (*b*) 17$\beta$-hydroxy-4,14-androstadien-3-one, (*c*) 17$\beta$-hydroxy-7$\beta$-methyl-4,14-estradien-3-one, (*d*) 17$\beta$-hydroxy-5$\alpha$-androstan-3-one monohydrate and (*e*) 17$\beta$-hydroxy-4-androsten-3-one monohydrate. Strong similarity is seen in (*a*), (*d*), and (*e*) despite appreciable conformational changes, while (*a*), (*b*) and (*c*) show little similarity in packing despite the structural similarity illustrated in Fig. 3.

water molecules link the steroids in a three-dimensional network and the order of the hydrogen-bond lengths remains the same (Table 2). The shortest hydrogen bond is that in which OH(17) is the H donor and it may be this association that is primarily responsible for the formation of the crystalline hydrate. The isomorphism is remarkable in view of the significant compositional differences in the three steroids.

Table 2. *Hydrogen bonds in the crystalline hydrates of* (*a*) *17$\beta$-hydroxy-7$\beta$-methyl-4,14-androstadien-3-one,* (*b*) *testosterone, and* (*c*) *17$\beta$-hydroxy-5$\alpha$-androstan-3-one*

| H-bond lengths | (*a*) | (*b*) | (*c*) |
|---|---|---|---|
| O(17)→$H_2O$ | 2·75 Å | 2·69 Å | 2·69 Å |
| $H_2O$→O(17) | 2·83 | 2·83 | 2·83 |
| $H_2O$→O(3) | 2·95 | 2·98 | 3·02 |
| H-bond orientation | | | |
| C(13)–C(17)–O(17)→$H_2O$ | −87° | −81° | −78° |
| $H_2O$→O(17)–C(17)–C(13) | 73 | 80 | 81 |
| $H_2O$→O(3)–C(3)–C(2) | 149 | 140 | 126 |

It appears that the hydrate formation and hydrogen bonding involving the water molecules is a more important factor in determining this particular isomorphism than similarity in molecular shape, which normally controls crystal packing (Kitaigorodsky, 1961).

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