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Structure of 4-Fluoro-1,3,5(10)-estratriene-3,17β-diol–Hemimethanol

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Abstract. $C_{18}H_{23}FO_2.\frac{1}{2}CH_3OH$, triclinic, $P\bar{1}$, a = 7·367 (1), b = 9·363 (6), c = 12·531 (1) Å, α = 89·31 (3), β = 93·38 (1), γ = 109·62 (3)°, V = 812·8 Å^3, Z = 2. The structure was solved by direct methods and refined by block-diagonal least squares to an R factor of 6·2% for 3043 observed reflections. The general features of the steroid are similar to those of other estratriene analogs. Molecules in the crystal are linked together in a head-to-tail fashion between the O at C(3) and at C(17), and sideways between the hydroxyls of the solvent and the steroid.

Introduction. Tumor inhibitory effects on estrogen administration have been observed in breast and prostatic cancers and attempts have been made to obtain modified steroidal estrogens that will be useful in cancer chemotherapy. In this connection it is seen that in contrast to the biologically inactive bromo analog, 4-fluoroestratrienediol (4FE2) is a very highly active estrogen. The present crystallographic study of the structure and conformation of 4FE2 was undertaken to establish the stereochemical reason, if any, for the striking difference in biological activity of the two analogs.

A crystal of about 1·3 × 0·8 × 0·3 mm crystallized from benzene was used to collect the diffraction data. The crystals are triclinic with space group $P\bar{1}$. Lattice parameters were refined by a least-squares fit to a set of 24 measured reflections in a θ range 10–34° (Cu $K\alpha$). Three-dimensional data were collected on an Enraf–Nonius CAD-4 automated diffractometer using Ni-filtered Cu $K\alpha$ radiation by ω–2θ scans within the Cu sphere of 2θ to 150°. The measured intensities were converted to structure amplitudes in the usual manner, and corrected for Lorentz, polarization, and absorption effects. There were 3436 unique reflections measured, of which 3043 had intensities greater than $2\sigma(I)$ and were used in the determination and refinement of the structure.

The space group $P\bar{1}$ with two molecules of the steroid in the asymmetric unit presented some difficulties in its structure solution. Many initial attempts using the direct-methods program *MULTAN* (Germain, Main & Woolfson, 1971) varying a number of parameters failed to give any phase sets that looked significantly better than any other. All of the phase sets obtained had figures of merit of 1·25 or higher and yielded maps showing repeating hexagonal rings with peaks in the middle of the hexagons also. Recycling procedures starting with many of the molecular fragments picked up by the program failed to develop into the correct model. Of the 20 phase sets calculated using 348 reflections with E values greater than 1·55, only one had a figure of merit less than 1·2 and the map for this set also gave a fragment with fused hexagonal rings. From this, 17 atomic positions were chosen corresponding to three fused hexagonal rings with three additional atoms as in a steroid nucleus. A weighted Fourier map with the 17-atom fragment as input showed another fragment of 12 atoms resembling part of a steroid molecule. The second partial molecule was also included in calculating the next weighted Fourier map which developed into a complete molecule showing the five-membered ring and with 19 of the 21 atoms indicated unambiguously. With these 36 atoms included, the next weighted Fourier map calculation clearly revealed all 42 non-H atoms in the two steroid molecules and also showed the presence of a solvent containing two covalently bonded atoms which was recognized as a methanol molecule and was included in the subsequent refinement. Assignment of atom types and ascribing anisotropic thermal parameters for these 44 atoms and a few more cycles of least-squares refinement gave an R of 8%. At this stage, most of the H positions were located from the difference Fourier maps. Inclusion of all H atoms and a few cycles of least-squares refinement gave a final R of 6·16% for 3043 reflections. The function minimized was $\sum w(|F_o|$

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$-|F_c|)^2$, where $w = 1/\sigma^2(F)$. The final parameters are given in Table 1.* Standard deviations were calculated using Cruickshank's (1965) expressions.

Discussion. A schematic representation of the steroid molecule showing the numbering of atoms and ring designation is given in Fig. 1. Fig. 2 gives the bond distances and angles for the two molecules in the asymmetric unit. Similar to the estratriene analogs (Norton, Kartha & Lu, 1964; Busetta & Hospital, 1972; Busetta, Courseille, Geoffre & Hospital, 1972; Duax, 1972), 4FE2 has an extended structure. Bond lengths and most bond angles do not deviate significantly among the estratriene analogs. However, there are a few differences in the bond angles that are worth noting. Angle C(3)–C(4)–C(5) appears to be larger than in steroids that have no substituent at C(4). This is also true for 2,4-dibromoestratrienediol (Cody, DeJar-

* Lists of structure factors, anisotropic thermal parameters for non-H atoms, final parameters for H atoms and hydrogen bonds and short intermolecular contacts of less than 3·5 Å have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38034 (20 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2 HU, England.

Table 1. *Fractional coordinates* (×10⁴) *for non*-H *atoms and their* B_{eq}

	x	y	z	B_{eq}* (Å²)
F	5041 (4)	7257 (4)	7645 (2)	5·1
O(3)	1659 (4)	6152 (3)	6544 (2)	4·1
O(17)	2041 (5)	8793 (4)	15145 (2)	4·4
C(1)	208 (5)	6860 (4)	9189 (3)	3·5
C(2)	28 (5)	6391 (4)	8131 (3)	3·7
C(3)	1678 (5)	6537 (4)	7594 (3)	3·5
C(4)	3433 (5)	7117 (4)	8163 (3)	3·3
C(5)	3662 (4)	7575 (4)	9216 (3)	3·1
C(6)	5656 (5)	8117 (5)	9762 (3)	4·2
C(7)	5764 (5)	8964 (5)	10806 (3)	3·9
C(8)	4071 (4)	8131 (4)	11489 (3)	3·0
C(9)	2171 (4)	8091 (4)	10879 (2)	2·9
C(10)	1991 (4)	7462 (4)	9754 (2)	2·9
C(11)	424 (5)	7307 (5)	11556 (3)	3·9
C(12)	632 (5)	8065 (5)	12654 (3)	3·9
C(13)	2506 (5)	8115 (4)	13263 (3)	3·3
C(14)	4202 (5)	8925 (4)	12553 (3)	3·3
C(15)	6002 (6)	9215 (6)	13326 (3)	4·8
C(16)	5307 (6)	9509 (6)	14413 (3)	4·9
C(17)	3131 (6)	9221 (4)	14211 (3)	3·8
C(18)	2421 (6)	6522 (4)	13613 (3)	4·3
F′	1450 (4)	2492 (4)	13467 (2)	5·6
O(3′)	5201 (5)	3390 (4)	14336 (2)	5·0
O(17′)	2696 (6)	1799 (4)	5668 (2)	5·0
C(1′)	5880 (6)	3860 (6)	11501 (3)	4·6
C(2′)	6291 (6)	3866 (6)	12587 (3)	4·8
C(3′)	4798 (6)	3390 (4)	13269 (3)	3·8
C(4′)	2929 (5)	2930 (4)	12806 (3)	3·6
C(5′)	2479 (5)	2920 (4)	11732 (3)	3·2
C(6′)	377 (5)	2355 (6)	11332 (3)	4·2
C(7′)	61 (5)	2653 (5)	10150 (3)	4·0
C(8′)	1558 (4)	2322 (4)	9499 (3)	3·0
C(9′)	3565 (5)	3454 (4)	9838 (3)	3·4
C(10′)	3996 (5)	3398 (4)	11037 (3)	3·3
C(11′)	5163 (5)	3278 (6)	9162 (3)	4·4
C(12′)	4666 (5)	3315 (5)	7950 (3)	4·1
C(13′)	2715 (5)	2157 (4)	7639 (3)	3·4
C(14′)	1175 (5)	2453 (4)	8305 (3)	3·3
C(15′)	−734 (7)	1462 (8)	7747 (4)	5·5
C(16′)	−298 (7)	1570 (8)	6553 (4)	5·7
C(17′)	1880 (6)	2353 (4)	6515 (3)	3·9
C(18′)	2807 (7)	555 (7)	7760 (3)	4·8
O(MeOH)	−1895 (6)	5343 (4)	5656 (3)	5·8
C(MeOH)	−2656 (8)	6545 (7)	5560 (5)	6·2

* $B_{eq} = 8\pi^2 U_{eq}$ where $U_{eq} = \frac{1}{3}\sum_i \sum_j U_{ij} a_i^* a_j^* (\mathbf{a}_i . \mathbf{a}_j)$.

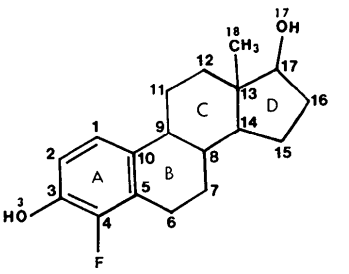

Fig. 1. A schematic representation of the steroid molecule showing the numbering of atoms and designation of rings.

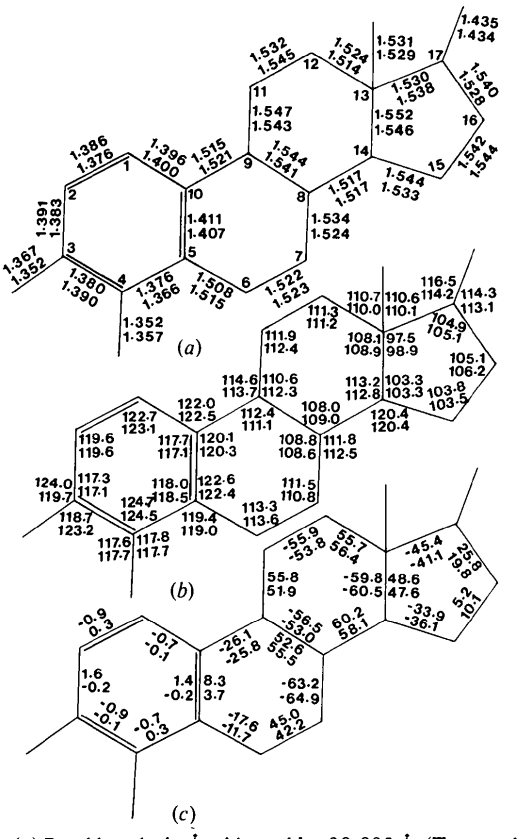

Fig. 2. (*a*) Bond lengths in Å with e.s.d.'s of 0·005 Å. (Top numbers refer to first molecule, bottom numbers to second molecule of the asymmetric unit.) (*b*) Bond angles in degrees with e.s.d.'s of 0·4°. (*c*) Torsion angles in degrees with e.s.d.'s of 0·5°.

nette, Duax & Norton, 1971) where this angle is 124°, while with the bromo substituent at C(2) only it is 122°. The bromo substituent at C(4) does create some distortion in the vicinity of C(4) due to its size, resulting in the torsion angle C(3)–C(4)–C(5)–C(10) of 6·8° showing greater deviation from the average value of about 2°. Another variation is in the angles C(2)–C(3)–O(3) and O(3)–C(3)–C(4), the first being larger than the second for 4-F-estratrienediol (124 *vs* 119°), 4-Br-estratrienediol (122 *vs* 120°), estratrienediol hemihydrate (121 *vs* 119°), estratrienediol–propanol (122 *vs* 119°) and also for 2,4-dibromoestratrienediol, while the reverse is true for estratrienediol–urea (119 *vs* 122°) and 4-F′-estratrienediol (120 *vs* 123°), the second molecule in this structure. Since both F′ of 4FE2 and the urea of the estratrienediol complex are involved in the hydrogen-bonding scheme, the variation could be the effect of the bondings that exist in the unit cell. Fig. 3 shows a stereoscopic view of the unit cell with the dotted lines indicating the hydrogen bonds.

The molecules are packed in a head-to-tail fashion and are held together by hydrogen bonds between O(17) and O(3), and also O(17′) and O(3′) of the next cell (primed atoms refer to the second molecule in the asymmetric unit). The H atom attached to O(17′) seems to be capable of taking up two possible positions in each of which it makes a hydrogen bond. In the main site, it is able to bond to the F′ atom and in the secondary site to O(17). Although the O–H···F distance between O(17′) and F′ of the next cell in the **c** direction (2·989 Å) seems to be rather long for this type of hydrogen bond, the difference synthesis clearly reveals the existence of the hydrogen bond. F′ being substituted to a conjugated triene may have reduced the electronegativity effect of F and thus formed only a very weak hydrogen bond. The same O(17′) is 2·770 Å from O(17) of its closest neighbor to which it is hydrogen-bonded through the H position in the secondary site. The other hydrogen bonds are O(3) to O(methanol) of the same cell and O(methanol) to O(3′) underneath it.

The conformation of the *A* ring is planar, the *B* ring is 7α,8β-half-chair, the *C* ring is a chair and the *D* ring between a 13β-envelope 13β,14α-half-chair. Basically the same conformation is observed for both the molecules in the asymmetric unit though deviations of

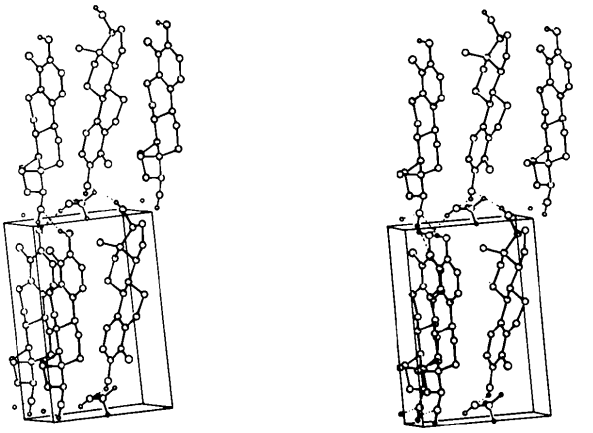

Fig. 3. Stereoscopic view of the unit cell with dotted lines indicating the hydrogen bonds. (*c* up, *b* to the right.)

torsional angles of over 4° occur around some bonds in rings *B* and *D*. Another interesting feature as revealed by the torsion angles concerns the effect of the substitution at C(4) on the planarity of the *A* ring. While the inactive bromo substituent tends to distort the *A* ring further, both molecules in the F substituents have significantly more planar *A* rings. Whether the deviation from planarity of the *A* ring has any direct relationship to the lack of biological activity of the bromo substituent is not yet clear.

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