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THE CRYSTAL STRUCTURE OF 21-BROMO-9α-FLUORO-11β-HYDROXY-16α, 17α-(β-METHYL-α-PHENYLMETHYLENEDIOXY)-4-PREGNENE-3.20, DIONE

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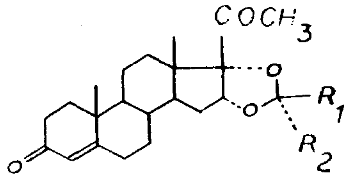
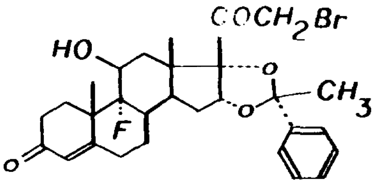
The progestational activity of steroids containing a dioxolane ring fused to the 16α-17α-positions of progesterone and unsymmetrically substitued at the 2′ position has been shown to be dependent on the stereochemistry of the substituents (1,2). Thus, 16α, 17α-(β-methyl-α-phenylmethylenedioxy)-4-pregnene-3,20-dione, I, is more active than progesterone, whereas the α-methyl-β-phenylmethylenedioxy derivative, II, which is thermodynamically more stable than I, is essentially inactive progestationally.



I $R_1 = CH_3$; $R_2 = \emptyset$

II $R_1 = \emptyset$; $R_2 = CH_3$



III

In spite of the sensitivity of progestational activity to this small stereochemical change, no studies have been made on the conformations of the D and E rings or the 17β-side chain of these compounds (3). Recently, a number of C_{21} substitued 9α-fluoro-11β-hydroxy-16α, 17α-(β-methyl-α-phenylmethylenedioxy)-4-pregnene-3,20-dione derivatives were prepared (4) and found to be potent progestational agents. It became of interest therefore, to both confirm the basis on which the stereochemistry of these compounds had been assigned, as well as to determine the conformations of the D and E rings and their substituents in this series. Accordingly, the crystal and molecular structure of 21-bromo-9α-fluoro-11β-hydroxy-16α, 17α-(β-methyl-α-phenylmethylenedioxy)-4-pregnene-3,20-dione, III, (4) was determined through three dimensional single crystal X-ray analysis.

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Crystals of III grown from methanolic solutions are orthorhombic with four molecules in a unit cell of dimensions a = 7.33, b = 28.29, c = 13.22 Å, and space group $P2_12_12_1$ (D_{obs} = 1.4 g/cm^3). The intensities of a few reflections from freshly crystallized specimens changed appreciably during the initial, approximately twenty hours, exposure to the X-ray beam, although they remained essentially constant thereafter. No significant change in the lattice parameters was observed.

Intensities from the reciprocal lattice layers 0kl - 5kl and hk0 - hk2 were estimated visually from equi-inclination Weissenberg photographs of several crystals and corrected only for the Lorentz-polarization factors. The data (CuKα) were correlated to produce a set of 1729 F^2 which was used in the analysis. Patterson and Fourier methods clearly revealed the steroid molecular structure, III, together with methanol molecules of crystallization. However, the solvent molecules were not well-defined. Considerations of electron density and site occupancy factors suggest that an average unit cell contained only two to three solvent molecules during the data acquisition. The initially observed variations in intensities were shown to be qualitatively consistent with the partial loss of methanol from the lattice.

Least squares refinements of all coordinates, anisotropic thermal parameters for the two halogens and isotropic thermal parameters for the other atoms converged to R = 0.14. The fractional atomic coordinates (Table 1) and selected torsional angles (Table 2) suggest a number of interesting conformational features: a) The stereochemistry that was assumed for the dioxolane substituents in III, by analogy to the previously assigned (2) 9, 11,21-unsubstituted compound I, is confirmed. b) The conformation of ring D, which is very similar to that in 4-bromo-estradiol (6), closely approximates a β-C(13)-envelope (7). c) The dioxolane ring is considerably less puckered with maximum torsional angle of only 32°. d) The phenyl ring is tucked well under the α-side of the steroid nucleus and extends as far as ring B resulting in a distance of 3.70±.03Å from the fluorine atom to the nearest phenyl carbon atom (Figure 1). e) The bromoacetyl side chain at C(17) is oriented so that the C(20) carbonyl is directed over ring D.** f) In spite of the previously observed dipole interactions of 2-bromoketones (9), the bromine atom is oriented essentially cis-coplanar with the carbonyl group (torsional angle O(34)-C(20)-C(21)-Br(35) = - 5°).

**The torsional angle C(16) - C(17) - C(20) - C(21) = (209°) is in good agreement with the value 210° calculated by Allinger _et al_. (8) from a conformational analysis and dipole moment study of the 17-β-acetyl side chain.

The effect of these conformational features on the chemical and biological properties of this system will be considered elsewhere.

Table 1

Fractional Atomic Coordinates of III (Least squares e.s.d.'s x 10^3 are given in parentheses)

Atom No.	x	y	z	Atom No.	x	y	z
C(1)	.161(4)	.027(1)	.129(2)	C(20)	-.555(6)	-.144(2)	.476(3)
C(2)	.265(4)	-.007(1)	.035(2)	C(21)	-.431(5)	-.150(2)	.566(2)
C(3)	.285(5)	-.036(1)	-.048(3)	C(22)	-.418(6)	-.236(2)	.354(3)
C(4)	.148(5)	-.074(1)	-.071(2)	C(23)	-.429(5)	-.274(2)	.436(2)
C(5)	-.014(5)	-.072(1)	-.015(2)	C(24)	-.305(5)	-.252(2)	.264(3)
C(6)	-.169(5)	-.099(2)	-.051(2)	C(25)	-.367(5)	-.278(2)	.173(3)
C(7)	-.282(4)	-.129(2)	.027(2)	C(26)	-.264(6)	-.291(2)	.095(3)
C(8)	-.296(4)	-.101(1)	.131(2)	C(27)	-.084(6)	-.279(2)	.096(3)
C(9)	-.122(4)	-.079(1)	.165(2)	C(28)	.002(6)	-.257(2)	.179(3)
C(10)	-.031(4)	-.046(1)	.090(2)	C(29)	-.112(5)	-.240(1)	.265(2)
C(11)	-.104(4)	-.065(1)	.277(2)	0(30)	.417(4)	-.036(1)	-.109(2)
C(12)	-.202(4)	-.097(1)	.352(2)	0(31)	-.183(3)	-.017(1)	.285(1)
C(13)	-.387(4)	-.113(1)	.317(2)	0(32)	-.602(3)	-.226(1)	.321(2)
C(14)	-.362(4)	-.136(1)	.212(2)	0(33)	-.351(3)	-.192(1)	.389(1)
C(15)	-.553(4)	-.162(1)	.189(2)	0(34)	-.713(4)	-.125(1)	.481(2)
C(16)	-.619(4)	-.174(1)	.296(2)	Br(35)	-.529(0)	-.118(0)	.688(0)
C(17)	-.471(4)	-.154(1)	.376(2)	F(36)	.009(2)	-.122(1)	.166(1)
C(18)	-.518(4)	-.068(1)	.320(2)	C(37)	.015(11)	.410(3)	.809(7)
C(19)	-.156(4)	-.002(1)	.067(2)	0(38)	.044(7)	.407(2)	.912(4)

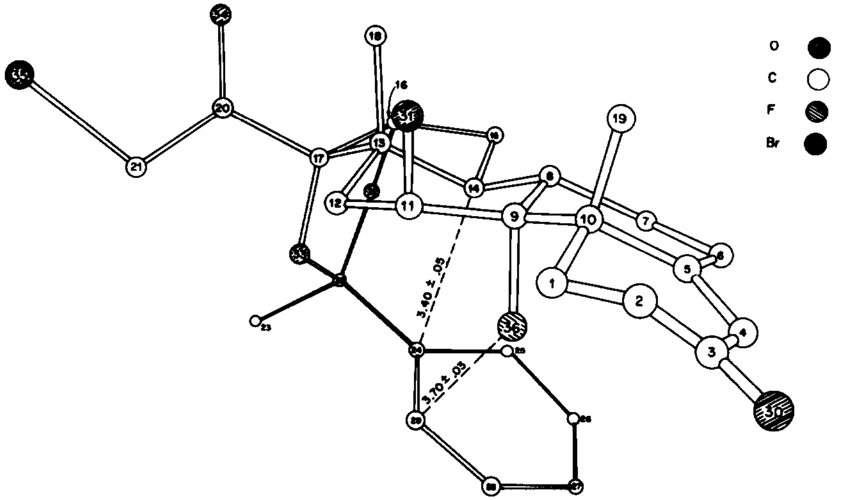

Figure I. The Solid State Molecular Conformation of III

Table 2

Selected Torsional Angles ***

Ring D	Ring E
C(17)-C(13)-C(14)-C(15) = 46°	O(32)-C(16)-C(17)-O(33) = 27°
C(13)-C(14)-C(15)-C(16) = - 29°	C(16)-C(17)-O(33)-C(22) = - 15°
C(14)-C(15)-C(16)-C(17) = 0°	C(17)-O(33)-C(22)-O(32) = - 5°
C(15)-C(16)-C(17)-C(13) = 27°	O(33)-C(22)-O(32)-C(16) = 25°
C(16)-C(17)-C(13)-C(14) = - 44°	C(22)-O(32)-C(16)-C(17) = - 32°

[***] Notation and sign of torsional angles are as defined by Geise et.al. (5)

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