Structure of Flurandrenolide

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The title compound, $C_{24}H_{33}FO_6$, is a glucocorticoid. The crystal belongs to space group $C2$ with the cell dimensions $a = 30.575(2)$, $b = 9.3616(9)$, $c = 17.012(5)$ Å and $\beta = 120.67(4)^\circ$. The final R value is 0.049. There are two crystallographically independent flurandrenolide molecules. The cyclohexenone rings in both molecules adopt different half-chair conformations. The dioxolane rings in both molecules take different puckered forms. The other corresponding rings in both molecules take essentially similar conformations.

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Flurandrenolide [(6 α ,11 β ,16 α)-6-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]pregn-4-ene-3,20-dione] is a corticosteroid that is available in ointment, cream, lotion, and tape formulations for the treatment of steroid-responsive dermatoses.¹

The X-ray analysis of the title compound (Fig. 1) was undertaken in order to disclose the inherent three-dimensional structure to understand the pharmacological activity based on the structure.

The title compound was purchased from Prestwick Chemicals Inc. The single crystals of the molecule were grown from a methanol solution. Flurandrenolide was crystallized as a methanol solvate. A colorless prism crystal with the size of $0.50 \times 0.30 \times 0.10$ mm was mounted on a glass fiber and used for data collection. The structure was solved by direct methods and non-H atoms were refined by full-matrix least squares method with anisotropic temperature factors. The positions of H-atoms of hydroxyl groups except for that of the methanol molecule were obtained from difference Fourier syntheses. The positions of other H-atoms were calculated geometrically. All the H-atoms were refined with the riding model. The absolute configuration was assigned based on the known configuration of the steroid skeleton. There are two crystallographically independent flurandrenolide molecules and a methanol

molecule in an asymmetric unit. The crystal and experimental data are shown in Table 1. Atomic parameters of non-H atoms are shown in Table 2.

Molecular structures of two crystallographically independent flurandrenolide molecules drawn by ORTEP-III⁴ are shown in Fig. 2. Selected bond lengths and bond angles are given in Table 3. Rings A in both molecules adopt half-chair conformations. The puckering patterns, however, are different. In molecule I, C102 and C119 are located on the same side with respect to a plane defined by C103, C104, C105 and C110. On the other hand, C201 and C219 are placed on the same side with respect to the corresponding plane in molecule II. The torsion angles of C102–C101–C110–C119 and C202–C201–C210–C219 are $-73.2(6)$ and $-160.3(5)^\circ$, respectively. Rings B and C in both molecules take similar chair conformations. Rings D in both molecules adopt very similar twisted conformations.

Fig. 1 Chemical structure of Flurandrenolide.

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Table 1 Crystal and experimental data

Formula:	$2C_{24}H_{33}FO_6 \cdot CH_4O$
Formula weight	= 905.07
Crystal system:	monoclinic
Space group:	$C2$ $Z = 4$
a	= 30.575(2) Å
b	= 9.3616(9) Å
c	= 17.012(5) Å
V	= 4188(1) Å ³
D_x	= 1.435 g/cm ³
No. of observations ($I > 2.00\sigma(I)$)	= 5581
θ_{max}	= 68.25° with Cu $K\alpha$
R ($I > 2.00\sigma(I)$)	= 0.049
$(\Delta/\sigma)_{max}$	= 0.002
$(\Delta\rho)_{max}$	= 0.81 e/Å ³
$(\Delta\rho)_{min}$	= -0.37 e/Å ³
Measurement:	Rigaku RAXIS-RAPID
Program system:	CrystalStructure 3.5.1 ²
Structure determination:	SIR92 ³
Refinement:	full-matrix

CCDC 284432 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 2 Atomic coordinates and equivalent isotropic thermal parameters (B_{eq})

atom	x	y	z	$B_{eq}(\text{\AA}^2)$
molecule I				
F(101)	0.26212(8)	0.2974(3)	0.1728(1)	5.95(6)
O(101)	0.4087(1)	0.2652(5)	0.4626(2)	8.0(1)
O(102)	0.1733(1)	0.4323(3)	0.3912(2)	5.02(7)
O(103)	0.0732(1)	-0.1037(3)	0.1468(2)	6.10(8)
O(104)	0.0900(6)	-0.0623(3)	0.2885(1)	3.78(6)
O(105)	-0.0127(1)	0.1082(4)	0.1941(2)	6.34(8)
O(106)	-0.0018(1)	0.0830(3)	0.3523(2)	6.51(8)
C(101)	0.2996(1)	0.3026(6)	0.4720(2)	5.8(1)
C(102)	0.3524(1)	0.3363(6)	0.5020(3)	6.8(1)
C(103)	0.3656(1)	0.2902(5)	0.4386(3)	5.1(1)
C(104)	0.3259(1)	0.2866(4)	0.3460(2)	4.26(9)
C(105)	0.2789(1)	0.3183(4)	0.3182(2)	3.79(9)
C(106)	0.2412(1)	0.3300(4)	0.2230(2)	4.26(9)
C(107)	0.1979(1)	0.2374(4)	0.1959(2)	3.98(9)
C(108)	0.1736(1)	0.2727(4)	0.2479(2)	3.47(8)
C(109)	0.2125(1)	0.2672(4)	0.3472(2)	3.36(8)
C(110)	0.2605(1)	0.3520(4)	0.3780(2)	4.01(9)
C(111)	0.1888(1)	0.2915(4)	0.4014(2)	3.89(9)
C(112)	0.1459(1)	0.1895(4)	0.3751(2)	3.71(8)
C(113)	0.1071(1)	0.1875(4)	0.2760(2)	3.49(8)
C(114)	0.1339(1)	0.1647(4)	0.2274(2)	3.63(8)
C(115)	0.0916(1)	0.1339(5)	0.1339(2)	4.39(9)
C(116)	0.0591(1)	0.0356(5)	0.1475(2)	4.5(1)
C(117)	0.0718(1)	0.0579(4)	0.2434(2)	3.71(8)
C(118)	0.0746(1)	0.3196(4)	0.2445(2)	4.52(9)
C(119)	0.2530(2)	0.5111(4)	0.3750(3)	6.1(1)
C(120)	0.0275(1)	0.0723(4)	0.2534(3)	4.5(1)
C(121)	0.0372(1)	0.0445(5)	0.3432(3)	5.9(1)
C(122)	0.0865(1)	-0.1725(4)	0.2258(3)	4.8(1)
C(123)	0.1323(2)	-0.2552(5)	0.2540(3)	6.2(1)
C(124)	0.0444(2)	-0.2591(5)	0.2151(3)	6.7(1)
molecule II				
F(201)	0.24521(8)	-0.0972(3)	0.2809(2)	6.37(7)
O(201)	0.3989(1)	-0.0267(4)	0.5615(2)	6.83(9)
O(202)	0.40478(9)	-0.3034(3)	0.2153(1)	4.35(6)
O(203)	0.3057(1)	0.2680(3)	0.0071(2)	5.41(7)
O(204)	0.38574(8)	0.1973(3)	0.0936(1)	3.81(5)
O(205)	0.3523(1)	0.0313(3)	-0.0973(2)	5.67(8)
O(206)	0.4481(1)	0.0125(5)	-0.0369(2)	9.5(1)
C(201)	0.4176(1)	-0.2372(5)	0.4188(3)	5.9(1)
C(202)	0.4309(2)	-0.1129(6)	0.4762(3)	6.1(1)
C(203)	0.3902(2)	-0.0782(5)	0.4915(3)	5.4(1)
C(204)	0.3397(1)	-0.0988(4)	0.4177(3)	4.8(1)
C(205)	0.3297(1)	-0.1590(4)	0.3438(3)	4.2(1)
C(206)	0.2792(1)	-0.1548(5)	0.2637(3)	4.8(1)
C(207)	0.2805(1)	-0.0647(4)	0.1953(2)	4.18(9)
C(208)	0.3203(1)	-0.1103(4)	0.1770(2)	3.44(8)
C(209)	0.3711(1)	-0.1273(4)	0.2638(2)	3.37(8)
C(210)	0.3683(1)	-0.2259(4)	0.3304(2)	4.19(9)
C(211)	0.4125(1)	-0.1632(4)	0.2467(2)	3.74(8)
C(212)	0.4149(1)	-0.0646(4)	0.1833(2)	3.42(8)
C(213)	0.3643(1)	-0.0456(4)	0.0977(2)	3.22(8)
C(214)	0.3262(1)	-0.0027(4)	0.1215(2)	3.06(7)
C(215)	0.2816(1)	0.0456(4)	0.0342(2)	3.98(8)
C(216)	0.3049(1)	0.1236(4)	-0.0088(2)	3.85(9)
C(217)	0.3598(1)	0.0796(4)	0.0395(2)	3.35(8)
C(218)	0.3488(1)	-0.1763(4)	0.0400(2)	4.31(9)
C(219)	0.3515(2)	-0.3753(4)	0.2957(3)	6.0(1)
C(220)	0.3792(1)	0.0545(4)	-0.0211(3)	4.19(9)
C(221)	0.4339(2)	0.0601(7)	0.0186(3)	7.6(1)
C(222)	0.3552(1)	0.3176(4)	0.0579(3)	4.6(1)
C(223)	0.3606(2)	0.4004(5)	0.1327(3)	7.0(1)
C(224)	0.3680(2)	0.3978(5)	0.0002(3)	6.8(1)
methanol				
C(301)	0.4714(3)	0.2245(8)	0.3600(4)	12.2(2)
O(301)	0.4714(3)	0.3487(6)	0.3970(4)	15.2(2)

$$B_{eq} = 8/3\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$$

Rings E in both molecules, however, take different conformations. In molecule I, it adopts a twisted conformation with both O104 and C122 being puckered. The ring takes an envelope conformation in molecule II with only O204 being puckered. Due to these conformational differences molecule II takes a more folded conformation than molecule I. Therefore intramolecular distances between O1 and O5 in both molecules are different, *i.e.* 11.357(6) and 10.566(5)Å in molecules I and II, respectively. All the bond lengths and angles are within the expected ranges. The O–C bond lengths in ring E, however, are significantly different between two molecules. Significant differences between the corresponding bond angles are also observed in some bond angles especially around the C6, C17, and C22 atoms. O101, O102, O105, O106, O201, O202 and O206 are engaged in intermolecular hydrogen bonds. Other oxygen and fluorine atoms, however, are not engaged in hydrogen bonds.

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Fig. 2 Molecular structure of Flurandrenolide along with the labeling atoms and rings. Thermal ellipsoids of non-H atoms are drawn at the 40% probability level.

Table 3 Selected bond lengths (Å) and bond angles (°)

molecule I		molecule II	
F(101)–C(106)	1.337(5)	F(201)–C(206)	1.331(6)
O(101)–C(103)	1.189(6)	O(201)–C(203)	1.181(6)
O(102)–C(111)	1.381(5)	O(202)–C(211)	1.391(4)
O(103)–C(116)	1.376(5)	O(203)–C(216)	1.377(5)
O(103)–C(122)	1.352(5)	O(203)–C(222)	1.384(5)
O(104)–C(117)	1.377(4)	O(204)–C(217)	1.395(4)
O(104)–C(122)	1.390(5)	O(204)–C(222)	1.389(5)
O(105)–C(120)	1.172(4)	O(205)–C(220)	1.147(4)
O(106)–C(121)	1.329(6)	O(206)–C(221)	1.303(8)
C(116)–O(103)–C(122)	112.3(4)	C(216)–O(203)–C(222)	110.8(3)
C(117)–O(104)–C(122)	109.1(2)	C(217)–O(204)–C(222)	108.8(2)
C(104)–C(103)–O(101)	123.1(5)	C(204)–C(203)–O(201)	122.1(5)
O(101)–C(103)–C(102)	120.2(3)	O(201)–C(203)–C(202)	120.3(4)
C(107)–C(106)–F(101)	108.5(3)	C(207)–C(206)–F(201)	106.6(3)
F(101)–C(106)–C(105)	109.5(3)	F(201)–C(206)–C(205)	112.4(4)
C(112)–C(111)–O(102)	112.3(3)	C(212)–C(211)–O(202)	112.3(3)
O(102)–C(111)–C(109)	108.6(3)	O(202)–C(211)–C(209)	107.2(3)
C(117)–C(116)–O(103)	103.6(3)	C(217)–C(216)–O(203)	105.0(3)
O(103)–C(116)–C(115)	110.7(4)	O(203)–C(216)–C(215)	111.0(4)
C(120)–C(117)–O(104)	110.2(3)	C(220)–C(217)–O(204)	107.2(3)
O(104)–C(117)–C(113)	109.4(2)	O(204)–C(217)–C(213)	110.7(2)
O(104)–C(117)–C(116)	104.0(3)	O(204)–C(217)–C(216)	104.2(3)
C(121)–C(120)–O(105)	121.9(5)	C(221)–C(220)–O(205)	121.6(5)
O(105)–C(120)–C(117)	123.7(5)	O(205)–C(220)–C(217)	121.2(4)
O(106)–C(121)–C(120)	111.6(3)	O(206)–C(221)–C(220)	112.5(4)
C(123)–C(122)–O(103)	109.4(5)	C(223)–C(222)–O(203)	109.3(4)
C(123)–C(122)–O(104)	107.5(3)	C(223)–C(222)–O(204)	107.7(3)
C(124)–C(122)–O(103)	110.1(8)	C(224)–C(222)–O(203)	109.9(3)
C(124)–C(122)–O(104)	112.9(5)	C(224)–C(222)–O(204)	111.5(4)
O(103)–C(122)–O(104)	103.6(3)	O(203)–C(222)–O(204)	106.1(3)

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References

1. G. G. Krueger, M. A. O'Reilly, M. Weidner, S. H. Dromgoole, and F. P. Killey, *J. Am. Acad. Dermatol.*, **1998**, 38, 186.
2. CrystalStructure, version 3.5.1, **2000–2003** Crystal Structure Analysis Package, Rigaku and Rigaku/MS.
3. SIR92: A. Altomare, G. Casciarano, C. Giacovazzo, A. Guagliardi, M. Burla, G. Polidori, and M. Camalli, *J. Appl. Cryst.*, **1994**, 27, 435.
4. ORTEP III, L. J. Farrugia, *J. Appl. Cryst.*, **1997**, 30, 565.