

Structure of Flucinonide

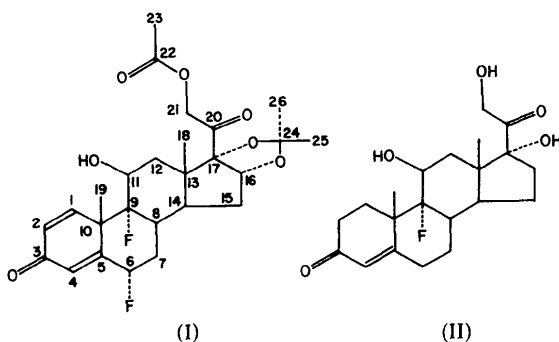
BY SUNG-IL CHO* AND B. M. CRAVEN

Department of Crystallography, University of Pittsburgh, Pittsburgh, PA 15260, USA

(Received 15 September 1986; accepted 13 November 1986)

Abstract. 6 α ,9 α -Difluoro-16 α ,17-isopropylidenedioxy-3,20-dioxo-1,4-pregnadiene-11 β ,21-diol 21-acetate, C₂₆H₃₂F₂O₇, $M_r = 494.6$, orthorhombic, $P2_12_12_1$, $a = 14.169(2)$, $b = 6.297(1)$, $c = 28.097(4)$ Å, $V = 2506.9(5)$ Å³, $Z = 4$, $D_m = 1.33$, $D_x = 1.31$ g cm⁻³, $\lambda(\text{Cu K}\alpha) = 1.5418$ Å (Ni filter), $\mu = 7.83$ cm⁻¹, $F(000) = 1048$, $T = 298$ K, final $R = 0.046$ for 1478 unique observed reflections. The molecule has conformational features in common with other corticosteroids. Thus the B, C and D rings are very similar to 9 α -fluorocortisol and the C(17) tail to cortisone acetate. A feature characteristic of flucinonide is the near coplanarity of all atoms in the A ring together with C(6) and F(6).

Introduction. Flucinonide (I) is a corticosteroid with anti-inflammatory activity. The crystal structure has been determined in order to compare the molecular conformation with those of other related drugs, in particular 9 α -fluorocortisol (II). The latter has anti-inflammatory activity, but also induces deposition of glycogen in the liver and reduces sodium excretion in the kidney. Special features in (I) are the two fluoro substituents in the B ring. Molecules (I) and (II) differ as a result of four chemical modifications, two at each end of the molecule.



Experimental. Sample from Sigma Chemical Co., St Louis, MO. Slow evaporation of methanol solution gave needles along *b*. Density by flotation in hexane/

bromoform. Crystal 0.16 × 0.16 × 0.50 mm with *b* close to ϕ axis of Enraf-Nonius CAD-4 diffractometer. Cell dimensions from 25 reflections at $\pm\omega$ ($27 < |\omega| < 35^\circ$). Intensity data by $\omega/2\theta$ scan, for octant $12 \geq h \geq 0$, $5 \geq k \geq 0$, $25 \geq l \geq 0$, $(\sin\theta)/\lambda \leq 0.52$ Å⁻¹, 1478 reflections measured. Three monitor reflections in range $\pm 2\sigma$ from average intensity. No absorption corrections. Structure determined by direct methods (MITHRIL; Gilmore, 1984); refined by full-matrix least squares (SHELX76; Sheldrick, 1976) to minimize $\sum w\Delta^2$ where $\Delta = |F_o| - |F_c|$ and $w = (\sigma^2 + 0.02F_o^2)^{-1/2}$; σ is the e.s.d. in $|F_o|$ due to counting statistics. $|F_o| = \sigma$ for weak reflections ($|F_o| < \sigma/2$). Atomic scattering factors of Cromer & Waber (1965) and Stewart, Davidson & Simpson (1965) assumed. The H atoms were located and refined, except those in methyl

Table 1. Atomic parameters

Fractional coordinates are $\times 10^4$; U_{eq} are isotropic mean-square amplitudes of thermal vibration (Å² $\times 10^3$) given by $(U_{11} + U_{22} + U_{33})/3$, where U_{ij} are anisotropic thermal parameters from the supplementary data.

	<i>x</i>	<i>y</i>	<i>z</i>	U_{eq}
C(1)	9768 (3)	4470 (7)	10001 (1)	48 (2)
C(2)	10605 (3)	3567 (7)	10072 (1)	52 (2)
C(3)	11451 (3)	4394 (7)	9849 (1)	52 (2)
C(4)	11361 (3)	6378 (7)	9573 (1)	47 (2)
C(5)	10532 (3)	7280 (6)	9509 (1)	40 (2)
C(6)	10418 (2)	9229 (6)	9199 (1)	53 (2)
C(7)	9774 (3)	8804 (6)	8790 (1)	51 (2)
C(8)	8830 (2)	7818 (6)	8933 (1)	41 (2)
C(9)	8996 (2)	5855 (6)	9258 (1)	36 (2)
C(10)	9620 (2)	6426 (6)	9710 (1)	40 (2)
C(11)	8109 (3)	4515 (6)	9363 (1)	41 (2)
C(12)	7505 (2)	4110 (6)	8912 (1)	41 (2)
C(13)	7312 (2)	6108 (5)	8623 (1)	41 (2)
C(14)	8267 (2)	7137 (6)	8504 (1)	39 (2)
C(15)	8042 (3)	8751 (7)	8116 (1)	57 (2)
C(16)	7310 (3)	7607 (6)	7804 (1)	51 (2)
C(17)	6916 (2)	5722 (6)	8110 (1)	47 (2)
C(18)	6634 (3)	7647 (7)	8586 (1)	57 (2)
C(19)	9183 (3)	8110 (7)	10032 (1)	58 (2)
C(20)	5856 (3)	5418 (7)	8080 (1)	53 (2)
C(21)	5498 (3)	3202 (8)	8105 (2)	65 (3)
C(22)	4256 (3)	3552 (8)	8650 (2)	68 (3)
C(23)	3192 (4)	3529 (16)	8703 (3)	102 (5)
C(24)	7698 (3)	4399 (7)	7432 (1)	66 (3)
C(25)	6946 (5)	3708 (10)	7067 (1)	100 (4)
C(26)	8622 (5)	3353 (14)	7336 (2)	126 (5)
F(6)	11302 (2)	9873 (4)	9027 (1)	76 (2)
F(9)	9557 (1)	4430 (3)	8987 (1)	42 (1)
O(3)	12221 (2)	3479 (5)	9878 (1)	76 (2)
O(11)	7572 (2)	5510 (5)	9725 (1)	53 (1)
O(16)	7773 (2)	6643 (5)	7415 (1)	72 (2)
O(17)	7376 (2)	3896 (4)	7902 (1)	46 (1)
O(20)	5345 (2)	6953 (5)	8035 (1)	77 (2)
O(21)	4491 (2)	3170 (6)	8200 (1)	70 (2)
O(22)	4823 (3)	3840 (7)	8955 (1)	93 (2)

* Permanent address: Department of Chemical Engineering, Seoul City University, Seoul 131, Korea.

groups C(23) and C(25). Convergence at $R = wR = 0.05$ with largest (shift/ σ) = 0.09. Maximum residual density 0.20 (5) e \AA^{-3} . Final parameters in Table 1.* Bond distances and angles in Table 2 and torsion angles in Table 3.

Discussion. As shown in Fig. 1, and from the torsion angles (Table 3), atoms in the *A* ring and the O(3) substituent, together with C(5) and F(6) are almost coplanar, whereas in the crystal structure of (II) (Weeks, Duax & Wolff, 1973), the *A* ring has only one

* Lists of anisotropic temperature factors for non-H atoms, H-atom parameters and structure factors have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43625 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. Bond distances (\AA) and angles ($^\circ$)

Values are uncorrected for thermal vibration effects.

C(1)=C(2)	1.330 (6)	C(3)=O(3)	1.236 (5)
C(2)-C(3)	1.449 (6)	C(6)-F(6)	1.402 (4)
C(3)-C(4)	1.476 (6)	C(9)-F(9)	1.420 (4)
C(4)=C(5)	1.317 (5)	C(10)-C(19)	1.525 (5)
C(5)-C(10)	1.509 (5)	C(11)-O(11)	1.416 (5)
C(10)-C(1)	1.493 (5)	C(13)-C(18)	1.552 (5)
C(5)-C(6)	1.514 (5)	C(16)-O(16)	1.412 (5)
C(6)-C(7)	1.492 (5)	C(17)-O(17)	1.445 (4)
C(7)-C(8)	1.528 (5)	O(16)-C(24)	1.418 (5)
C(8)-C(9)	1.555 (4)	O(17)-C(24)	1.433 (5)
C(9)-C(10)	1.589 (4)	C(24)-C(25)	1.542 (7)
C(9)-C(11)	1.542 (5)	C(24)-C(26)	1.490 (8)
C(11)-C(12)	1.550 (5)	C(17)-C(20)	1.516 (5)
C(12)-C(13)	1.522 (4)	C(20)-O(20)	1.214 (5)
C(13)-C(14)	1.537 (4)	C(20)-C(21)	1.486 (6)
C(14)-C(8)	1.508 (4)	C(21)-O(21)	1.452 (6)
C(14)-C(15)	1.524 (5)	O(21)-C(22)	1.329 (6)
C(15)-C(16)	1.537 (5)	C(22)=O(22)	1.189 (6)
C(16)-C(17)	1.568 (5)	C(22)-C(23)	1.515 (10)
C(17)-C(13)	1.566 (4)		
C(10)-C(1)=C(2)	124.1 (4)	C(14)-C(13)=C(17)	100.4 (2)
C(1)=C(2)-C(3)	121.3 (4)	C(15)-C(14)-C(13)	104.6 (3)
C(2)-C(3)-C(4)	117.4 (3)	C(14)-C(15)-C(16)	103.7 (3)
C(3)-C(4)=C(5)	120.9 (4)	C(15)-C(16)-C(17)	106.4 (3)
C(4)=C(5)-C(10)	124.0 (3)	C(2)-C(3)=O(3)	122.3 (4)
C(1)-C(10)-C(5)	112.2 (3)	C(4)-C(3)=O(3)	120.4 (4)
C(1)-C(10)-C(9)	109.2 (3)	C(5)-C(6)-F(6)	109.7 (3)
C(4)=C(5)-C(6)	121.6 (3)	C(7)-C(6)-F(6)	109.4 (3)
C(8)-C(9)-C(10)	112.0 (4)	C(8)-C(9)-F(9)	105.8 (2)
C(9)-C(10)-C(5)	105.0 (3)	C(10)-C(9)-F(9)	105.1 (2)
C(10)-C(5)-C(6)	114.4 (3)	C(11)-C(9)-F(9)	102.3 (3)
C(5)-C(6)-C(7)	111.3 (3)	C(1)-C(10)-C(19)	107.8 (3)
C(6)-C(7)-C(8)	113.9 (3)	C(5)-C(10)-C(19)	108.8 (3)
C(7)-C(8)-C(9)	110.2 (3)	C(9)-C(10)-C(19)	113.9 (3)
C(10)-C(9)-C(11)	115.1 (3)	C(9)-C(11)-O(11)	109.5 (3)
C(7)-C(8)-C(14)	111.6 (3)	C(12)-C(11)-O(11)	111.3 (3)
C(11)-C(12)-C(13)	113.5 (3)	C(12)-C(13)-C(18)	111.9 (3)
C(9)-C(11)-C(12)	112.6 (3)	C(14)-C(13)-C(18)	112.7 (3)
C(8)-C(9)-C(11)	115.1 (3)	C(17)-C(13)-C(18)	108.3 (3)
C(9)-C(8)-C(14)	108.9 (3)	C(15)-C(16)-O(16)	109.2 (3)
C(8)-C(14)-C(13)	114.3 (3)	C(13)-C(17)-O(17)	109.5 (3)
C(12)-C(13)-C(14)	107.8 (2)	C(17)-C(16)-O(16)	105.3 (3)
C(12)-C(13)-C(17)	115.3 (3)	C(16)-O(16)-C(24)	111.6 (3)
C(8)-C(14)-C(15)	119.5 (3)	C(16)-C(17)-O(17)	102.7 (3)
C(16)-C(17)-C(13)	105.1 (3)	C(17)-O(17)-C(24)	109.9 (3)
O(16)-C(24)-O(17)	106.0 (3)	C(17)-C(20)=O(20)	119.7 (3)
O(16)-C(24)-C(25)	108.1 (3)	C(17)-C(20)-C(21)	117.0 (3)
O(17)-C(24)-C(26)	111.6 (4)	O(20)-C(20)-C(21)	123.3 (4)
O(17)-C(24)-C(25)	109.3 (3)	C(20)-C(21)-O(21)	110.9 (4)
O(17)-C(24)-C(26)	110.4 (4)	C(21)-O(21)-C(22)	114.7 (4)
C(25)-C(24)-C(26)	111.2 (4)	O(21)-C(22)=O(22)	123.0 (5)
C(13)-C(17)-C(20)	115.2 (3)	O(21)-C(22)-C(23)	109.9 (5)
C(16)-C(17)-C(20)	114.7 (3)	O(22)=C(22)-C(23)	127.1 (5)
O(17)-C(17)-C(20)	108.9 (3)		

double bond and a ($1\alpha,2\alpha$) half-chair conformation. Bond distances and angles for the *A* ring in (I) (Table 2) agree with those in the crystal structure of another 1,4-pregnadiene derivative (Declercq, Germain & Van Meerse, 1972a) where the *A* ring is also nearly planar. In (I) and (II) there is agreement between the corresponding bond lengths and angles of the *B*, *C* and *D* rings, except that the presence of the 6α -fluorine substituent in (I) appears to cause a shortening of the C(6)-C(7) bond, 1.492 (5) *versus* 1.539 (5) \AA . This bond is also short when compared with the structure of a related 6α -methyl-9 α -fluoro derivative [1.544 (7) \AA ; Dideberg, Dupont & Campsteyn, 1974]. The *B* and *C* rings have chair conformations, with the *B* ring slightly flatter in (II), as shown by a smaller average value in the magnitude of the *B* ring torsion angles (51.9 *versus* 55.5 $^\circ$). The other chemical modifications between (I)

Table 3. Bond torsion angles ($^\circ$)

C(10)-C(1)=C(2)-C(3)	-2.7 (6)	C(6)-C(7)-C(8)-C(14)	-171.9 (3)
C(11)=C(2)-C(3)-C(4)	5.0 (6)	C(5)-C(10)-C(9)-C(11)	167.7 (3)
C(2)-C(3)-C(4)=C(5)	-4.1 (6)	C(9)-C(8)-C(14)-C(15)	-177.4 (3)
C(3)-C(4)=C(5)-C(10)	0.9 (6)	C(11)-C(12)-C(13)-C(17)	166.3 (3)
C(4)=C(5)-C(10)-C(1)	1.5 (5)	C(14)-C(15)-C(16)-O(16)	-95.8 (3)
C(5)-C(10)-C(1)=C(2)	-0.6 (5)	C(14)-C(13)-C(17)-O(17)	76.9 (3)
C(10)-C(5)-C(6)-C(7)	-58.0 (4)	C(1)=C(2)-C(3)=O(3)	-173.9 (4)
C(5)-C(6)-C(7)-C(8)	51.1 (4)	C(5)=C(4)-C(3)=O(3)	174.8 (4)
C(6)-C(7)-C(8)-C(9)	-50.8 (4)	C(4)=C(5)-C(6)-F(6)	-2.4 (5)
C(7)-C(8)-C(9)-C(10)	55.1 (3)	C(8)-C(7)-C(6)-F(6)	172.6 (3)
C(8)-C(9)-C(10)-C(5)	-58.4 (3)	C(7)-C(8)-C(9)-F(9)	-58.8 (3)
C(9)-C(10)-C(5)-C(6)	59.8 (4)	C(5)-C(10)-C(9)-F(9)	56.0 (3)
C(14)-C(8)-C(9)-C(11)	-48.2 (4)	C(12)-C(11)-C(9)-F(9)	-69.6 (3)
C(8)-C(9)-C(11)-C(12)	44.6 (4)	C(2)=C(1)-C(10)-C(19)	-120.4 (4)
C(9)-C(11)-C(12)-C(13)	-48.5 (4)	C(6)-C(5)-C(10)-C(19)	-62.5 (4)
C(11)-C(12)-C(13)-C(14)	55.1 (3)	C(11)-C(9)-C(10)-C(19)	-73.4 (4)
C(12)-C(13)-C(14)-C(8)	-61.6 (3)	F(9)-C(9)-C(10)-C(19)	174.9 (3)
C(13)-C(14)-C(8)-C(9)	57.5 (3)	F(9)-C(9)-C(11)-O(11)	166.1 (3)
C(17)-C(13)-C(14)-C(15)	44.8 (3)	C(8)-C(9)-C(11)-O(11)	-79.7 (4)
C(13)-C(14)-C(15)-C(16)	-39.3 (3)	C(13)-C(12)-C(11)-O(11)	74.8 (4)
C(14)-C(15)-C(16)-C(17)	17.5 (4)	C(11)-C(12)-C(13)-C(18)	-69.4 (4)
C(15)-C(16)-C(17)-C(13)	9.9 (3)	C(15)-C(14)-C(13)-C(18)	-70.2 (3)
C(16)-C(17)-C(13)-C(14)	-32.8 (3)	C(20)-C(17)-C(13)-C(18)	-41.7 (4)
C(2)=C(1)-C(10)-C(9)	115.4 (4)	O(16)-C(16)-C(17)-O(17)	11.2 (3)
C(4)=C(5)-C(6)-C(7)	118.9 (4)	C(16)-C(17)-O(17)-C(24)	-20.2 (3)
C(17)-O(17)-C(24)-O(16)	21.8 (4)	C(15)-C(16)-C(17)-C(20)	137.4 (3)
O(17)-C(24)-O(16)-C(16)	-14.0 (4)	C(16)-C(17)-C(20)-C(21)	145.6 (4)
C(24)-O(16)-C(16)-C(17)	1.5 (4)	C(16)-C(17)-C(20)=O(20)	-34.0 (5)
C(16)-O(16)-C(24)-C(25)	103.1 (4)	C(17)-C(20)-C(21)-O(21)	164.7 (3)
C(16)-O(16)-C(24)-C(26)	-134.2 (4)	C(20)-C(21)-O(21)-C(22)	-77.1 (5)
C(17)-O(17)-C(24)-C(25)	-94.5 (4)	C(21)-O(21)-C(22)-C(23)	178.7 (5)
C(17)-O(17)-C(24)-C(26)	142.9 (4)	C(21)-O(21)-C(22)=O(22)	-2.0 (7)
C(14)-C(13)-C(17)-C(20)	-160.0 (3)		

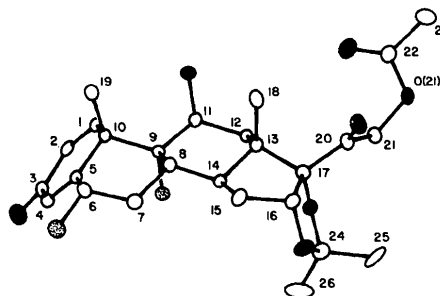


Fig. 1. Molecular structure and atom numbering in fluocinonide. Atoms are shown as 50% probability thermal ellipsoids (C, open; O, solid; F, dotted).

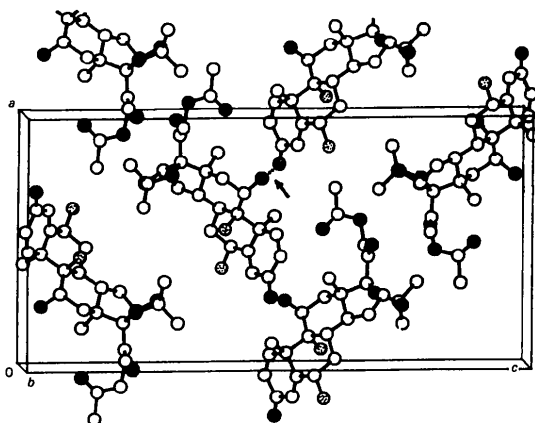


Fig. 2. The crystal structure of fluocinonide. Circles represent C atoms (open), O (solid) and F (dotted). The arrow points to the H bond.

and (II) involve the isopropylidenedioxy group bridging C(16) to C(17) on the *D* ring, and the 21-acetoxy group. These appear to have little effect on the conformation of the *D* ring which has the (13 β ,14 α) half-chair form in both molecules. The additional five-membered ring has a flattened O(17)-envelope conformation. In (I), the C(17) side chain as far as O(21) has an extended conformation similar to the side chain in (II) and cortisone acetate (Declercq, Germain & Van Meerssche, 1972*b*). The terminal acetoxy group is planar. Torsion angles for the C(21)—O(21) bond are

also similar in (I) and cortisone acetate, -77.1 (5) versus -82 (1) $^\circ$.

In the crystal structure of (I) (Fig. 2), molecules are H bonded in discrete pairs through the interaction O(11)—H \cdots O(3), where the O(11)—H bond length is 0.92 (6) Å, the O(11) \cdots O(3) and H \cdots O(3) distances are 2.79, 1.96 Å and the angles C(11)—O(11)—H, O—H \cdots O are 110 (4) and 150 $^\circ$ respectively. The shortest intermolecular distances involving fluorine atoms are F(6) \cdots O(3), 3.55 Å; F(9) \cdots C(6), 3.55 Å; F(9) \cdots C(7), 3.60 Å; F(6) \cdots F(9), 3.79 Å.

S-IC is grateful to the Korean Science and Engineering Foundation for a research fellowship. This work was supported in part by NIH Grant HL-20350.

References

- CROMER, D. T. & WABER, J. T. (1965). *Acta Cryst.* **18**, 104–109.
 DECLERCQ, J.-P., GERMAIN, G. & VAN MEERSSCHE, M. (1972*a*). *Cryst. Struct. Commun.* **1**, 5–7.
 DECLERCQ, J.-P., GERMAIN, G. & VAN MEERSSCHE, M. (1972*b*). *Cryst. Struct. Commun.* **1**, 59–62.
 DIDEBERG, O., DUPONT, L. & CAMPSTEYN, H. (1974). *Acta Cryst.* **B30**, 702–710.
 GILMORE, C. J. (1984). *J. Appl. Cryst.* **17**, 42–46.
 SHELDRIK, G. M. (1976). *SHELX*. Program for crystal structure determination. Univ. of Cambridge, England.
 STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.
 WEEKS, C. M., DUAX, W. L. & WOLFF, M. E. (1973). *J. Am. Chem. Soc.* **95**, 2865–2868.

Acta Cryst. (1987). **C43**, 919–922

Structure and Stereochemistry of a Carbapenam Derivative

BY DENIS DÉSILETS, FRANCINE BÉLANGER-GARIÉPY, STEPHEN HANESSIAN AND FRANÇOIS BRISSE

Département de Chimie, Université de Montréal, CP 6128, Succ. A, Montréal, Québec, Canada H3C 3J7

(Received 6 June 1986; accepted 26 November 1986)

Abstract. *p*-Nitrobenzyl 6-(1-*tert*-butyldimethylsiloxyethyl)-3-nitromethyl-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylate, $C_{23}H_{33}N_3O_8Si$, $M_r = 507.62$, orthorhombic, $P2_12_12_1$, $a = 7.7817$ (12), $b = 10.5608$ (15), $c = 33.062$ (7) Å, $V = 2717.1$ Å 3 , $Z = 4$, $D_x = 1.241$ Mg m $^{-3}$, $\lambda(\text{Cu } K\alpha) = 1.54178$ Å, $\mu = 1.16$ mm $^{-1}$, $F(000) = 1080$, $T = 293$ K, $R = 0.070$ for 2139 observed reflections. The absolute configuration was confirmed. In the β -lactam system, the five-membered ring has an envelope conformation and the four-membered ring is nearly planar. The *tert*-butyldimethylsilyl group shows disorder, and in the *p*-

nitrophenyl system the nitro group is tilted 17 $^\circ$ out of the plane of the aromatic ring.

Introduction. An operationally novel entry into the medically important carbapenam nucleus (Ratcliffe & Albers-Schönberg, 1982) was realized by an internal Michael-type ring closure of (1) to give the carbapenam structure (2) as shown in Scheme 1 (Hanessian & Désilets, 1987; Désilets, 1986). Given the bicyclic ring structure of the product, it was deemed of interest to ascertain the stereochemical course of the event, since a related cyclization in the penam series had most