The Crystal and Molecular Structure of
9α-Fluoro-16α-methyl-11β,17,21-trihydroxy-1,4-pregnadiene-3,20-dione
21-Acetate Monohydrate

By A. Terzis

Chemistry Department, Dalhousie University, Halifax, Nova Scotia B3H 4J3, Canada

and T. Theophanides

Chemistry Department, University of Montreal, Montreal, Quebec H3C 3V1, Canada

The synthetic steroid 9α-fluoro-16α-methyl-11β,17,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-acetate, $C_{24}H_{31}O_6F$, is a potent inducer of liver microsomal enzymes as well as a powerful glucocorticoid. The structure was determined from room-temperature counter-collected data by direct methods. The space group is $P2_12_12_1$ with cell dimensions $a = 15\cdot292$ (3), $b = 19\cdot143$ (3), $c = 7\cdot808$ (2) Å. $D_m = 1\cdot27$, $D_x = 1\cdot308$ g cm^{-3} and $Z = 4$ for the formula $C_{24}H_{31}O_6F \cdot H_2O$. 2141 reflexions were collected and the structure was refined to an R index of 2·8%. The molecules are hydrogen bonded to each other in such a way as to form long helices, with their axes along **c**, which in turn are hydrogen bonded to each other through the water of crystallization.

Introduction

9α-Fluoro-16α-methyl-11β,17,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-acetate (dexamethasone acetate), a synthetic steroid, is a potent inducer of liver microsomal enzymes, as well as a powerful glucocorticoid. It has these two activities which are usually independent of each other. Indeed, pregnenolone-16α-carbonitrile (PCN), a synthetic steroid which is a strong enzyme inducer, is totally devoid of any glucocorticoid or any other steroidal activity. We determined the structure of the title compound, which should possess features of both of these classes of steroids, in order to compare it with PCN (Terzis & Theophanides, 1975) as well as with the series of glucocorticoids studied by Weeks, Duax & Wolff (1973). This analysis along with the biochemical results will be published elsewhere (Terzis, Theophanides & Kourounakis, 1975). Here we report on the structure of dexamethasone acetate and compare it with the most potent glucocorticoid in the series studied by Weeks, Duax & Wolff (1973).

Experimental

Crystals of dexamethasone acetate* suitable for X-ray work were obtained from a H_2O/acetone solution. A prismatic crystal was mounted on a Picker FACS-1 X-ray diffractometer with the c axis along the φ axis of the diffractometer. The unit-cell constants were obtained by a least-squares refinement of the angular measurements of 12 reflexions occurring at 2θ values between 60 and 70°. The space group $P2_12_12_1$ was

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* Dexamethasone acetate was a gift from the Institute of Experimental Medicine and Surgery, University of Montreal, courtesy of Dr P. Kourounakis.

assigned from the systematic absences ($h00$ for h odd, $0k0$ for k odd, $00l$ for l odd) and the crystal data are: $C_{24}H_{31}O_6F \cdot H_2O$, M.W. 450·1, space group $P2_12_12_1$; $a = 15\cdot292$ (3), $b = 19\cdot143$ (3), $c = 7\cdot808$ (2) Å; $V = 2285\cdot67$ Å^3; $Z = 4$; $F(000) = 968$; $D_m = 1\cdot27$, $D_x = 1\cdot308$ g cm^{-3}. A crystal of dimensions $0\cdot10 \times 0\cdot12 \times 0\cdot25$ mm was mounted on a Picker FACS-1 four-circle diffractometer with its c axis almost parallel to the instrument φ axis. The intensities of 2141 reflexions with 2θ less than 120° were measured by the θ–2θ scan technique with scan range 1·7°, employing stationary-crystal stationary-counter background counts of 40 s at each end of the scan range, using Cu $K\alpha$ radiation and a graphite monochromator. A plot of the intensities of three monitor reflexions (measured after every 30 reflexions) as a function of time showed that the crystal had not suffered any deterioration during data collection. The standard deviation for the net intensity, $\sigma(I)$, was calculated according to the expression:

$$\sigma^2(I) = \{N_T + 0\cdot25(t/t_B)^2(B_1 + B_2) + (0\cdot032I)^2 + [0\cdot025(N_c - I)]^2\}/T,$$

where N_T is the total count, t is the scan time, t_B is the time for each background count B_1 and B_2, N_c the net count corrected for absorption and T is the transmission coefficient. The third term in $\sigma^2(I)$ represents the influence of long-term instrumental instability (Corfield, Doedens & Ibers, 1967) and the fourth any errors in the absorption correction. The data were corrected for Lorentz, polarization and absorption effects. The transmission factors ranged from 0·89 to 0·94. Simultaneously with the absorption correction, $dA^*/d\mu$ was evaluated for secondary extinction corrections (Åsbrink & Werner, 1966). Only data for which $I > 1\cdot96\sigma(I)$ were used which left 1949 reflexions to be entered into the least-squares refinement.

The programs used were locally modified versions of the NRC crystallographic programs (Ahmed, Hall, Pippy & Huber, 1966) and *NUCLS*, originally *ORFLS*, modified by Doedens & Ibers, further modified locally by J. Sygusch to include block-diagonal approximation and secondary extinction correction.

Structure determination and refinement

The structure was solved by use of the direct-methods program *MULTAN* (Germain, Main & Woolfson, 1971). The phases of 239 reflexions with $E \geq 1.50$ were determined by the symbolic addition procedure. The solution with the highest Absolute Figure of Merit (=0.98) allowed us to calculate an E map which revealed all the nonhydrogen atoms. Refinement proceeded normally using the block-diagonal (9×9) approximation and unit weights with isotropic thermal parameters to an R value of 0.142. Introducing anisotropic temperature factors and a secondary extinction correction reduced R to 0.074. A three-dimensional difference Fourier map revealed the positions of 29 hydrogen atoms. Inclusion of these in the refinement and a calculation of a second difference Fourier map revealed the positions of the remaining hydrogen atoms. Inclusion and refinement of the hydrogen positions and their isotropic temperature factors as well as the introduction at this stage of a counting-statistics weighting scheme gave $R = 0.028$

and $R_w = [\sum(|F_o| - |F_c|)^2 / \sum wF_o^2]^{1/2} = 0.029$. Including the unobserved data in the refinement gave $R = 0.032$ and $R_w = 0.029$. A final difference electron-density map showed a maximum density of 0.21 e Å^{-3} and a minimum of -0.23 e Å^{-3}. The function $\sum w(|F_o| - |F_c|)^2 / N$, where N is the number of reflexions in the particular range, showed no significant variation with $|F_o|$, h (the slowest varying index during data collection) or $\sin \theta / \lambda$. The scattering factors for the heavy atoms were from Cromer & Waber (1965) and for the hydrogen atoms those of Stewart, Davidson & Simpson (1965). Tables 1 and 2 show the final positional and thermal parameters for the nonhydrogen and hydrogen atoms respectively.*

Thermal vibrational analysis

All rigid-body calculations were carried out by use of Schomaker & Trueblood's (1968) program.

The shapes and orientations of the thermal vibration ellipsoids are shown in Fig. 1. When the thermal motion of the molecule is analysed in terms of the rigid-body motion of the steroid nucleus, C(1)–C(17)

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* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30778. Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 1. *Positional* ($\times 10^5$) *and thermal* ($\times 10^4$) *parameters of the non-hydrogen atoms*

Thermal parameters are listed in the form: $\exp\{-2\pi^2(U_{11}h^2a^{*2} + 2U_{12}hka^*b^* + \ldots)\}$.

	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
F(9)	29322 (6)	4289 (5)	74804 (15)	345 (5)	465 (5)	459 (6)	−24 (2)	8 (3)	26 (3)
O(3)	36749 (10)	−19712 (7)	64930 (21)	579 (9)	393 (7)	538 (9)	−34 (3)	−30 (4)	−12 (4)
O(11)	47580 (9)	12647 (7)	94528 (23)	441 (8)	651 (10)	682 (11)	68 (4)	−96 (4)	−113 (4)
O(17)	16938 (8)	24889 (7)	82423 (18)	338 (6)	460 (7)	420 (8)	0 (3)	5 (3)	29 (3)
O(20)	30681 (12)	39494 (7)	84243 (25)	879 (12)	406 (8)	680 (11)	−73 (4)	79 (5)	25 (4)
O(21)	25258 (10)	40371 (7)	116591 (22)	626 (9)	469 (8)	650 (10)	−16 (4)	33 (5)	−80 (4)
O(23)	38434 (13)	35706 (10)	120508 (29)	796 (12)	801 (12)	981 (16)	106 (5)	−2 (6)	18 (6)
O(W)	48830 (10)	22750 (8)	121081 (25)	445 (9)	855 (12)	776 (14)	−35 (4)	−18 (4)	−57 (5)
C(1)	43567 (14)	−3974 (10)	84876 (30)	457 (12)	388 (11)	389 (12)	21 (4)	−47 (5)	−17 (5)
C(2)	41430 (14)	−10640 (10)	83076 (30)	484 (12)	363 (10)	432 (12)	9 (5)	−19 (5)	20 (5)
C(3)	39109 (13)	−13518 (10)	66442 (30)	351 (10)	369 (10)	460 (12)	11 (4)	−6 (5)	−20 (5)
C(4)	39503 (14)	−8850 (10)	51811 (28)	466 (12)	413 (11)	361 (12)	−6 (5)	14 (5)	−18 (5)
C(5)	41470 (13)	−2127 (10)	53387 (28)	373 (11)	400 (11)	420 (13)	18 (4)	40 (5)	−6 (5)
C(6)	41167 (17)	2692 (11)	38211 (30)	703 (16)	462 (12)	399 (14)	23 (6)	68 (6)	1 (6)
C(7)	34955 (16)	8741 (11)	41790 (29)	640 (15)	432 (11)	330 (12)	31 (5)	20 (6)	23 (5)
C(8)	37251 (13)	12584 (10)	58466 (27)	374 (11)	367 (10)	355 (11)	−4 (4)	17 (5)	20 (5)
C(9)	37757 (12)	7486 (9)	73722 (27)	276 (9)	371 (10)	370 (11)	−8 (4)	5 (4)	2 (5)
C(10)	44059 (12)	1141 (10)	70335 (28)	348 (11)	349 (10)	443 (13)	2 (4)	−1 (5)	−10 (5)
C(11)	38655 (13)	11002 (10)	91450 (29)	395 (11)	382 (10)	394 (12)	25 (4)	−21 (5)	18 (5)
C(12)	32632 (13)	17389 (9)	93667 (27)	366 (10)	363 (10)	311 (11)	7 (4)	−6 (5)	−0 (4)
C(13)	32768 (12)	22471 (9)	78579 (26)	308 (9)	341 (10)	350 (12)	0 (4)	14 (4)	11 (4)
C(14)	30578 (13)	18252 (9)	62431 (26)	353 (10)	365 (10)	308 (11)	4 (4)	10 (4)	24 (4)
C(15)	28697 (15)	23751 (11)	48714 (30)	522 (13)	462 (12)	380 (12)	46 (5)	14 (5)	46 (5)
C(16)	24835 (15)	30021 (10)	58658 (29)	518 (13)	428 (11)	412 (12)	48 (5)	35 (6)	61 (5)
C(17)	25187 (12)	27988 (9)	77962 (26)	336 (10)	334 (9)	361 (12)	−5 (4)	17 (5)	34 (4)
C(18)	41630 (13)	26322 (10)	77142 (32)	343 (11)	454 (12)	583 (15)	−29 (4)	22 (5)	3 (6)
C(19)	53881 (14)	3340 (11)	68722 (37)	357 (11)	517 (13)	798 (19)	15 (5)	27 (6)	−41 (7)
C(20)	26678 (14)	34440 (10)	89148 (30)	425 (12)	349 (10)	526 (14)	12 (4)	22 (5)	32 (5)
C(21)	22731 (16)	34346 (11)	106869 (34)	666 (16)	469 (12)	550 (15)	−71 (6)	53 (7)	−52 (6)
C(22)	15686 (19)	32076 (14)	52560 (34)	717 (18)	902 (19)	427 (15)	177 (8)	26 (7)	107 (7)
C(23)	33419 (17)	40429 (12)	122599 (35)	642 (15)	579 (14)	586 (16)	−20 (6)	28 (7)	12 (7)
C(24)	35195 (22)	46926 (15)	132582 (51)	894 (23)	829 (20)	1099 (26)	−118 (9)	−37 (11)	−147 (11)

Table 2. *Positional and thermal parameters* $(\times 10^{-3})$ *for the hydrogen atoms*

	x	y	z	U_{Iso}
H(1)	448 (1)	−22 (1)	963 (3)	43 (6)
H(2)	414 (1)	−139 (1)	924 (3)	57 (7)
H(4)	378 (1)	−108 (1)	403 (3)	46 (6)
H(6A)	472 (1)	43 (1)	365 (3)	50 (6)
H(6B)	374 (1)	1 (1)	274 (3)	59 (7)
H(7A)	353 (1)	120 (1)	321 (3)	44 (6)
H(7B)	284 (1)	71 (1)	423 (3)	58 (7)
H(8)	432 (1)	147 (1)	570 (2)	30 (5)
H(11)	366 (1)	73 (1)	1001 (3)	44 (6)
H(12A)	265 (1)	153 (1)	947 (3)	38 (5)
H(12B)	340 (1)	198 (1)	1047 (2)	30 (5)
H(14)	248 (1)	160 (1)	645 (2)	34 (5)
H(15A)	344 (1)	250 (1)	439 (2)	41 (6)
H(15B)	245 (2)	217 (1)	393 (3)	69 (8)
H(16)	290 (1)	344 (1)	581 (3)	42 (6)
H(18A)	464 (1)	229 (1)	756 (3)	49 (6)
H(18B)	415 (2)	297 (1)	678 (3)	59 (7)
H(18C)	425 (2)	290 (1)	870 (3)	73 (8)
H(19A)	561 (2)	45 (1)	800 (4)	97 (10)
H(19B)	575 (14)	−61 (1)	646 (3)	59 (7)
H(19C)	545 (2)	75 (1)	594 (3)	72 (8)
H(21A)	162 (2)	339 (1)	1060 (4)	98 (10)
H(21B)	247 (1)	300 (1)	1127 (3)	57 (7)
H(22A)	163 (2)	342 (1)	406 (4)	112 (11)
H(22B)	114 (2)	283 (1)	539 (3)	63 (7)
H(22C)	135 (2)	360 (1)	599 (4)	86 (9)
H(24A)	407 (2)	476 (1)	1333 (4)	115 (13)
H(24B)	345 (3)	508 (2)	1245 (5)	174 (17)
H(24C)	301 (2)	478 (2)	1393 (4)	126 (12)
H(O11)	482 (2)	160 (1)	1022 (3)	785 (9)
H(O17)	163 (2)	233 (1)	929 (4)	91 (9)
H(OWA)	542 (2)	235 (1)	1212 (4)	107 (11)
H(OWB)	460 (2)	273 (2)	1219 (5)	151 (16)

plus C(18), C(19), and F, we find that the molecule does in fact behave very nearly as a rigid body. The root-mean-square error for the U_{ij}'s, $[\Sigma(\Delta U_{ij})^2/(n-s)]^{1/2}$, where n is the number of U_{ij}'s and s the number of rigid-body parameters, was only 0·003 Å² for the above-mentioned 20 atoms. The other substituent groups, however, have a small amount of additional independent motion. The root-mean-square differences between the U_{ij} terms calculated from the anisotropic β_{ij} terms and those calculated from rigid-body parameters are reported in Table 3. The rigid-body mo-

tions are principally translational and are almost isotropic with an average amplitude of translation of 0·19 Å. Rotational motion (Table 4) is limited by the close packing of the irregularly shaped molecules and by the intermolecular hydrogen bonds and it amounts to only 4·4° about the long axis of the molecule. The correction (Schomaker & Trueblood, 1968) for rigid-body motion resulted in a systematic lengthening of the bonds by an average of 0·003 Å, the largest correction being 1σ. (All standard deviations reported in this paper have been doubled to allow for the block-diagonal least-squares approximation.)

Table 3. *Differences* $(\text{Å}^2 \times 10^4)$ *between* U_{ij} *derived from the input* β_{ij} *and those calculated from the rigid-body parameters*

$$\sigma(U) = \left[\frac{\Sigma(\Delta U_{ij})^2}{120-20}\right]^{1/2} = 0\cdot003 \text{ Å}^2$$

C(1)	28	−5	−38	−9	−25	−25
C(2)	4	−22	5	−32	−16	38
C(3)	−64	−18	15	14	−16	−23
C(4)	9	−4	−47	−28	24	−7
C(5)	−45	−13	24	26	36	−4
C(6)	30	2	7	−9	12	−7
C(7)	19	−21	−8	8	7	21
C(8)	0	−33	−8	−8	−28	7
C(9)	−21	−8	14	−12	10	−11
C(10)	33	−46	1	−1	−1	−12
C(11)	−4	1	18	22	15	34
C(12)	−40	−4	−29	−4	−18	−33
C(13)	−1	−29	−13	13	−8	−22
C(14)	−5	−31	−30	4	−5	−4
C(15)	−76	18	26	27	−7	12
C(16)	24	9	22	47	35	30
C(17)	3	−40	−20	−14	−24	−5
C(18)	19	69	−10	−28	−22	5
C(19)	49	81	−3	18	26	−19
F	38	92	74	−34	4	24

Results and discussion

The interatomic distances and angles which are presented in Fig. 2 are normal. A wide range of $C(sp^3)$–$C(sp^3)$ bond lengths is found with values ranging from 1·523 (6) to 1·574 (6) Å. This is most likely the
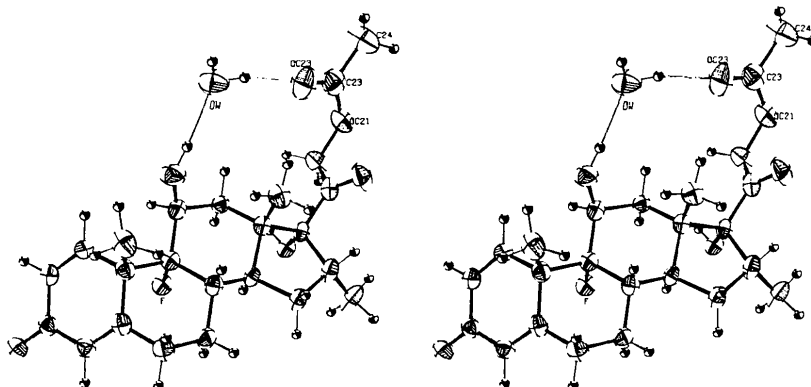

Fig. 1. Bond distances and angles.

Table 4. *Rigid-body vibration parameters for the nuclei*
C(1)–C(19) *and* F

Standard deviations are given in parentheses.

Components of the tensors **T**, **L** and **S** ($\times 10^4$)

T(Å^2)	302 (11)	−9 (7)	16 (9)
		383 (7)	23 (7)
			349 (10)
L(rad^2)	8 (1)	−13 (2)	−3 (1)
		56 (3)	7 (1)
			6 (1)
S(Å rad)	7 (3)	9 (2)	3 (2)
	−22 (3)	3 (4)	−27 (4)
	1 (1)	2 (2)	−10 (30)

Magnitudes of principal axes

T(Å)	0·20	0·19	0·17
L(°)	4·4	1·4	1·0

result of (*a*) interaction between non-bonded neighbouring substituents, (*b*) the effect of ring closure, and (*c*) the effect of electron-withdrawing substituents. It will be noticed that the longest bonds [C(13)–C(17) 1·571, C(9)–C(10) 1·574 Å] are between carbon atoms which have non-hydrogen substituents (larger non-bonded interactions) some of which are electron withdrawing (methyl group, F, OH). These same bonds are also the longest ones in the pregnenolone-16α-carbonitrile structure (Terzis & Theophanides, 1975).

On the other hand, the shortest C(sp^3)–C(sp^3) bonds [C(6)–C(7) 1·525, C(8)–C(14) 1·523 Å] are between carbon atoms which have several hydrogen substituents (smaller non-bonding interactions) and are not in the immediate vicinity of electron-withdrawing groups. All C–H bond lengths vary between 0·94 and 1·06 Å
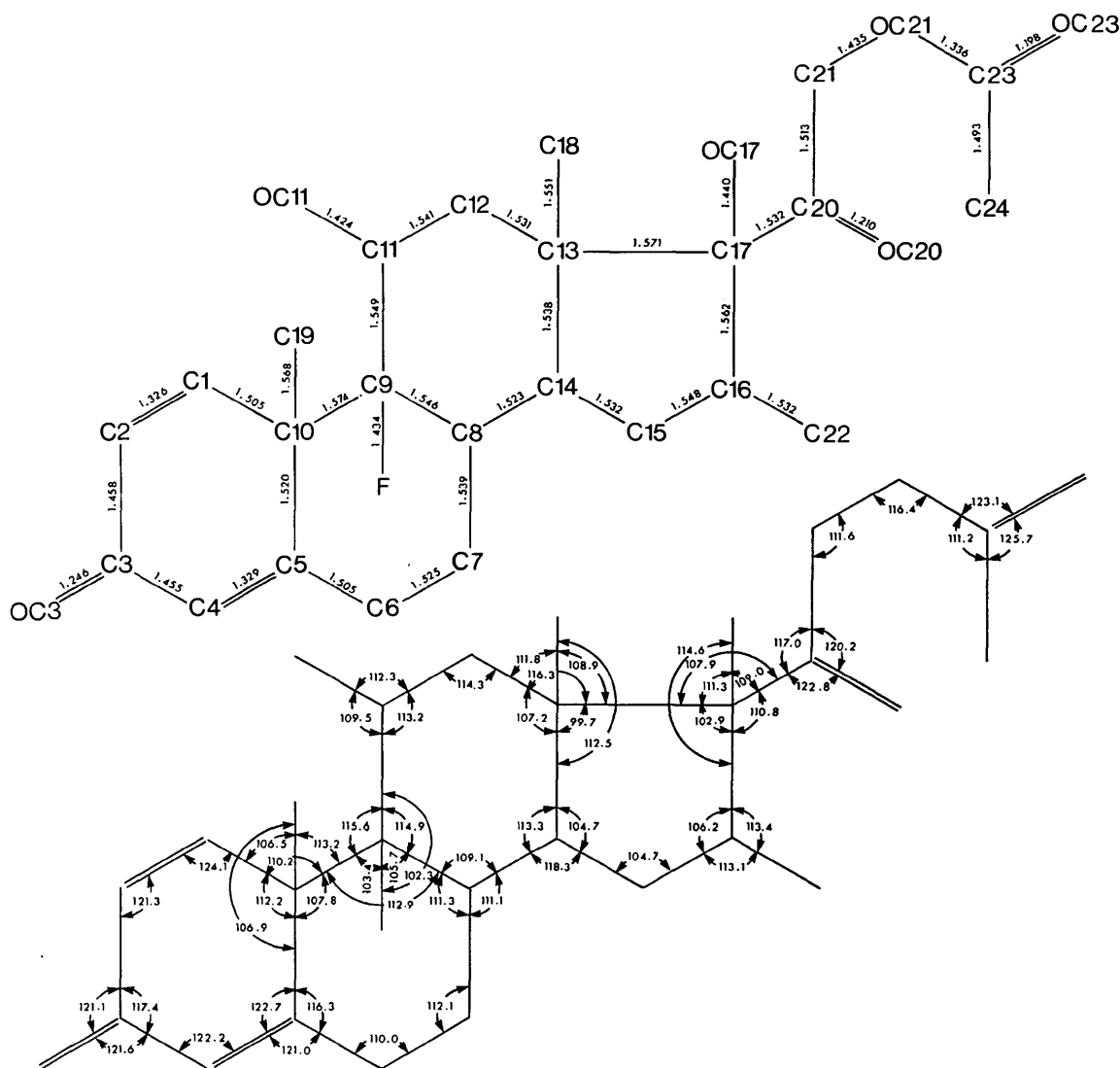

Fig. 2. A stereoscopic view of the structure showing 45 % probability ellipsoids for the nonhydrogen atoms (*ORTEP* program by C. K. Johnson).

(average 1·00 Å) and have standard deviations between 0·04 and 0·06 Å. The O–H bond lengths vary between 0·84 and 0·96 Å. All tetrahedral (sp^3) angles involving hydrogens vary between 103° and 115° (average 109°) with standard deviations of 2–5°, while all sp^2 angles involving hydrogens vary between 115 and 123° (average 119°). As shown by the intra-ring torsional angles (Table 5), the A ring is almost planar and the B and C rings have chair conformations. The D-ring conformation is intermediate between a half-chair and a C(13) or β envelope, but more nearly a β envelope as shown by the parameters $\Delta = 26\cdot3°$ and $\varphi_m = 46\cdot9°$ (Altona, Geise & Romers, 1968) and the torsional angles in Table 5. The C(17) side chain orientation which may be observed in Fig. 2 and in the Newman projection, Fig. 3, closely resembles the orientation in similar structures. The torsional angle C(16)–C(17)–C(20)–O(20), which is here $-29\cdot7°$, is usually observed between -18 and $-35°$ (Weeks & Duax, 1974; Watson, Go & Purdy, 1973; Dupont, Dideberg & Campsteyn, 1973).

In a study by Weeks, Duax & Wolff (1973), they reported a relationship between glucocorticoid activity and A-ring conformation. They found that the more the A-ring is bent out the C(5)–C(17) mean plane, the higher the anti-inflammatory activtity of cortisol, 6α-fluorocortisol, 6α-methylprednisolone, 9α-fluorocortisol, the last one having the highest activity. It is known (Kourounakis, Svabo & Selye, 1973; Selye, Svabo, Tache, Kourounakis, Mecs & Tache, 1974) that dexamethasone is considerably more potent than 9α-fluorocortisol. It can be seen in Fig. 4 that while dexamethasone follows the trend established by Weeks *et al.*, the small difference in the distance of O(3) from the mean plane for dexamethasone (2·57 Å) and 9α-

fluorocortisol (2·43 Å) cannot account for the large difference in activity between these steroids. This suggests that while the A-ring conformation may be important in determining glucocorticoid activity, there must be other contributing factors as well (Terzis, Theophanides & Kourounakis, 1975).

Molecular packing

The water molecule and the many OH and C=O substituents on the steroid make for an extended hydrogen-bond network. It is, however, the severe bending of the A-ring away from the C(5)–C(17) mean plane (Fig. 5) that enables the molecules to take the very interesting packing arrangement of long helices joined together by the water molecule.

Hydrogen bonds I and II (Table 6) hold the water molecule between O(11) and O(23). Hydrogen bond III is an intrahelical bond which connects the molecules (beginning to end) to form the helix and hydrogen bond IV is an interhelical bond which helps to hold the helices together.
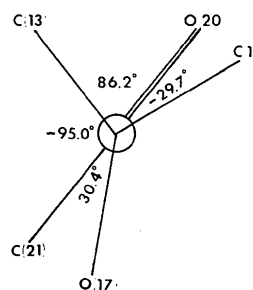

Fig. 3. Newman projection down the C(17)–C(20) bond.

Table 5. *Torsion angles* (°) *in the rings*

φ_{A-B} is the torsion angle about the A–B bond, in which the other two atoms required to define the angle are those attached to either end of the bond and are in the ring in question. The sign convention for the direction of the torsion angle is that of Klyne & Prelog (1960).

Ring A		Ring B		Ring C		Ring D	
Bond	φ_{A-B}	Bond	φ_{A-B}	Bond	φ_{A-B}	Bond	φ_{A-B}
C(1)–C(2)	−1·7	C(5)–C(6)	−56·8	C(8)—C(9)	−48·3	C(13)–C(14)	45·7
C(2)–C(3)	2·0	C(6)–C(7)	54·1	C(9)—C(11)	43·0	C(14)–C(15)	−31·0
C(3)–C(4)	−3·3	C(7)–C(8)	−54·1	C(11)–C(12)	−46·8	C(15)–C(16)	3·3
C(4)–C(5)	4·2	C(8)–C(9)	53·3	C(12)–C(13)	55·0	C(16)–C(17)	24·6
C(5)–C(10)	−3·5	C(9)–C(10)	−51·6	C(13)–C(14)	−62·6	C(13)–C(17)	−42·5
C(1)–C(10)	2·3	C(5)–C(10)	54·6	C(8)—C(14)	59·3		

Table 6. *Summary of the geometry of the hydrogen bonding*

Standard deviations are in parentheses.

Hydrogen bond		Position of O	Distance H···O	Distance O···O	Angle O–H···O
I	O(W)–H(OWB)···O(23)	1/000*	1·99 (7) Å	2·946 (5) Å	168 (6)°
II	O(11)–H(O11)····O(W)	1/000	1·96 (5)	2·842 (5)	173 (5)
III	O(17)–H(O17)····O(3)	2/00$\overline{1}$	1·91 (6)	2·782 (4)	171 (5)
IV	O(W)–H(OWA)···O(17)	3/$\overline{1}$02	1·99 (6)	2·819 (4)	171 (6)

* Equivalent position nomenclature: C(1)–C(2) 2/0$\overline{1}$2 is taken to mean atom C(1) at equivalent position 1 to atom C(2) at equivalent-position 2, translated 0, -1, and 2 unit cells in the a, b and c directions respectively. The equivalent positions are: $1 = x,y,z$; $2 = 0\cdot5-x, -y, 0\cdot5+z$; $3 = 0\cdot5+x, 0\cdot5-y, -z$; $4 = -x, 0\cdot5+y, 0\cdot5-z$.
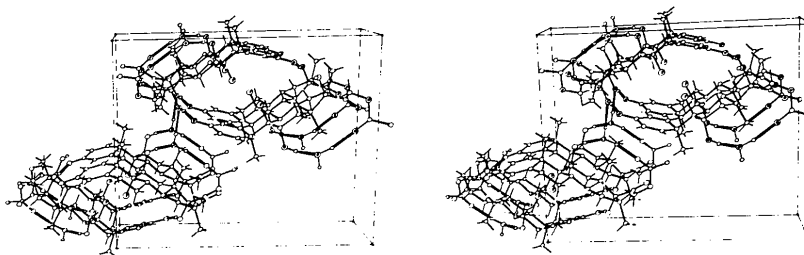
Fig. 4. Molecular packing viewed along the *c* axis.

Fig. 5. Projection parallel to the least-squares plane passed through atoms C(5) to C(17) inclusive, for 9α-fluorocortisol and dexamethasone acetate (large circles).

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