Crystal and Molecular Structure of Cortisol (11β,17α,21-Trihydroxypregn-4-ene-3,20-dione) Methanol Solvate

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Cortisol methanol solvate crystallises in the orthorhombic space group $P2_12_12_1$, with $a = 14{\cdot}372(4)$, $b = 18{\cdot}400(5)$, $c = 7{\cdot}706(2)$ Å, $Z = 4$. The structure was solved from diffractometer data by direct methods and refined to R 0·044 for 1908 observed reflexions.

Ring A is a distorted 'sofa', rings B and C are in the 'chair' configuration and ring D is close to a C(13) envelope, with a pseudorotational parameter Δ of 26·1°. The ring junctions B/C and C/D are both *trans*. The molecule as a whole is slightly convex towards the β-side, with an angle of 10·9° between the C(10)–C(19) and C(13)–C(18) vectors. The conformation of the C(17) side chain is compared with theoretical predictions based on MO and o.r.d. calculations.

CORTISOL is one of the steroids normally secreted by the adrenal cortex. It represents approximately 4/5 of the total 17-hydroxy-steroid content of blood and has important biological functions. In recent years considerable evidence has accumulated about the transport of steroid hormones by serum proteins.[1-3] Trans-

[1] A. A. Sandberg, H. Rosenthal, S. I. Schneider, W. R. Slaunwhite, jun., in 'Steroid Dynamics,' eds. T. Nakao, G. Pinkus, and J. F. Tait, Academic Press, New York, 1966, p. 1.

[2] U. S. Seal and R. P. Doe, in ref. 1, p. 63.

[3] V. Westphal, in 'Biochemical Action of Hormones,' vol. 1, ed. G. Litwack, Academic Press, New York, 1970, p. 209.

cortin, an α-globulin, has been identified as having a high affinity but low capacity for specific binding of cortisol and corticosterone. It has been proposed that the function of transport proteins is to provide a reservoir of steroid which is only gradually released in accord with the high K value of the complex. The transport protein may also protect the steroid against metabolism, and may prevent the undesirable accumulation of free steroid outside the target cell.

At present little is known about the structure of transcortin and the precise nature of the complex. The detailed stereochemistry of steroids in the crystalline state can, however, be established and we report here the X-ray structure analysis of cortisol. It is hoped that the accumulation of such structural information about the principal steroid molecules will eventually lead to a better understanding of the binding and other *in vivo* properties of this class of hormones. In the present paper particular emphasis is placed on a discussion of hydrogen bonding in cortisol and related compounds, calculated from published data.

EXPERIMENTAL

Crystal Data.—$C_{21}H_{30}O_5,CH_3OH$, $M = 394{\cdot}6$. Orthorhombic, $a = 14{\cdot}372(4)$, $b = 18{\cdot}400(5)$, $c = 7{\cdot}706(2)$ Å, $U = 2037{\cdot}8(4)$ Å^3, $D_m = 1{\cdot}25$ (by density gradient), $Z = 4$, $D_c = 1{\cdot}287$, $F(000) = 856$. λ(Cu-K_α) = 1·5418 Å, μ(Cu-K_α) = 7·6 cm^{-1}. Space group $P2_12_12_1$ (D_2^4, No. 19) from systematic absences.

Commercial cortisol (Koch–Light) was recrystallised from several solvents. Ethanol yielded monoclinic, dichloromethane hexagonal, and methanol orthorhombic crystals. The orthorhombic habit was chosen for structure analysis. Unit-cell and space-group data were obtained by photographic methods. Cell parameters were refined by least-squares treatment of θ values measured for 20 reflexions on an automatic Picker diffractometer by use of Cu-K_α radiation reflected from a graphite monochromator. Intensities were measured for a crystal of length 0·20, cross-section 0·38 × 0·36 mm. The diffractometer was operated in the θ—2θ scan mode with a range in 2θ of $(3{\cdot}0 + 0{\cdot}383 \tan\theta)°$.

Reflexions in the range $0{\cdot}0 \leqslant \sin\theta < 0{\cdot}5$ were traversed at 2° min^{-1} and those in the range $0{\cdot}5 < \sin\theta \leqslant 0{\cdot}895$ at 0·5° min^{-1}. The standard deviation of an intensity was calculated from counting statistics using $\sigma^2(I) = S + B + (dS)^2$ where S = scan count, B = background, interpolated from background curve, and corrected to scan time, $I = S - B$, and d is an empirical constant which allows for instrumental errors, taken as 0·05. Of 1950 independent reflexions with 2θ(Cu-K_α) ⩽ 127° (minimum interplanar spacing 0·86 Å), 42 had $I/\sigma(I) < \sqrt{2}$ and were classified as unobserved. No absorption correction was made. Lorentz and polarisation factors were applied and the structure amplitudes and normalised structure amplitudes (E values) were derived.

The structure was determined by direct methods involving tangent formula refinement [4,5] by use of 179 reflexions with $|E| \geqslant 1{\cdot}57$. The iteration was begun with the six 'known' phases (Table 1). Four of these were used to define the origin and enantiomorph and held constant while two were treated as symbolic phases and allowed to assume the values $\pm\pi/4$, $\pm 3\pi/4$. For the first 10 cycles

TABLE 1

Reflexions used in starting set

3	0	1	π/2
4	1	0	0
0	14	5	0
0	3	3	π/2
4	11	3	$a = \pm\pi/4, \pm 3\pi/4$
3	13	2	$b = \pm\pi/4, \pm 3\pi/4$

of refinement only the 65 highest $|E|$ values were used. In subsequent cycles more terms were included and during the last five cycles [(21)—(25)] all 179 reflexions were utilised. In these calculations phases generated by single interactions were not accepted, unless all three $|E|$ values exceeded 2·0. Phases were also rejected if they differed by more than π/2 from the value assigned on the previous cycle. An important indication of the correctness of a phase set is the R_{Karle} value.[4] Of the phase sets generated, one had an outstandingly low R_{Karle} of 0·25 while the remaining 15 had R_{Karle} between 0·29 and 0·36. Tangent refinement was continued on the first set alone for 30 cycles during which R_{Karle} dropped to 0·19.

An E map was next computed using these phases for the 179 E values. From this map the positions of all 26 non-hydrogen atoms of the cortisol molecule could be identified. These positions were refined by one cycle of full-matrix least-squares refinement minimising $\Sigma w|F_o - F_c|^2$, with isotropic temperature factors and scattering factors taken from ref. 6. At the end of this cycle the values of R and R' were lowered to only 0·245 and 0·272 respectively $[R' = (\Sigma w|F_o - F_c|^2/\Sigma w|F_o|)^{\frac{1}{2}}]$, suggesting that some part of the structure had not yet been accounted for. It was then realised that two peaks on the E map, separated by 1·38 Å and previously regarded as spurious probably represented a molecule of methanol.

To verify this a difference-Fourier map was calculated. Since the same two peaks were present they were included as additional oxygen and carbon atoms in the next cycle of isotropic least-squares refinement. The weighting scheme used was $w = 0$ for unobserved and $w = \{A + B|F_o| + C|F_o|^2 + D|F_o|^3\}^{-1}$ for observed terms where A, B, C, and D were chosen so as to minimise the deviation from constant $w\Delta^2$ over the whole range of $|F_o|$. Final values were 0·1865, 0·0389, −0·001539, and 0·000074.

The 21 fixed hydrogen atoms were located from a second difference-Fourier map. They were included with B values of 4·0 in the next cycle of a full-matrix anisotropic calculation where, however, only the positional and thermal parameters of the 26 carbon and oxygen atoms of the cortisol molecule were refined, the remaining atoms being kept fixed. R was reduced to 0·084 and a difference map indicated the position of the remaining 6 methyl and 3 hydroxy-hydrogen atoms. After two cycles of refinement varying the thermal parameters of all carbon and oxygen atoms anisotropically and those of hydrogen isotropically, the four hydrogen atoms of the methanol solvate appeared on a difference-Fourier map. These were included in the refinement which then converged at R 0·044 and R' 0·058.

[4] J. Karle and I. Karle, *Acta Cryst.*, 1966, **21**, 879.

[5] O. Kennard, N. W. Isaacs, W. D. S. Motherwell, J. C. Coppola, D. L. Wampler, A. C. Larson, and D. G. Watson, *Proc. Roy. Soc.*, 1971, *A*, **325**, 401.

[6] 'International Tables for X-Ray Crystallography,' vol. III, Kynoch Press, Birmingham, 1965, p. 201.

The final shifts for all variable parameters were small fractions of their standard deviations.

Final positional and thermal parameters are listed in Tables 2 and 3 respectively. In these Tables the standard

TABLE 2

Fractional co-ordinates with standard deviations in parentheses. Isotropic B values (Å^2) are also given for the hydrogen atoms

Atom	x/a	y/b	z/c	B
C(1)	0·4521(3)	0·4483(2)	−0·7874(5)	
C(2)	0·4936(3)	0·3732(2)	−0·7574(5)	
C(3)	0·4588(2)	0·3190(2)	−0·8855(5)	
C(4)	0·4303(2)	0·3460(2)	−1·0544(5)	
C(5)	0·4373(2)	0·4167(2)	−1·1021(5)	
C(6)	0·4268(3)	0·4381(2)	−1·2885(5)	
C(7)	0·3684(3)	0·5062(2)	−1·3123(5)	
C(8)	0·4006(2)	0·5689(2)	−1·1955(4)	
C(9)	0·3998(2)	0·5426(2)	−1·0051(4)	
C(10)	0·4659(2)	0·4758(2)	−0·9737(4)	
C(11)	0·4090(2)	0·6030(2)	−0·8675(4)	
C(12)	0·3467(2)	0·6694(2)	−0·9054(4)	
C(13)	0·3558(2)	0·6968(2)	−1·0922(4)	
C(14)	0·3340(2)	0·6358(2)	−1·2152(4)	
C(15)	0·3251(3)	0·6689(2)	−1·3932(5)	
C(16)	0·2859(3)	0·7458(2)	−1·3538(5)	
C(17)	0·2802(2)	0·7522(2)	−1·1538(5)	
C(18)	0·4527(2)	0·7282(2)	−1·1283(5)	
C(19)	0·5703(2)	0·4925(2)	−1·0068(5)	
C(20)	0·2960(2)	0·8298(2)	−1·0875(5)	
C(21)	0·2454(3)	0·8522(2)	−0·9251(5)	
C(22)	0·1519(6)	0·9163(3)	−0·4774(8)	
O(3)	0·4565(2)	0·2533(1)	−0·8533(4)	
O(11)	0·5039(2)	0·6235(1)	−0·8483(4)	
O(17)	0·1926(1)	0·7274(1)	−1·0883(3)	
O(20)	0·3464(2)	0·8719(1)	−1·1630(4)	
O(21)	0·2806(2)	0·9198(1)	−0·8690(4)	
O(22)	0·1703(2)	0·9659(1)	−0·6060(3)	
H(1A)	0·488(3)	0·483(2)	−0·704(5)	3·4(8)
H(1B)	0·383(3)	0·453(2)	−0·768(6)	4·6(10)
H(2A)	0·568(3)	0·374(2)	−0·774(6)	5·0(10)
H(2B)	0·478(3)	0·356(2)	−0·653(6)	4·8(9)
H(4)	0·410(3)	0·312(2)	−1·150(6)	4·0(9)
H(6A)	0·489(3)	0·446(2)	−1·325(6)	3·6(9)
H(6B)	0·401(3)	0·400(2)	−1·348(5)	3·0(7)
H(7A)	0·381(3)	0·526(3)	−1·445(7)	5·2(11)
H(7B)	0·313(2)	0·491(2)	−1·284(5)	2·7(7)
H(8)	0·465(2)	0·584(2)	−1·231(5)	2·6(7)
H(9)	0·335(2)	0·523(2)	−0·986(4)	2·2(6)
H(11)	0·396(3)	0·586(2)	−0·757(5)	2·5(7)
H(12A)	0·290(3)	0·658(2)	−0·879(6)	4·4(9)
H(12B)	0·366(2)	0·707(2)	−0·811(5)	2·4(7)
H(14)	0·273(2)	0·619(2)	−1·185(5)	2·7(7)
H(15A)	0·397(4)	0·677(3)	−1·447(7)	6·2(13)
H(15B)	0·284(3)	0·645(2)	−1·462(6)	4·1(10)
H(16A)	0·325(3)	0·785(2)	−1·393(6)	3·9(9)
H(16B)	0·230(3)	0·753(2)	−1·396(6)	3·4(8)
H(18A)	0·458(3)	0·746(2)	−1·250(6)	5·2(10)
H(18B)	0·499(3)	0·690(2)	−1·118(5)	3·8(8)
H(18C)	0·461(3)	0·765(2)	−1·058(6)	4·3(9)
H(19A)	0·589(3)	0·522(3)	−1·114(7)	5·9(11)
H(19B)	0·621(4)	0·450(3)	−0·997(9)	8·6(16)
H(19C)	0·601(3)	0·531(3)	−0·900(7)	6·2(11)
H(21A)	0·173(3)	0·861(2)	−0·946(6)	5·1(10)
H(21B)	0·258(3)	0·819(2)	−0·827(6)	4·7(9)
H(22A)	0·138(3)	0·937(2)	−0·335(6)	11·4(9)
H(22B)	0·142(3)	0·874(3)	−0·520(6)	10·2(12)
H(22C)	0·212(3)	0·917(2)	−0·418(6)	10·1(10)
H(O11)	0·510(3)	0·654(2)	−0·786(6)	3·6(9)
H(O17)	0·155(4)	0·748(3)	−1·171(7)	6·6(14)
H(O21)	0·240(4)	0·938(3)	−0·782(7)	5·5(17)
H(O22)	0·173(3)	1·012(2)	−0·555(5)	10·0(9)

chemical numbering scheme shown in (I) was adopted for the carbon atoms while the oxygen and hydrogen atoms are labelled according to the numbering of the carbon atom to which they are attached. The carbon atom of the methanol is C(22). The standard deviations in Tables 2 and 3 were calculated from the inverse matrix of the last refinement cycle.

TABLE 3

Anisotropic thermal parameters ($\times 10^5$) *

Atom	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
C(1)	430(18)	178(10)	968(56)	24(11)	4(28)	−11(19)
C(2)	562(20)	214(10)	1309(62)	48(12)	54(31)	−148(24)
C(3)	368(16)	171(9)	1594(66)	36(10)	−192(31)	−10(23)
C(4)	365(16)	163(9)	1357(62)	23(10)	−87(28)	71(20)
C(5)	275(14)	172(9)	1072(54)	40(9)	−48(24)	44(20)
C(6)	470(18)	207(10)	941(56)	31(11)	−6(28)	103(21)
C(7)	475(18)	200(10)	1049(56)	34(11)	124(28)	71(21)
C(8)	316(15)	175(9)	917(51)	7(10)	10(24)	3(19)
C(9)	260(13)	159(9)	939(53)	−5(9)	−30(23)	13(19)
C(10)	293(14)	143(8)	985(51)	4(9)	−29(24)	−15(19)
C(11)	421(16)	169(9)	862(51)	35(10)	14(25)	−3(20)
C(12)	368(16)	173(9)	1007(53)	36(10)	−17(26)	15(19)
C(13)	315(14)	151(8)	1056(52)	4(9)	−5(25)	−5(19)
C(14)	336(15)	172(9)	976(52)	2(10)	27(25)	21(19)
C(15)	515(19)	229(11)	1087(57)	74(12)	143(30)	−20(22)
C(16)	484(18)	215(10)	1252(63)	36(12)	139(30)	−66(23)
C(17)	316(14)	177(9)	1237(59)	−1(10)	16(25)	−42(20)
C(18)	344(15)	218(10)	1498(64)	−41(11)	13(30)	2(23)
C(19)	294(15)	210(10)	1699(70)	30(10)	−31(28)	−6(24)
C(20)	378(16)	167(9)	1467(61)	48(10)	72(30)	−83(21)
C(21)	444(17)	190(9)	1812(75)	22(11)	−81(34)	43(24)
C(22)	1302(51)	343(16)	2291(109)	58(23)	400(63)	268(38)
O(3)	627(15)	161(7)	2142(60)	45(9)	−122(27)	−160(18)
O(11)	432(12)	208(7)	1865(53)	33(8)	378(23)	202(18)
O(17)	302(9)	222(6)	1837(43)	5(6)	71(18)	−29(15)
O(20)	735(17)	196(7)	2067(56)	−73(9)	−272(27)	−28(17)
O(21)	587(14)	220(7)	2023(54)	−18(9)	−127(27)	171(19)
O(22)	1017(19)	227(7)	1520(42)	−24(10)	152(27)	−55(16)

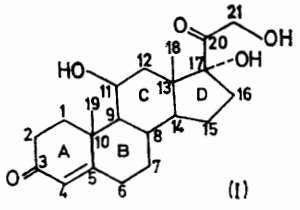
* Coefficients in the temperature factor expression:

$$\exp\{-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)\}.$$

Observed and calculated structure factors are listed in Supplementary Publication No. SUP 20649 (11 pp., 1 microfiche).*

DISCUSSION

Molecular Geometry.—The chemical formula of cortisol, together with the numbering scheme used is shown in (I). Figure 1 is a stereo-view of the molecular structure,



(I)

including the methanol of solvation. Individual bond lengths and the valency angles with their standard deviations are listed in Tables 4 and 5. Mean C(sp^3)–C(sp^3) and C(sp^3)–C(sp^2) bond lengths are 1·539 and 1·505 Å. As usual in steroid molecules, valency angles in the six-membered rings are generally larger and those in the five-membered ring are generally smaller than the tetrahedral value. External valency angles at C(13) and C(14) are also larger than the tetrahedral value, reflecting the misfit between five- and six-membered rings.

* For details see Notice to Authors No. 7 in *J. Chem. Soc.* (*A*), 1970, Issue No. 20.

The bond lengths in the conjugated O(3)–C(3)–C(4)–C(5) system are close to those reported for a number of 4-en-3-one steroids.[7-9] Planarity of the four atoms is not completely attained probably because of the steric influence of ring B. The sofa configuration for ring A would require the torsion angle ϕ [C(4)–C(5)–C(10)–C(1)] to be *ca.* −27°. This in turn would require the torsion angle ϕ [C(6)–C(5)–C(10)–C(9)] to approach 33°, resulting in considerable flattening of ring B. A compromise is achieved with ϕ [C(4)–C(5)–C(10)–C(1)] reduced to −18·7°.

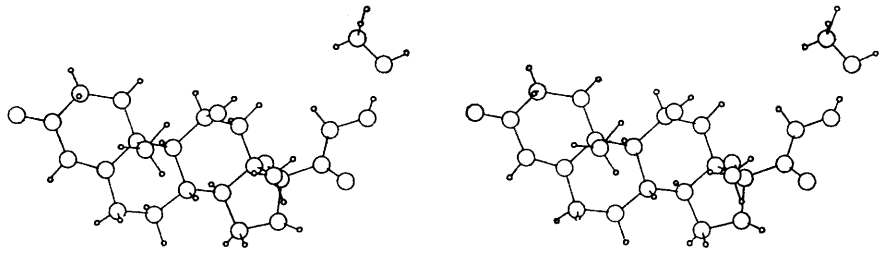


FIGURE 1 Stereo-view of the cortisol molecule and the methanol of solvation

TABLE 4

Bond distances (Å) with standard deviations in parentheses

C(1)–C(2)	1·523(5)	C(11)–C(12)	1·543(5)
C(1)–C(10)	1·534(5)	C(11)–O(11)	1·423(4)
C(2)–C(3)	1·490(5)	C(12)–C(13)	1·530(5)
C(3)–C(4)	1·453(5)	C(13)–C(14)	1·501(4)
C(3)–O(3)	1·235(4)	C(13)–C(17)	1·563(4)
C(4)–C(5)	1·355(4)	C(13)–C(18)	1·534(5)
C(5)–C(6)	1·498(5)	C(14)–C(15)	1·506(5)
C(5)–C(10)	1·527(4)	C(15)–C(16)	1·552(5)
C(6)–C(7)	1·519(5)	C(16)–C(17)	1·548(5)
C(7)–C(8)	1·535(5)	C(17)–C(20)	1·533(5)
C(8)–C(9)	1·545(5)	C(17)–O(17)	1·430(4)
C(8)–C(14)	1·567(4)	C(20)–C(21)	1·505(5)
C(9)–C(10)	1·573(4)	C(20)–O(20)	1·210(4)
C(9)–C(11)	1·541(4)	C(21)–O(21)	1·410(4)
C(10)–C(19)	1·552(4)	C(22)–O(22)	1·373(6)
C(1)–H(1A)	1·04(4)	C(16)–H(16A)	0·96(4)
C(1)–H(1B)	1·01(4)	C(16)–H(16B)	0·87(4)
C(2)–H(2A)	1·08(4)	C(18)–H(18A)	0·99(5)
C(2)–H(2B)	0·90(4)	C(18)–H(18B)	0·97(4)
C(4)–H(4)	1·01(4)	C(18)–H(18C)	0·87(4)
C(6)–H(6A)	0·95(4)	C(19)–H(19A)	1·03(5)
C(6)–H(6B)	0·92(4)	C(19)–H(19B)	1·07(6)
C(7)–H(7A)	1·10(5)	C(19)–H(19C)	1·17(5)
C(7)–H(7B)	0·86(3)	C(21)–H(21A)	1·07(4)
C(8)–H(8)	1·01(3)	C(21)–H(21B)	0·99(4)
C(9)–H(9)	1·01(3)	C(22)–H(22A)	1·18(4)
C(11)–H(11)	0·93(4)	C(22)–H(22B)	0·85(5)
C(12)–H(12A)	0·86(4)	C(22)–H(22C)	0·97(4)
C(12)–H(12B)	1·04(3)	O(11)–H(O11)	0·75(4)
C(14)–H(14)	0·95(3)	O(17)–H(O17)	0·91(5)
C(15)–H(15A)	1·13(5)	O(21)–H(O21)	0·95(5)
C(15)–H(15B)	0·91(4)	O(22)–H(O22)	0·94(4)

The mean deviation of the four atoms of the conjugated system from their mean plane is 0·03 Å, which is significant in terms of the standard deviations of the atomic positions. Similar deviations were found in some other steroids containing the 4-en-3-one system.[9,10] By use of published data, we have calculated the planarity of this system in cortisone [11] where the root-mean-square deviation is 0·05 Å and cortisone acetate [12] where it is 0·02 Å. However, in two structures, 17α-androst-4-en-3-one (epitestosterone) [8] and 21β-acetoxy-17α-hydroxypregn-4-ene-3,11,20-trione (17α-hydroxyprogesterone) [13] the 4-en-3-one system was found to be planar with a root-mean-square deviation of only 0·002 Å.

The torsion angles in the rings are listed in Table 6 which gives, for comparison, torsion angles in three related compounds: cortisone, cortisone acetate, and 4-chlorocortisone. For rings A and B the greatest difference between torsion angles in the four compounds is that of 4-chlorocortisone, particularly about bond C(5)–C(10). This evidently arises from the effect of the van der Waals interaction between the chlorine and the hydrogen on C(6). Note the differences in torsion angles around C(2)–C(3) and C(3)–C(4) between

TABLE 5

Valency angles (deg.) for non-hydrogen atoms with standard deviations in parentheses

C(2)–C(1)–C(10)	113·0(3)	C(9)–C(11)–O(11)	110·2(2)
C(1)–C(2)–C(3)	112·0(3)	C(12)–C(11)–O(11)	111·4(2)
C(2)–C(3)–C(4)	117·4(3)	C(11)–C(12)–C(13)	112·9(2)
C(2)–C(3)–O(3)	122·1(3)	C(12)–C(13)–C(14)	109·3(2)
C(4)–C(3)–O(3)	120·5(3)	C(12)–C(13)–C(17)	116·1(2)
C(3)–C(4)–C(5)	123·4(3)	C(12)–C(13)–C(18)	111·8(3)
C(4)–C(5)–C(6)	120·4(3)	C(14)–C(13)–C(17)	98·7(2)
C(4)–C(5)–C(10)	121·9(3)	C(14)–C(13)–C(18)	110·9(3)
C(6)–C(5)–C(10)	117·4(2)	C(17)–C(13)–C(18)	109·3(2)
C(5)–C(6)–C(7)	112·9(3)	C(8)–C(14)–C(13)	113·5(2)
C(6)–C(7)–C(8)	112·5(3)	C(8)–C(14)–C(15)	117·3(3)
C(7)–C(8)–C(9)	108·6(2)	C(13)–C(14)–C(15)	106·9(2)
C(7)–C(8)–C(14)	110·5(2)	C(14)–C(15)–C(16)	102·8(3)
C(9)–C(8)–C(14)	109·5(2)	C(15)–C(16)–C(17)	106·5(3)
C(8)–C(9)–C(10)	112·7(2)	C(13)–C(17)–C(16)	102·4(3)
C(8)–C(9)–C(11)	115·3(2)	C(13)–C(17)–C(20)	113·7(2)
C(10)–C(9)–C(11)	113·9(2)	C(13)–C(17)–O(17)	107·2(2)
C(1)–C(10)–C(5)	109·7(2)	C(16)–C(17)–C(20)	113·2(3)
C(1)–C(10)–C(9)	108·9(2)	C(16)–C(17)–O(17)	112·0(2)
C(1)–C(10)–C(19)	110·1(3)	C(20)–C(17)–O(17)	108·1(2)
C(5)–C(10)–C(9)	107·2(2)	C(17)–C(20)–C(21)	117·4(3)
C(5)–C(10)–C(19)	107·1(2)	C(17)–C(20)–O(20)	121·7(3)
C(9)–C(10)–C(19)	113·8(2)	C(21)–C(20)–O(20)	120·9(3)
C(9)–C(11)–C(12)	113·0(2)	C(20)–C(21)–O(21)	108·9(3)

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cortisone and the other three compounds. The lack of planarity in this part of ring A in cortisone affects the entire shape of the molecule as illustrated in Figure 2 where the molecules are viewed perpendicular to the flattening introduced by the hydroxy-function at C(11) in cortisol.

Rings B, C, and D are *trans*-fused and the two six-membered rings are in the chair conformation. The

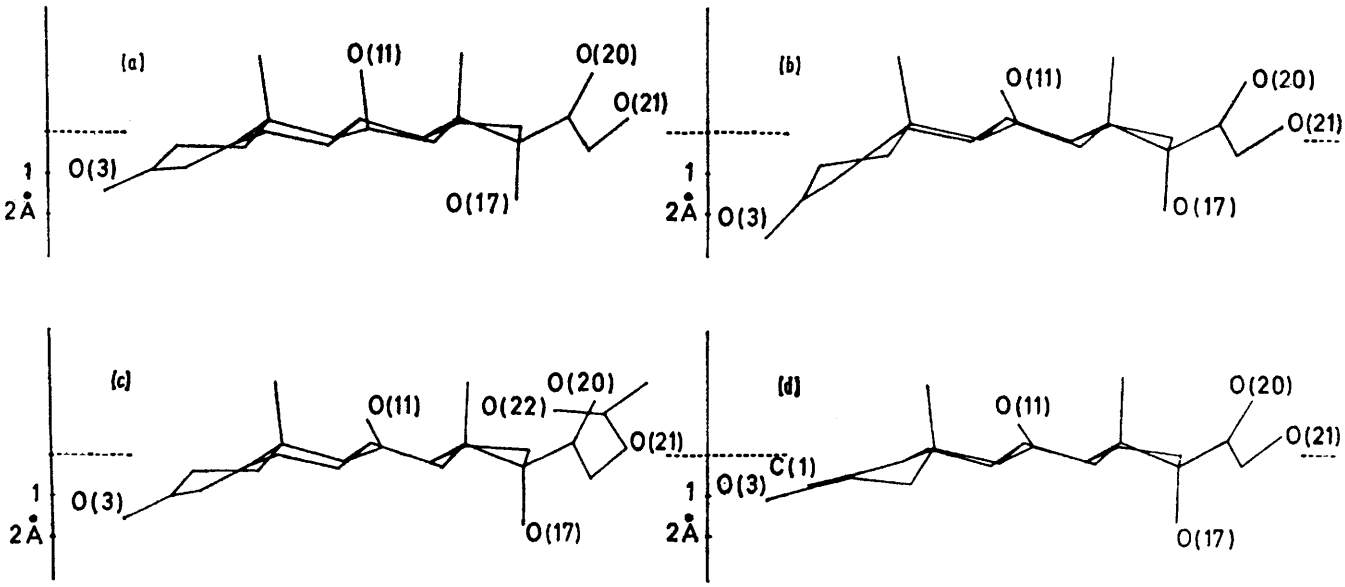

FIGURE 2 Comparison of (a) cortisol, (b) cortisone, (c) cortisone acetate, and (d) 4-chlorocortisone, all viewed perpendicular to the mean plane through atoms C(5)—C(17)

mean plane through atoms C(5)–C(17). Finally a comparison of torsion angles in ring C emphasises the

TABLE 6

Comparison of ring torsion angles in various corticosteroid derivatives: *A*, cortisol; *B*, cortisone; *C*, cortisone acetate; and *D*, 4-chlorocortisone

Ring A	*A*	*B* *	*C* *	*D*
C(1)–C(2)	−53·9	−56·7	−53·9	−53·2
C(2)–C(3)	27·6	40·8	30·6	25·4
C(3)–C(4)	2·7	−11·7	−1·0	−0·3
C(4)–C(5)	−7·1	−4·8	−7·0	4·0
C(5)–C(10)	−18·7	−10·5	−16·1	−31·0
C(1)–C(10)	48·5	41·2	45·6	54·8
Ring B				
C(5)–C(6)	−48·7	−54·2	−49·2	−44·8
C(6)–C(7)	50·3	51·4	51·6	52·3
C(7)–C(8)	−55·9	−51·4	−56·0	−58·0
C(8)–C(9)	59·8	55·1	59·2	57·3
C(9)–C(10)	−55·1	−53·5	−54·4	−47·8
C(5)–C(10)	49·5	53·3	49·1	41·4
Ring C				
C(8)–C(9)	−46·2	−52·3	−49·6	−52·2
C(9)–C(11)	44·8	58·0	54·1	53·3
C(11)–C(12)	−49·1	−59·6	−57·9	−54·6
C(12)–C(13)	56·4	57·0	58·2	55·8
C(13)–C(14)	−60·2	−59·6	−62·7	−60·4
C(8)–C(14)	54·9	56·1	57·1	58·2
Ring D				
C(13)–C(14)	47·2	46·8	48·4	48·0
C(14)–C(15)	−31·8	−34·7	−32·6	−36·1
C(15)–C(16)	2·8	9·1	3·1	9·3
C(16)–C(17)	25·2	19·3	26·9	19·5
C(13)–C(17)	−42·9	−40·1	−46·5	−40·4

* Calculated from published co-ordinates.

equations of the best least-squares planes through four ring atoms are given in Table 7 together with the distance of the excluded ring atoms from the planes. Ring D is generally characterised by the parameters ϕ_m, the maximum obtainable torsion angle during pseudorotation, and Δ, the phase angle, which locates the exact point on the pseudorotation circuit.[14] Values of ϕ_m for most steroids cluster around 47°; for cortisol the value is 47·8°. Values of Δ for the C(14) envelope, the half-chair, and the C(13) envelope are −36, 0, and 36°. Hence, ring D in cortisol, with Δ 26·1° is best described as a slightly distorted C(13) envelope. The steroid skeleton as a whole is slightly convex towards the β-side, the vectors C(10)–C(19) and C(13)–C(18) enclosing an angle of 10·9°.

From MO calculations on cortisol using the C(14) envelope as a model for the D ring, a C(17) side-chain conformation was predicted[15] in which O(20) is equidistant from C(13) and C(16) and in which the entire side chain including C(17) and O(17) is planar [Figure 3 (a) and (b)]. Wellman and Djerassi,[16] by use of o.r.d. and the half-chair conformation as a model for ring D, have assigned Figure 3 (c) as the preferred conformation. Our results [Figures 3 (d) and (e)] confirm their assignment although ring D is in the C(13) envelope conformation. This conformation of the C(17) side-chain was

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TABLE 7

Equations of least-squares planes in rings B and C in the form $lX + mY + nZ = p$ where X, Y, and Z are co-ordinates in Å, referred to the orthogonal axes a, b, and c. Δ is the root-mean-square deviation (Å) of the included atoms from the calculated plane

	l	m	n	p	Δ	Displacements (Å) of other ring atoms
Ring B: C(6), C(7), C(9), C(10)	0·7941	0·5193	−0·3158	12·21	0·020	C(5) −0·559, C(8) 0·703
Ring C: C(8), C(11), C(12), C(14)	0·7998	0·5684	−0·1931	12·32	0·018	C(9) −0·550, C(13) 0·686

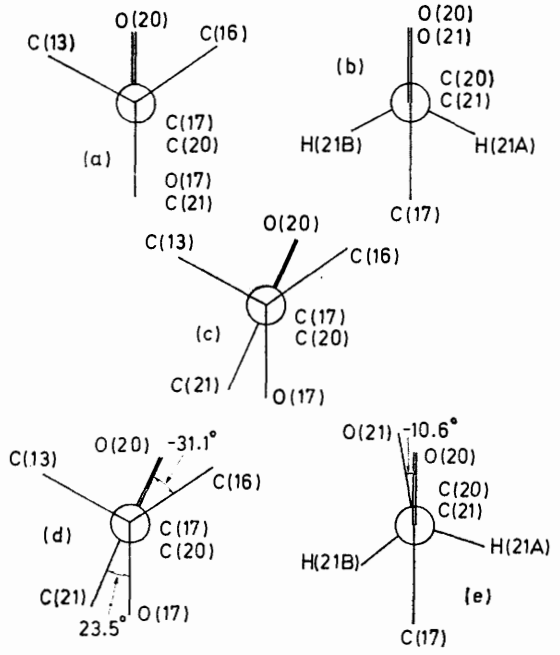

FIGURE 3 Newman projections of the C(17) side-chain: (a) and (b) as predicted in ref. 15, (c) as predicted in ref. 16, (d) and (e) observed in cortisol

usual helical arrangement of hydrogen bonds between the O(21) hydroxy-groups and the methanol of solvation. Each of the oxygen atoms acts both as donor and acceptor. The relevant distances and angles are: O(21)–H(21) · · · O(22) 2·7 Å, 174°; O(21) · · · H(22)–O(22) 2·83 Å, 142°. Additional linkage is provided by O(3) which behaves as an acceptor and forms two hydrogen bonds, one with O(11) at 2·90 Å [∠O(3) · · · H(11)–O(11) 168°] and the other with O(17) at 2·98 Å [∠O(3) · · · H(17)–O(17) 153°].

According to a review,[19] bent hydrogen bonds are not unexpected in a complex crystal packing arrangement. Nevertheless the deviation from linearity observed in the present structure is considerable.

In steroids with a carbonyl group attached to C(3) and a hydroxy-group at C(17), or in the C(17) side-chain, the most common way of packing the molecules in the crystal structures is by a 'head-to-tail' hydrogen bonding with the carbonyl oxygen as acceptor and the hydroxy as donor. Solvent molecules may also be involved in intermolecular hydrogen bonding. If, as in the present structure, there is more than one hydroxy-group attached to the steroid nucleus the hydrogen-bonding pattern is more complex and generally involves a solvent molecule.

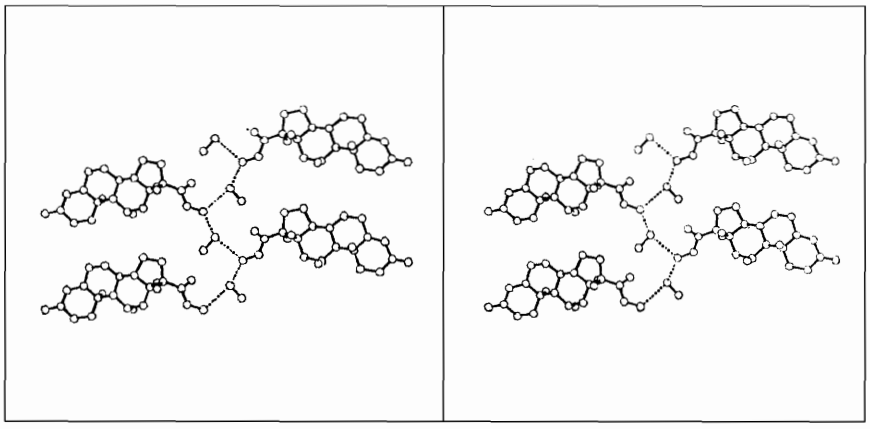

FIGURE 4 The extended crystal structure of cortisol showing the helical arrangement of hydrogen bonds between the hydroxy-groups and the methanol of solvation

also reported for 4-chlorocortisone[17] and 6α-fluorocortisol.[18]

The Extended Crystal Structure and Hydrogen Bonding.—The packing of the cortisol molecules in the crystal structure is illustrated in Figure 4 which shows the un-

The structures of three related steroids, cortisone,[11] cortisone acetate,[12] and 17α-hydroxyprogesterone,[13] have recently been published. In view of the probable importance of hydrogen bonding in the interpretation

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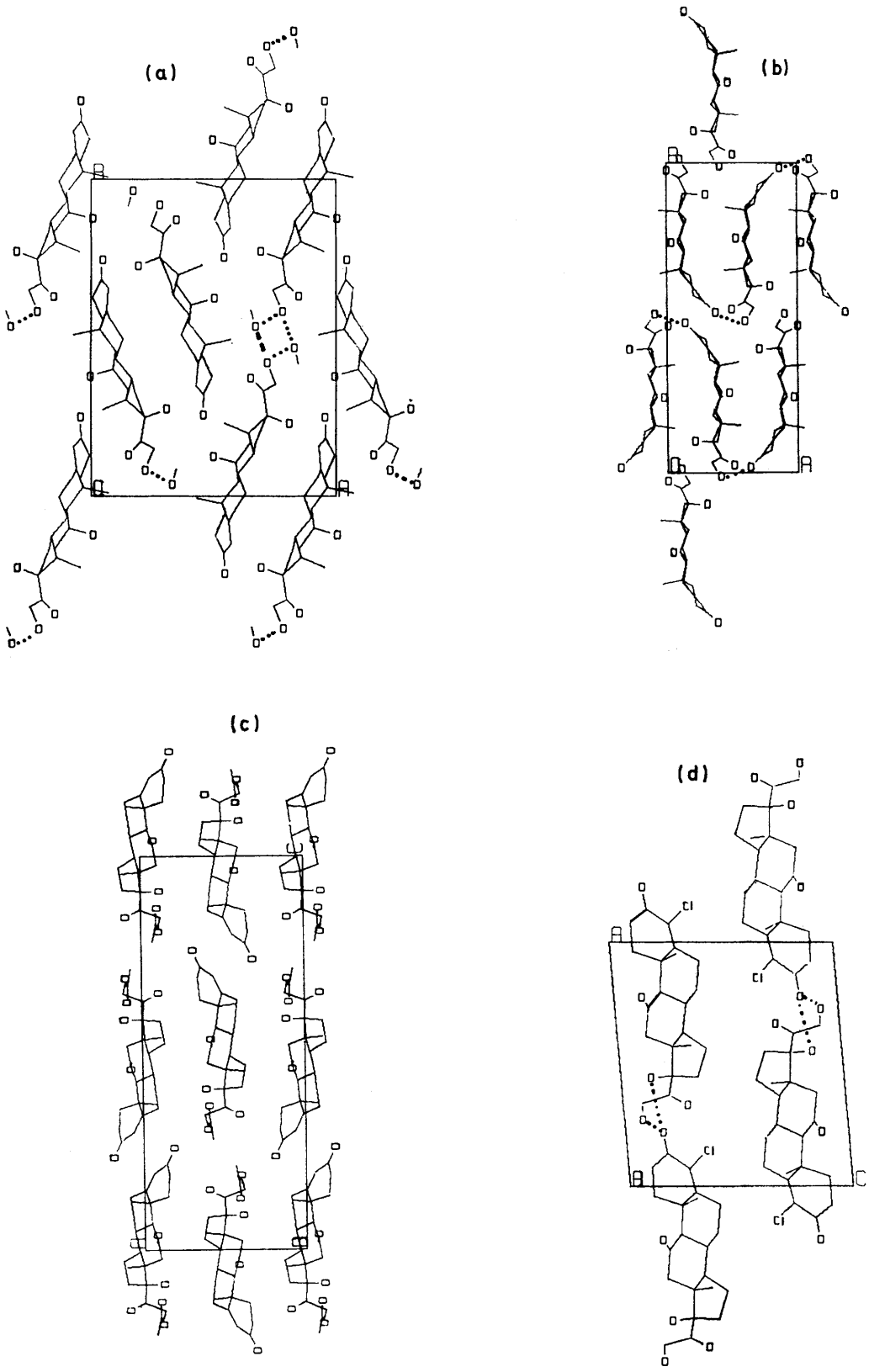

FIGURE 5 Packing arrangements in (a) cortisol, (b) cortisone, (c) cortisone acetate, and (d) 4-chlorocortisone. Dashed lines indicate that one of the molecules has been translated one unit cell in the direction of the axis of projection

of the biological properties of steroids we have used the published data to examine the pattern of packing of the molecules in these structures.

Figure 5(b) illustrates the packing arrangement in the crystal structure of cortisone where the molecules are linked by a hydrogen bond of length 2·70 Å between O(3) and O(21). Cortisone acetate [Figure 5(c)] exhibits a very unusual packing arrangement involving hydrogen bonds between O(17) and O(21) of a molecule one unit cell apart in the direction of the *b* crystallographic axis. The linked molecules thus form infinite columns about the *b* axis. In this structure O(3) is not involved in hydrogen bonding. In 4-chlorocortisone,[17] the more usual head-to-tail packing is observed, with O(3) hydrogen-bonded to O(21) and O(17) of neighbouring molecules.

We thank the M.R.C. and O.S.T.I. for financial support and the Director and staff of the Institute of Theoretical Astronomy for computing facilities.

[2/2004 *Received, 24th August,* 1972]